Evidence report for biologics in ulcerative colitis

Prepared by EBSCO Health Innovations and EBM Development Department:

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Scoping

Prepared by EBSCO Information Services

December 16, 2019

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Abbreviations

General abbreviations that may appear in this report

CI – confidence interval
CrI – credible interval
HR – hazard ratio
IQR – interquartile range
MA – meta-analysis
MD – mean difference
NA, N/A – not applicable
NMA – network meta-analysis
NR – not reported
OR – odds ratio
RCT – randomized, controlled trial
RR – risk ratio, relative risk
RtR – rate ratio
SD – standard deviation
SE – standard error
SMD – standardized mean difference
SR – systematic review
SRMA – systematic review and meta-analysis

Abbreviations specific to this report that may appear in this report

5-ASA – 5-aminosaliclyate
CD – Crohn's disease/Crohn disease/Morbus Crohn
EQ-5D – EuroQol 5 Dimensions (a quality of life scale)
IBD – Inflammatory bowel disease
IBDQ – Inflammatory Bowel Disease Questionnaire (this is a disease-specific quality of life scale with 4 categories of questions: bowel symptoms, systemic symptoms, emotional function, and social function; the total score ranges from 32 to 224, with higher scores being better)
IL – interleukin
QoL/QOL – quality of life
SF-36 – 36-Item Short Form Survey (this is a quality of life scale with 7 categories of questions: physical functioning, role limitations due to physical health, role limitations due to emotional health, energy/fatigue, emotional well-being, social functioning, pain, and general health; the total score and score for each subscale ranges from 0 to 100, with higher scores being better)
TNF – tumor necrosis factor
TNFa – tumor necrosis factor alpha
UC – ulcerative colitis/Colitis Ulcerosa

General note about terminology

The biologics are sometimes referred to as biologicals, monoclonal antibodies (or "MAbs"), or biosimilars.

The anti-TNF alpha agents are sometimes referred to as anti-TNF agents, TNF inhibitors, TNF alpha inhibitors, anti-TNF antibodies, and anti-TNF therapy.

Methods

Using an established, structured template that delineates key elements for scoping (i.e., the population, interventions, and key outcomes to consider), we collaboratively agreed with UKSH on the scope of the present evidence report. Scoping was completed on December 17, 2019.

Results – Criteria Selection for Critical Appraisal

Population:

Inclusion criteria

Adult patients whose moderate-to-severe ulcerative colitis/Colitis Ulcerosa (UC) has not responded well to standard treatment (such as 5-ASA for induction and/or maintenance of remission or corticosteroids for induction of remission or disease flares) or specific non-biologic treatments alone (such as immunosuppressants / immunomodulators like azathioprine / 6-mercaptopurine or methotrexate), where trying or adding biologics might be indicated. This might be before or after trying thiopurines.

Exclusion criteria

Patients with contraindications to biologics, including comorbidities precluding treatment with biologics.

Intervention and Comparator/Options:

Anti-TNF alpha agents

The specific agents being considered in this class are any of the following: infliximab, adalimumab, and golimumab. They will be considered as a composite option of anti-TNF alpha agents (i.e., drug class effects), not as individual medications.

Anti-integrin agent

The specific agent being considered is vedolizumab, an anti-α4β7-integrin.

Anti-interleukin agent

The specific agent being considered is ustekinumab, an anti-IL12 and anti-IL23 agent.

Note about ustekinumab:

Presently, RCT evidence for the use of this agent in UC appears limited to a single trial, namely the recently-published UNIFI trial (Sands 2019). This is evidenced by a recent guideline (Lamb 2019) discussing the abstract presentation of this trial and a broad-based search of MEDLINE®/PubMed® with the terms *ustekinumab AND ulcerative colitis AND (randomized controlled trial[pt] OR systematic[sb] OR meta-analysis[ti])*. Accordingly, in the outcomes section below where we specify the type of evidence we will consider for a given outcome, wherever we specify we will seek evidence from systematic reviews of RCTs, it should be understood we mean we will utilize the UNIFI trial for ustekinumab as appropriate.

Note about comparator:

The preferred comparator for each of the above therapies will be placebo; more specifically, the preferred comparison will be: standard treatment plus the biologic agent vs. standard treatment plus placebo. In the absence of placebo-controlled evidence, we will consider evidence comprised of standard treatment plus the biologic agent vs. standard treatment alone, and we will downgrade for risk of bias as appropriate. If we encounter evidence with a mixture of these comparator groups, we will report overall effect estimates if (1) the effect estimates are not importantly different between the two types of comparator groups or (2) only overall effect estimates are reported; in the latter case, we will again downgrade for risk of bias as appropriate. Otherwise, we may report effect estimates only for the evidence comprised of placebo-controlled comparator groups. We will not attempt to make any direct comparisons of one biologic agent to another biologic agent (e.g., vedolizumab vs. ustekinumab). If we are unable to find evidence comparing standard treatment without the biologic agent (with or without placebo) vs. the same standard treatment plus the biologic agent, we may then consider evidence comparing treatment using standard non-biologic therapies vs. biologic agent-based therapy (with or without standard treatments). If this occurs, we will downgrade for indirectness.

Note about other biologics:

The pace of development and approval for biologic agents for various conditions is currently fairly rapid. Accordingly, we have included in this evidence report the most relevant biologic options that currently have approval. However, newer agents may be available or may become available in some areas during creation of this evidence report. We will make a note about this in the background information for this evidence report (e.g., in Evidence Synthesis and possibly also the sample patient decision aid). If we note references to such agents during our evidence review for the formally scoped agents, we will also make note of this, but any such agents will not be treated as formally scoped options for the evidence review processes of search and selection, critical appraisal, and evidence synthesis.

Outcomes:

Where outcomes will be answered with systematic searches, critical appraisal, and evidence synthesis, we will state the intended approach after we state the outcome(s) of interest for that FAQ. For example, we might say: "The outcome of interest is all-cause mortality. We will obtain effect estimates from systematic reviews and meta-analyses of randomized, controlled trials or from individual trials if systematic reviews do not exist or meta-analysis is not the most appropriate method of synthesis." Otherwise, where we say: "We will include a description of", "We will include descriptive responses", or something similar, we will answer the FAQ with descriptive responses, which do not involve systematic evidence searches, critical appraisal, or evidence synthesis.

FAQ 1: What does the treatment involve?

We will include a description of the treatment, which will include frequency of dosing and route of administration. We will also include a description of pre-treatment testing or monitoring during treatment that is needed/recommended (e.g., screening for tuberculosis prior to initiation, monitoring for skin cancer).

Descriptive responses are acceptable, and this does not involve systematic evidence searches, critical appraisal, or evidence synthesis.

FAQ 2: Will it help my symptoms?

The outcomes of interest are induction and maintenance of remission. We will obtain effect estimates from systematic reviews of RCTs. We will prioritize patient-relevant definitions of remission and will not consider surrogate markers of remission – such as endoscopically-defined remission or mucosal healing – unless no other data exist. If definitions of remission solely comprised of patient-relevant outcomes are not separately reported, we will consider composite measures of remission that include such elements if they also include patient-relevant symptoms (e.g., Mayo Score for UC or the UC Disease Activity Index, which include both the patient's symptoms as well as the endoscopic appearance of the colon and the clinician's impression of the disease activity). Patient-relevant symptoms include things like abdominal pain/cramping; bowel movement urgency, consistency (e.g., soft vs. formed), composition (e.g., bloody vs. not), continence, and frequency; rectal pain; and/or systemic symptoms such as fever, weight loss, malnutrition, and anemia.

If existing evidence does not clearly answer both remission questions (i.e., induction and maintenance), we will note this explicitly. If the evidence is unclear, such as reporting "clinical remission" or something similar without explicitly noting if the remission pertains to induction vs. maintenance, we will either report this as such or attempt (as possible) to infer whether it pertains more to induction or maintenance based on the time of reporting. For instance, an otherwise-undifferentiated remission outcome measured at 4 to 8 weeks would provide more insight into induction of remission, whereas an outcome measured at 26 to 52 weeks would provide more insight into maintenance of remission.

FAQ 3: Will it impact my quality of life?

The outcome of interest is quality of life. We will obtain effect estimates from systematic reviews of RCTs. Although a condition-specific quality of life scale would possibly be preferable (such as the IBDQ), we are aware that quality of life measurements for the biologic agents are not always measured on such a scale when studied in patients with UC (e.g., some measure using the SF-36 or EQ-5D). Accordingly, we

will not restrict to any scale, but we may limit our evidence synthesis to a qualitative synthesis of the available quantitative information, if multiple scales are used.

FAQ 4: Will it impact my need for surgery?

The outcome of interest is UC-related surgery. We will obtain effect estimates from systematic reviews of RCTs. Evidence for this outcome may not be available for all the scoped options, but it is considered a highly patient-relevant outcome, so omitting it due to the possibility of insufficient evidence for certain options would seem a disservice to patients. If evidence is found to be lacking for a given option, we will state that explicitly.

FAQ 5: Will it impact my risk of having to go into the hospital?

The outcome of interest is hospitalization. We will obtain effect estimates from systematic reviews of RCTs. Evidence for this outcome may not be available for all the scoped options, but it is considered a highly patient-relevant outcome, so omitting it due to the possibility of insufficient evidence for certain options would seem a disservice to patients. If evidence is found to be lacking for a given option, we will state that explicitly.

FAQ 6: What are the risks or side effects?

The risks of interest for quantitative evidence review are infection and malignancy. We will ideally obtain estimates from systematic reviews. If systematic reviews are found to be insufficient or lacking, we will obtain estimates from studies utilizing patient registries/databases in preference to other types of observational studies. We will seek estimates specific to the interventions being used for the target condition and population (also considering evidence for the broader classification of inflammatory bowel disease as being acceptable). In the absence of sufficient evidence, we may draw from evidence for other conditions and populations (e.g., rheumatoid arthritis or psoriasis) with a downgrade for indirectness as appropriate.

We will also include a description of common side effects or other serious risks of the interventions, drawing from guidelines (Kucharzik 2019, Lamb 2019) and product monographs.

Kucharzik T, Dignass AU, Atreya R, Bokemeyer B, Esters P, Herrlinger K, Kannengießer K, Kienle P, Langhorst J, Lügering A, Schreiber S, Stallmach A, Stein J, Sturm A, Teich N, Siegmund B, Andus T, Autschbach F, Bachmann O, Baretton G, Baumgart DC, Bettenworth D, Bläker M, Buderus S, Büning J, Ehehalt R, Fellermann K, Fichtner-Feigl S, Götz M, Gross C, Hartmann F, Hartmann P, In der Smitten S, Häuser W, Helwig U, Kaltz B, Kanbach I, Keller KM, Klaus J, Koletzko S, Kroesen A, Kruis W, Kühbacher T, Leifeld L, Maaser C, Matthes H, Moog G, Ockenga J, Pace A, Reinshagen M, Rijcken E, Rogler G, Stange E, Veltkamp C, Zemke J. Updated S3-Guideline Ulcerative Colitis. German Society for Digestive and Metabolic Diseases (DGVS). Z Gastroenterol. 2019 Feb;57(2):162-241. doi: 10.1055/a-0824-0861. Epub 2019 Jan 17. PubMed

Lamb CA, Kennedy NA, Raine T, Hendy PA, Smith PJ, Limdi JK, Hayee B, Lomer MCE, Parkes GC, Selinger C, Barrett KJ, Davies RJ, Bennett C, Gittens S, Dunlop MG, Faiz O, Fraser A, Garrick V, Johnston PD, Parkes M, Sanderson J, Terry H; IBD guidelines eDelphi consensus group, Gaya DR, Iqbal TH, Taylor SA, Smith M, Brookes M, Hansen R, Hawthorne AB. British Society of Gastroenterology consensus guidelines on the management of inflammatory bowel disease in adults. Gut. 2019 Dec;68(Suppl 3):s1-s106. doi: 10.1136/gutjnl-2019-318484. Epub 2019 Sep 27. Review. PubMed

Sands BE, Sandborn WJ, Panaccione R, O'Brien CD, Zhang H, Johanns J, Adedokun OJ, Li K, Peyrin-Biroulet L, Van Assche G, Danese S, Targan S, Abreu MT, Hisamatsu T, Szapary P, Marano C; UNIFI Study Group. Ustekinumab as Induction and Maintenance Therapy for Ulcerative Colitis. N Engl J Med. 2019 Sep 26;381(13):1201-1214. doi: 10.1056/NEJMoa1900750. PubMed

UPDATE: Concluding Assessment by SHARE TO CARE Evidence Team (04/10/22)

Due to new data for biological drugs the decision aid was updated: Abreu *et al.* 2020 report long-term follow-up data for ustekinumab trough 3 years. Consequently, the respective parts of the decision aid have been adjusted, i.e., the symptomatic remission rate at 1 year, the continued effect over 3 years as well as the tendency of side effects to decrease over time.

The study will be fully considered as part of the next comprehensive update of the evidence report.

Abreu, M. T., Rowbotham, D. S., Danese, S., *et al.* (2022). Efficacy and Safety of Maintenance Ustekinumab for Ulcerative Colitis Through 3 Years: UNIFI Long-term Extension. Journal of Crohn's & colitis, 16(8), 1222–1234. https://doi.org/10.1093/ecco-jcc/jjac030

Evidence report for biologics in ulcerative colitis

Evidence Synthesis

Prepared by EBSCO Information Services

December 28, 2019
Revised February 15, 2020 with additional data for FAQ6 (risks for infection and malignancy) from Evidence report for biologics in Crohn's disease

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Methods

Where evidence is very limited, or the FAQ is scoped as a descriptive response, such that no evidence synthesis or processing is applied, the descriptive summary/-ies will be given.

For each FAQ for which evidence synthesis or processing is considered, the key concepts (results and factors affecting certainty of the results) from the included studies that are most relevant to evidence synthesis will be summarized in Evidence Review Tables. For each outcome, Evidence Synthesis Process tables will then articulate the method selected for evidence synthesis and justification of that method. We will do this for the effect estimate (i.e., answering the question "Is there a difference between the intervention and comparator?") and results will be presented with GRADE-based certainty of evidence ratings related to the certainty of effect estimates. For FAQs which require noncomparative/option-specific responses (i.e., the FAQ is "What will happen with this option?" rather than "How do things change with this option?") the Evidence Synthesis Process tables will be extended to include the method to produce noncomparative responses.

For summary statements representing a plain language summary of evidence appraisal and synthesis

We will include the following 2 items immediately after the summary statement as a parenthetical, regardless of whether they occur in the Summary of Findings section or the individual FAQs in the body of the Evidence Synthesis document:

- our certainty in the summary statement (categorized as High, Moderate, Low, or Very low), and
- the number and type of studies informing the statement, as well as a label for the studies in "[Author] [Year]" format.

If the study informing the summary statement is a systematic review and meta-analysis, then unless there are compelling reasons to proceed in a different manner, we will cite the systematic review and meta-analysis as the source. We will do this even if the result on which our summary statement is based comes from a subset of studies in that systematic review and meta-analysis (e.g., a meta-analysis of 5 out of 10 studies, because only 5 of the 10 reported on the outcome of interest). If EBSCO Information Services conducts its own meta-analysis of studies to inform a summary statement, we will list the individual studies.

For summary statements representing a plain language summary of descriptive sources

Certainty rating and provision of details about contributing studies do not apply. Accordingly, we will not include a parenthetical at the end of the summary statement. However, when descriptive summaries appear in the Summary of Findings section, we will include a general parenthetical citation of the references we consulted. We will place this at the end of the relevant FAQ in the Summary of Findings section. For summary statements occurring in the body of the Evidence Synthesis document, we will provide this general parenthetical citation as part of the longer descriptive summary component that precedes the simplified summary statement.

Results – Summary of Findings

FAQ 1: What does the treatment involve?

Anti-TNF alpha agents

The medicine may be given in your vein or under your skin. If the medicine is given under your skin, you can do this yourself after you learn how. After the first dose of the medicine, you will receive another dose about 2 weeks later. After that, the medicine will be given every 2 to 8 weeks. How the medicine is given and how often it is given depend on the medicine used.

Before starting this medicine, you should be tested for tuberculosis and hepatitis. Your clinician will also monitor you for infections and skin and blood cancers. You should also tell your clinician if you notice any changes in your skin, fevers, night sweats, or significant weight loss.

Vedolizumab

The medicine is given in your vein. You will receive 2 more doses of the medicine at 2 weeks and 6 weeks after the first dose. After that, the medicine will be given every 8 weeks.

Before starting this medicine, you should be tested for tuberculosis. Your clinician will also monitor you for infections. You will also be monitored for signs of an allergic reaction when you are getting the medicine in your vein. Sometimes allergic reactions happen after you get the medication. You should tell your clinician right away if you have any symptoms like shortness of breath or feeling tightness or swelling in your chest, face, mouth, or throat. Your clinician will also monitor you for new or worsening symptoms related to your nervous system, like numbness, weakness, clumsiness, or difficulty thinking. You should also tell your clinician if you notice anything like this.

Ustekinumab

The medicine is given in your vein the first time. It is then given under your skin every 8 weeks. You can give yourself the medication under your skin once you learn how.

Before starting this medicine, you should be tested for tuberculosis. Your clinician will also monitor you for infections. Your clinician will also monitor you for skin cancer while you take the medicine. You should also tell your clinician if you notice any changes in your skin. You should also tell your clinician if you develop new or worsening headache, vision changes, difficulty thinking, or seizures.

Sources consulted in preparing these descriptive responses include: DynaMed 2018, Kucharzik 2019, Lamb 2019

FAQ 2: Will it help my symptoms?

Anti-TNF alpha agents

Symptoms of ulcerative colitis include things like pain or cramping in your stomach or intestines, feeling like you suddenly need to move your bowels, having to move your bowels many times during the day, and sometimes losing control of your bowels. Some people also have fever, weight loss, or fatigue.

Out of 100 people who do not take a biologic agent:

- 5 to 12 (5% to 12%) have symptoms under control at 8 weeks. (About 9 out of 100)
- 10 to 15 (10% to 15%) have symptoms under control at 1 year. (About 13 out of 100)
- 4 to 7 (4% to 7%) have symptoms under control at 8 weeks and at 1 year. (About 5 out of 100)

Taking a TNF alpha medicine helps people have a better chance of getting their symptoms under control. Out of 100 people who take a TNF alpha medicine:

- 9 to 36 (9% to 36%) have symptoms under control at 8 weeks. (About 22 out of 100) (High certainty; based on 3 systematic reviews: Bonovas 2018, Lopez 2015, Singh 2018)
- 21 to 30 (21% to 30%) have symptoms under control at 1 year. (About 26 out of 100) (High certainty; based on 3 systematic reviews: Bonovas 2018, Lv 2014, Lopez 2015)
- 8 to 21 (8% to 21%) have symptoms under control at 8 weeks and at 1 year. (About 15 out of 100) (High certainty; based on 2 randomized trials: Rutgeerts 2005, Sandborn 2012)

Effects may vary with the specific drug used.

Vedolizumab

Symptoms of ulcerative colitis include things like pain or cramping in your stomach or intestines, feeling like you suddenly need to move your bowels, having to move your bowels many times during the day, and sometimes losing control of your bowels. Some people also have fever, weight loss, or fatigue.

Taking vedolizumab helps people have a better chance of getting their symptoms under control.

Out of 100 people who do not take a biologic agent, 5 to 12 (5% to 12%) have symptoms under control at 8 weeks. (About 9 out of 100)

Out of 100 people who take vedolizumab, 19 to 41 (19% to 41%) have symptoms under control at 8 weeks. (About 30 out of 100)

Out of 100 people who have a good response to vedolizumab early on but then stop taking it, 16 to 31 (16% to 31%) have symptoms under control at 1 year. (About 23 out of 100)

Out of 100 people who have a good response to vedolizumab early on and keep taking it, 38 to 75 (38% to 75%) have symptoms under control at 1 year. (About 57 out of 100)

(High certainty; based on 1 systematic review: Bonovas 2018)

Ustekinumab

Symptoms of ulcerative colitis include things like pain or cramping in your stomach or intestines, feeling like you suddenly need to move your bowels, having to move your bowels many times during the day, and sometimes losing control of your bowels. Some people also have fever, weight loss, or fatigue.

Taking ustekinumab helps people have a better chance of getting their symptoms under control.

Out of 100 people who do not take a biologic agent, 5 to 12 (5% to 12%) have symptoms under control at 8 weeks. (About 9 out of 100)

Out of 100 people who take ustekinumab, 15 to 34 (15% to 34%) have symptoms under control at 8 weeks. (About 25 out of 100)

Out of 100 people who have a good response to ustekinumab early on but then stop taking it, 16 to 31 (16% to 31%) have symptoms under control at 1 year. (About 23 out of 100)

Out of 100 people who have a good response to ustekinumab early on and keep taking it, about 29 to 56 (29% to 56%) have symptoms under control at 1 year. (About 43 out of 100)

(High certainty; based on 1 trial: Sands 2019)

FAQ 3: Will it impact my quality of life?

Anti-TNF alpha agents

Out of 100 people who do not take a biologic agent:

- 46 to 50 (46% to 50%) have improvement in quality of life at 8 weeks (About 48 out of 100)
- 15 (15%) may have improvement in quality of life at 1 year

Out of 100 people who take a TNF medicine:

- 61 to 66 (61% to 66%) have improvement in quality of life at 8 weeks (About 64 out of 100) (High certainty; based on 1 systematic review: LeBlanc 2015)
- 26 (26%) may have improvement in quality of life at 1 year (Moderate certainty; based on 1 systematic review: LeBlanc 2015)

People who have a good response to a TNF medicine early on and keep taking it may often still have an improved quality of life at 1 year.

People who have a good response to a TNF medicine early on but then stop taking it may often no longer have an improved quality of life at 1 year.

(Low certainty; based on 1 systematic review [LeBlanc 2015] and indirect extrapolation from other biologic agents)

Vedolizumab

Out of 100 people who do not take a biologic agent, 46 to 50 (46% to 50%) have improvement in quality of life at 8 weeks. (About 48 out of 100)

Out of 100 people who take vedolizumab, 75 to 81 (75% to 81%) may have improvement in quality of life at 8 weeks. (About 78 out of 100)

(Moderate certainty; based on 1 systematic review [LeBlanc 2015] containing 1 trial for vedolizumab [Feagan 2013])

Out of 100 patients who have a good response to vedolizumab early on but stop taking it, 38 (38%) may have good quality of life at 1 year.

Out of 100 patients who have a good response to vedolizumab early on and keep taking it, 64 (64%) may have good quality of life at 1 year.

(Low certainty; based on 1 systematic review [LeBlanc 2015] containing 1 trial for vedolizumab [Feagan 2013])

People who have a good response to vedolizumab early on and keep taking it may often still have an improved quality of life at 1 year.

People who have a good response to vedolizumab early on but then stop taking it may often no longer have an improved quality of life at 1 year.

(Low certainty; based on 1 trial: Feagan 2013)

Ustekinumab

Out of 100 people who do not take a biologic agent, 46 to 50 (46% to 50%) have improvement in quality of life at 8 weeks. (About 48 out of 100)

Out of 100 people who take ustekinumab, 66 to 71 (66% to 71%) have improvement in quality of life at 8 weeks. (About 68 out of 100)

Out of 100 patients who have a good response to ustekinumab early on but stop taking it, 19 (19%) may have an additional improvement in quality of life at 1 year.

Out of 100 patients who have a good response to ustekinumab early on and keep taking it, 32 (32%) may have an additional improvement in quality of life at 1 year.

People who have a good response to ustekinumab early on and keep taking it may often still have an improved quality of life at 1 year.

People who have a good response to ustekinumab early on but then stop taking it may often no longer have an improved quality of life at 1 year.

(Moderate certainty; based on 1 trial [Sands 2019])

FAQ 4: Will it impact my need for surgery?

Anti-TNF alpha agents

Out of 100 people who do not use a biologic agent:

- 2 to 8 (2% to 8%) may have their colon removed in the next year (About 5 out of 100)

Out of 100 people who use a TNF alpha medicine:

- 2 to 5 (2% to 5%) may have their colon removed in the next year (About 3 out of 100)

Effects may vary with the specific drug used. (Low certainty; based on a meta-analysis of 4 trials [2 each in Sandborn 2009 and Feagan 2014])

Vedolizumab

There is not enough research yet to answer this question.

Ustekinumab

There is not enough research yet to answer this question.

FAQ 5: Will it impact my risk of having to go to the hospital?

Anti-TNF alpha agents

Out of 100 people who do not take a biologic agent, 10 to 18 (10% to 18%) may have to be in the hospital due to their ulcerative colitis within 1 year. (About 14 out of 100)

Out of 100 people who take a TNF alpha medicine, 7 to 12 (7% to 12%) may have to be in the hospital due to their ulcerative colitis within 1 year. (About 9 out of 100)

(Moderate certainty; based on a meta-analysis of 4 trials [2 each in Sandborn 2009 and Feagan 2014])

Vedolizumab

Out of 100 people who do not take a biologic agent, 10 to 18 (10% to 18%) may have to be in the hospital due to their ulcerative colitis within 1 year. (About 14 out of 100)

Out of 100 people who take vedolizumab, 7 to 12 (7% to 12%) may have to be in the hospital due to their ulcerative colitis within 1 year. (About 9 out of 100)

(Very low certainty; based on one trial comparing vedolizumab and adalimumab [Sands 2019V])

Ustekinumab

Out of 100 people who do not take a biologic agent, 10 to 18 (10% to 18%) may have to be in the hospital due to their ulcerative colitis within 1 year. (About 14 out of 100)

Out of 100 people who take ustekinumab, 7 to 12 (7% to 12%) may have to be in the hospital due to their ulcerative colitis within 1 year. (About 9 out of 100)

(Moderate certainty; based on 1 randomized trial [Sands 2019])

FAQ 6: What are the risks or side effects?

Infection

Anti-TNF alpha agents

TNF medicines increase your risk for serious infections, but the increase is small.

TNF medicines increase your risk for infections due to a weak immune system, but the risk is low.

Out of 100 people who do not take a TNF medicine:

- about 2 (2%) may get a serious infection within 3 months
- about 5 (5%) may get a serious infection within 1 year
- less than 1 (less than 1%) may get an infection due to a weak immune system within 6 months

Out of 100 people who take a TNF medicine:

- about 3 to 5 (3% to 5%) may get a serious infection within 3 months (Moderate certainty; based on 2 national cohort studies: Kirchgesner 2018, Nyboe Andersen 2015)
- about 7 to 12 (7% to 12%) may get a serious infection within 1 year (Moderate certainty; based on 2 national cohort studies: Kirchgesner 2018, Nyboe Andersen 2015)
- about 3 (3%) may get an infection due to a weak immune system within 6 months (Moderate certainty; based on 1 systematic review and 1 national cohort study: Bonavas 2016, Kirchgesner 2018)

Vedolizumab

People who take vedolizumab may have a higher risk of infection compared to people who do not take vedolizumab. (Low certainty; based on 1 randomized trial, Sandborn 2013)

Out of 100 people who take vedolizumab:

- 4 to 10 (4% to 10%) may get a serious infection within 1 year (Moderate certainty; based on 1 systematic review: Schreiber 2018)

Ustekinumab

People who take ustekinumab likely have a higher risk of infection compared to people who do not take ustekinumab. There is not enough research yet to use numbers when talking about this risk.

Malignancy

Anti-TNF alpha agents

Out of 1,000 people who do not take a TNF medicine, about 2 to 4 (0.18% to 0.38%) may get lymphoma within about 7 years. (About 3 out of 1,000)

Out of 1,000 people who take a TNF medicine, about 4 to 9 (0.43% to 0.89%) may get lymphoma within about 7 years. (About 7 out of 1,000)

(Moderate certainty; based on 1 national cohort study: Lemaitre 2017)

To match "out of 100" phrasing for the rest of the decision aid this can be simplified to:

TNF medicines may increase your risk for lymphoma (a cancer of the blood), but the risk is low.

Out of 100 people who do not take a TNF medicine, less than 1 (less than 1%) may get lymphoma within 7 years

Out of 100 people who take a TNF medicine, about 1 (1%) may get lymphoma within 7 years

TNF medicines may also increase your risk for some skin cancers, but there is not enough research to use numbers to describe the risk. (Low certainty; based on 1 systematic review, Askling 2011)

Vedolizumab
There is not enough research yet to answer this question.

Ustekinumab
There is not enough research yet to answer this question.

Side effects

Anti-TNF alpha agents
Side effects with TNF alpha medicine may include, but are not limited to:

- Headache
- Nausea or stomach pain
- Pain, itching, or redness where you get the injection
- Rash
- Cough, common cold, sore throat, sinus infection, or chest cold
- Bladder infection
- Feeling tired
- Increased blood pressure
- Dizziness

Vedolizumab
Side effects with vedolizumab may include, but are not limited to:

- Common cold, sore throat, sinus infection, or chest cold
- Joint pain
- Headache
- Nausea
- Feeling tired
- Fever
- Rash
- Itching

Ustekinumab
Side effects with ustekinumab may include, but are not limited to:

- Headache
- Nausea, vomiting, or diarrhea
- Redness where you get the injection
- Itching
- Common cold, sore throat, sinus infection, or chest cold

- Bladder infection or yeast infection
- Feeling tired

Sources consulted when preparing the descriptive response for side effects include: DynaMed 2018, FDA 2018, FDA 2019

Search summary:

Number of articles screened and selected

	Screened	Selected (first stage)*	Selected (second stage)*
1st-round (DynaMed)	44	5	3
2nd-round (Systematic review searches)	117	19	9
3rd-round (Original article searches)	124	6	6†
4th-round (Citation tracing)	7	7	7†
Total	*292*	*37*	*25*

* Number shown is after deduplication

† Second stage selection not applicable

	Articles selected for evaluation (Author Year)
Systematic reviews	11 (Bonovas 2016, Bonovas 2018, Bye 2017, Colombel 2017, LeBlanc 2015, Lopez 2015, Lv 2014, Mao 2017, Paschos 2018, Schreiber 2018, Singh 2018)
Randomized, controlled trials	9 (Feagan 2013, Feagan 2014, Motoya 2019, Rutgeerts 2015, Sandborn 2009, Sandborn 2012, Sandborn 2014, Sands 2019, Sands 2019V)
Other article types	5: 1 umbrella review (Bonovas 2018U), 4 cohort studies (Kobayashi 2019, Lemaitre 2017, Nyboe Andersen 2014, Nyboe Andersen 2015)

In addition to the evidence noted above, the following studies were identified during searches for "Biologics for Crohn's disease" and contributed to FAQ6 responses. Details of these studies can be found in the full report for biologics for Crohn's disease, though they are not included in the counts above:

Askling 2011
Kirchgesner 2018
Sandborn 2013
Schreiber 2018
Siegel 2009

Results

Note: Other biologic agents

Biologics other than the scoped agents that were noted in the systematic reviews used for this evidence review include:

- Certolizumab pegol – an anti-TNF alpha agent
  - Bonovas 2016 includes data for infections and malignancies
- Natalizumab – an anti-integrin agent
  - Bonovas 2016 includes data for infections and malignancies
- Rituximab – an anti-CD20 antibody
  - LeBlanc 2015 includes data for induction of remission and improvement in IBDQ
- Tofacitinib – a Janus kinase inhibitor
  - Bonovas 2018 includes data for induction of remission
  - Singh 2018 includes data for induction of remission and infections

FAQ 1: What does the treatment involve?

Because of the common sources used for descriptive summaries for this FAQ, we present references at the end of this FAQ rather than after each treatment option.

Anti-TNF alpha agents

Descriptive Summary (pre-synthesis and synthesis efforts not applicable for descriptive summaries)

The anti-TNF alpha agents are monoclonal antibodies for the proinflammatory cytokine TNF alpha. By antagonizing TNF alpha (by binding to and blocking TNF alpha receptor sites), anti-TNF alpha agents lead to a reduction in cytokine-driven inflammatory processes. As the name implies, TNF alpha also has a complex role in cancer dynamics as well.

Infliximab is given intravenously. The first 3 doses are given more closely together (second dose 2 weeks after first dose, third dose 4 weeks after second dose). Thereafter, doses occur every 8 weeks.

Adalimumab is given subcutaneously, and this can be administered by the patient after s/he learns how. The first dose may be given on day 1 or split between 2 consecutive days. The second dose occurs on day 15. Thereafter, doses are given every other week (i.e., every 2 weeks).

Golimumab is given subcutaneously. The second dose is given 2 weeks after the first dose. Thereafter, doses are given every 4 weeks.

In addition to general vigilance concerning monitoring for infections during treatment, patients should be evaluated for tuberculosis and hepatitis B prior to beginning therapy. Patients should also be monitored periodically during treatment for tuberculosis. Patients who are carriers of hepatitis B should also be monitored during therapy (and for several months following discontinuation).

Patients should be monitored for dermatologic and hematologic cancers throughout treatment, especially if they have risk factors. Patients with heart failure should be monitored for new or worsening signs of heart failure.

Descriptive Summary Results

The medicine may be given in your vein or under your skin. If the medicine is given under your skin, you can do this yourself after you learn how. After the first dose of the medicine, you will receive another dose about 2 weeks later. After that, the medicine will be given every 2 to 8 weeks. How the medicine is given and how often it is given depend on the medicine used.

Before starting this medicine, you should be tested for tuberculosis and hepatitis. Your clinician will also monitor you for infections and skin and blood cancers. You should also tell your clinician if you notice any changes in your skin, fevers, night sweats, or significant weight loss.

Vedolizumab

Descriptive Summary (pre-synthesis and synthesis efforts not applicable for descriptive summaries)

Vedolizumab is considered a relatively gut-specific monoclonal antibody. It blocks the $\alpha_4\beta_7$ integrin from interacting with the mucosal/mucosal vascular addressin cell adhesion molecule-1 (MAdCAM-1), which inhibits lymphocytes from migrating into the gastrointestinal parenchyma. It is in the same class as natalizumab, which is less specific (e.g., natalizumab is also used in multiple sclerosis); however, natalizumab still works by blocking integrin association with vascular receptors via antagonist activity to the α_4 subunit of integrin molecules, thereby impeding/limiting leukocytes from migrating from the vasculature into inflamed tissues.

Vedolizumab is given intravenously. The first 3 doses are given more closely together (second dose 2 weeks after first dose, third dose 4 weeks after second dose). Thereafter, doses occur every 8 weeks.

In addition to general vigilance concerning monitoring for infections during treatment, patients should be evaluated for tuberculosis prior to beginning therapy and periodically during therapy. Patients should also be monitored for hypersensitivity reactions during their treatment and should be counseled on the signs and symptoms of such, as hypersensitivity reactions can be delayed to several hours after completing the infusion. Patients should also be monitored for and counseled to report any new or worsening neurological symptoms due to the rare but serious risk of progressive multifocal leukoencephalopathy.

Descriptive Summary Results

The medicine is given in your vein. You will receive 2 more doses of the medicine at 2 weeks and 6 weeks after the first dose. After that, the medicine will be given every 8 weeks.

Before starting this medicine, you should be tested for tuberculosis. Your clinician will also monitor you for infections. You will also be monitored for signs of an allergic reaction when you are getting the medicine in your vein. Sometimes allergic reactions happen after you get the medication. You should tell your clinician right away if you have any symptoms like shortness of breath or feeling tightness or swelling in your chest, face, mouth, or throat. Your clinician will also monitor you for new or worsening symptoms related to your nervous system, like numbness, weakness, clumsiness, or difficulty thinking. You should also tell your clinician if you notice anything like this.

Ustekinumab

Descriptive Summary (pre-synthesis and synthesis efforts not applicable for descriptive summaries)

Ustekinumab is a monoclonal antibody that antagonizes (by blocking) the proinflammatory cytokines interleukin-12 and interleukin-23 (IL-12 and IL-23). IL-12 and IL-23 activate natural killer cells and activate and differentiate CD4+ T-cells. Ustekinumab also antagonizes (via reducing expression of) monocyte chemotactic protein-1 (MCP-1), TNF alpha, interferon-inducible protein-10 (IP-10), and interleukin-8 (IL-8). Some of these (e.g., TNF alpha, natural killer cells) have a complex role in cancer dynamics.

Ustekinumab is given intravenously with the first dose, then given subcutaneously every 8 weeks. Patients can self-administer the medication subcutaneously once they learn how.

In addition to general vigilance concerning monitoring for infections during treatment, patients should be evaluated for tuberculosis prior to beginning therapy and periodically during therapy. Patients should be monitored for skin cancer throughout treatment, especially if they have risk factors. Patients should also be counseled on signs/symptoms of reversible posterior leukoencephalopathy (also known as posterior reversible encephalopathy syndrome [PRES]), including headache, vision changes, seizure, and altered mental status/function, and they should report any such signs/symptoms immediately.

Descriptive Summary Results

The medicine is given in your vein the first time. It is then given under your skin every 8 weeks. You can give yourself the medication under your skin once you learn how.

Before starting this medicine, you should be tested for tuberculosis. Your clinician will also monitor you for infections. Your clinician will also monitor you for skin cancer while you take the medicine. You should also tell your clinician if you notice any changes in you r skin. You should also tell your clinician if you develop new or worsening headache, vision changes, difficulty thinking, or seizures.

(DynaMed 2018, Kucharzik 2019, Lamb 2019)

FAQ 2: Will it help my symptoms?

In accordance with Scoping, we did not consider evidence using definitions of "remission" that relied solely on changes in surrogate markers, such as improvement in blood tests showing inflammation, endoscopic evaluation of mucosal healing, and the like. Although these surrogate markers may be linked to the pathophysiology of ulcerative colitis, how these surrogate markers change may not correlate in a one-to-one fashion with improvement in patient-relevant symptoms. Patient-relevant symptoms include things like abdominal pain/cramping; bowel movement urgency, consistency (e.g., soft vs. formed), composition (e.g., bloody vs. not), continence, and frequency; rectal pain; and/or systemic symptoms such as fever, weight loss, malnutrition, and anemia. Patients with ulcerative colitis ultimately care about these symptoms, not blood tests or how the insides of their intestines look on endoscopy.

Sands 2019V is the only head-to-head trial comparing different biologic agents for ulcerative colitis (specifically, vedolizumab vs. adalimumab). However, despite the trial favoring vedolizumab over adalimumab, because it is a first-of-kind trial and provides data for only 769 patients, we do not consider it possible to make firm inferences from head-to-head data at present. Additionally, there is considerable heterogeneity in the population in consideration and in the control group event rates in the body of evidence for biologic therapy in ulcerative colitis. A harmonized framework for comparing results across biologic agent options requires establishing a common estimate for patients who do not receive a biologic agent (i.e., a common control group event rate). Although one could pool the control group event rates from the various trials informing this evidence report, we consider this less appropriate than presenting a range of plausible control group risks given the population heterogeneity. Additionally, for the outcome of maintaining remission, the biologic agents were studied differently. The anti-TNF alpha trials were typically designed to have a single trial assessing induction and maintenance. That is, the trials typically assigned patients to an anti-TNF alpha agent or placebo at the start of the trial and intended for patients to keep taking the assigned treatment for the full duration of the trial. For vedolizumab and ustekinumab, there were separate trials to assess induction and maintenance. In the induction trials, patients were randomly assigned to the biologic agent (vedolizumab or ustekinumab) or placebo, and those who showed a response to induction therapy (induction responders) were eligible for re-randomization in the maintenance trial. In the maintenance trials, induction responders were randomly assigned to the biologic agent studied in the induction trial (vedolizumab or ustekinumab) or placebo. This is a key methodologic difference in how maintenance therapy was studied for these agents. The vedolizumab and ustekinumab maintenance trials only included patients who had a good response to induction therapy (and would therefore be expected to fare better in the maintenance trial than all-comers). In contrast, the anti-TNF alpha agent trials largely did not do this (i.e., conducting a single trial where people were continued on the assigned therapy for the entire trial duration). Although some might consider the methods of the vedolizumab and ustekinumab maintenance trials to give an unfair advantage to these agents (by only including induction responders), it should also be noted that the approach these trials took also more closely matches clinical practice: if a patient with ulcerative colitis does not show a good response to induction therapy with a given biologic agent, s/he will not be continued on the agent anyway. As such, this actually calls into question the methods of the trials of anti-TNF alpha agents. Lastly, it should be noted that golimumab (an anti-TNF alpha agent) does have some maintenance data more closely mirroring the methods of the vedolizumab and ustekinumab trials; however, these data suffer from lower certainty and are too imprecise to permit meaningful conclusions.

For FAQ 2 the ranges for control group event rates are:

- for the outcome of induction of remission -- 5.3% to 11.7%
- for the outcome of remission maintenance at 1 year among induction responders -- 15.9% to 31%

- for the outcome of remission at 1 year -- 10.4% to 15.4% (this excludes one univariate estimate [19.5%] where the effect estimate was rated as Very low certainty, and the univariate estimate is also considered to have substantively lower certainty than the other univariate estimates)
- for the outcome of remission at both 8 weeks and 1 year -- 4.1% to 6.6%

Anti-TNF alpha agents

Evidence Review Tables – anti-TNF alpha agents

Effects of intervention vs. placebo on induction of remission (6 to 8 weeks)

Agent(s) and Study	No. of patients (studies)	Estimated rate with intervention*	Control group event rate (% with remission)	Risk ratio or odds ratio (95% CI)	Certainty (reason for downgrade)
Anti-TNF alpha agents – Lopez 2015	2,808 (5)	21.9%	8.1% (174/2,138)	RR 0.85 (0.81 to 0.90) for non-remission RR 2.69 (2.13 to 3.14) for remission†	Moderate (inconsistency)[1]
Adalimumab – Bonovas 2018	927 (4)	16.2%	9.3% (43/464)	OR 1.89 (1.19 to 3.00) RR 1.75 (1.17 to 2.53)‡	Moderate (inconsistency)[2]
Adalimumab – Singh 2018	741 (3)	17.5%	10.5% (39/371)	OR 1.80 (1.18 to 2.76) RR 1.66 (1.16 to 2.33)‡	Moderate (inconsistency)[2]
Infliximab – Bonovas 2018	776 (4)	34.2%	11.6% (45/389)	OR 3.97 (2.32 to 6.79) RR 2.95 (2.01 to 4.07)‡	High
Infliximab – Singh 2018	667 (4)	35.8%	11.7% (39/334)	OR 4.22 (2.80 to 6.35) RR 3.07 (2.31 to 3.91)‡	High
Golimumab – Bonovas 2018	644 (3)	17.8%	7.2% (23/320)	OR 2.80 (1.67 to 4.67) RR 2.48 (1.59 to 3.70)‡	High
Golimumab – Singh 2018	644 (2)	17.9%	7.2% (23/320)	OR 2.81 (1.69 to 4.69) RR 2.49 (1.61 to 3.71)‡	High

* Calculated from control group event rate and effect estimate (risk ratio or odds ratio)
† RR for remission for Lopez 2015 was estimated in two steps: First, the OR for remission (3.17 [2.37 to 3.88]) was calculated from the RR for non-remission (0.85 [95% CI 0.81 to 0.90]) and corresponding control group event rate (1,964/2,138 = 91.9%) in the standard fashion. This is a necessary intermediate step because the OR has a certain kind of symmetry for the occurrence and non-occurrence of events, whereas the RR does not. Then, with the OR for remission (3.17 [2.37 to 3.88]), the RR for remission could be calculated using the OR for remission and corresponding control group event rate (174/2,138) in the standard fashion.
‡RRs calculated from the reported OR and control group event rate in the standard fashion (RR not reported directly by these studies)
[1] heterogeneity with one trial arm (lower-dose adalimumab) suggesting no effect
[2] heterogeneity with one trial (Suzuki 2014) suggesting no effect

Effects of intervention vs. placebo on remission at 52 to 54 weeks

Agent(s) and Study	No. of patients (studies)	Estimated rate with intervention*	Control group event rate (% with remission)	Risk ratio or odds ratio (95% CI)	Certainty (reason for downgrade)
Anti-TNF alpha agents – Lopez 2015	858 (2)	24.5%	11.2% (41/367)	RR 0.85 (0.74 to 0.98) for non-remission RR 2.19 (1.16 to 3.07) for remission†	Moderate (imprecision)
Anti-TNF alpha agents (at 30 to 54 weeks) – Lv 2014	1,222 (3)	25.2%	11.02% (54/490)	RR 2.29 (1.73 to 3.03)	High
Adalimumab – Bonovas 2018§	481 (2)	21.1%	10.4% (25/241)	OR 2.31 (1.37 to 3.87) RR 2.03 (1.32 to 2.98)‡	High
Infliximab – Bonovas 2018§	776 (4)	30.2%	15.4% (60/389)	OR 2.37 (1.63 to 3.44) RR 1.96 (1.49 to 2.50)‡	High
Golimumab – Bonovas 2018 (specific to induction responders) §	368 (2)	51.8%	19.5% (36/185)	OR 4.44 (0.58 to 34.22) RR 2.66 (0.63 to 4.58)‡	Low (inconsistency, imprecision)[1,2]

* Calculated from control group event rate and effect estimate (risk ratio or odds ratio)
† RR for remission for Lopez 2015 was estimated in two steps: First, the OR for remission (2.58 [95% CI 1.18 to 4.15]) was calculated from the RR for non-remission (0.85 [95% CI 0.74 to 0.98]) and corresponding control group event rate (326/367 = 88.8%) in the standard fashion. This is a necessary intermediate step because the OR has a certain kind of symmetry for the occurrence and non-occurrence of events, whereas the RR does not. Then, with the OR for remission (2.58 [95% CI 1.18 to 4.15]), the RR for remission could be calculated using the OR for remission and corresponding control group event rate (41/367 = 11.2%) in the standard fashion.
‡ RRs for Bonovas 2018 were calculated from the reported OR and control group event rate in the standard fashion (not reported directly in this study)
§ Singh 2018 reported results consistent with Bonovas 2018

[1] In maintenance of remission studies of golimumab, only induction responders were eligible and were re-randomized at beginning of maintenance study; the goal of studies using this design was to determine whether remission can be maintained among patients who had previously been treated with the agent and responded. This selective population is considered to less directly match patients who would be using the decision aid (presumably before starting the biologic agent) and would thus warrant a downgrade for indirectness if trying to apply this evidence to all-comers with ulcerative colitis. However, we specified the outcome is specific to induction responders to convey the group for whom we have higher certainty (i.e., the group for whom this indirectness downgrade would not apply), and the practical clinical reality is that if a patient does not show a response to induction therapy, s/he will not be maintained on the medication any way. .
[2] Two trials had different effect sizes (odds ratio 1.80 and 14.5) with very little overlap of confidence intervals.

Effects of intervention vs. placebo on sustained maintenance of remission (at 8 weeks and at 52 to 54 weeks)

Agent(s) and Study	No. of patients (studies)	Intervention group event rate (%)	Control group event rate (%)	Difference	Certainty (reason for downgrade)
Adalimumab – Sandborn 2012 (ULTRA 2)	494 (1)	8.5% (21/248)	4.1% (10/246)	P = 0.047	Moderate (imprecision)
Infliximab – Rutgeerts 2005 (ACT 1)	364 (1)	19.8% and 20.5%	6.6%	P = 0.002	High
Golimumab – Indirectly derived from Bonovas 2018 estimates (8-week remission rate x 52-week remission rate among induction responders)	Indirectly derived	18% x 51.8% = 9.3%	7.2% x 19.5% = 1.4%	Indirectly derived	Very low (very serious indirectness and imprecision)[1]

[1] Indirectly derived and derivation uses estimates downgraded for indirectness based on the population

Evidence Synthesis Process – anti-TNF alpha agents

Outcome	Approach taken and justification: measure of comparative effect	Results: measure of comparative effect	Approach taken and justification: option-specific measure	Results: option-specific measure
Induction of remission (remission rate at 6 to 8 weeks)	**Range of relative effect estimates:** Three systematic reviews with analyses combining or splitting three different drugs are consistent in direction but variable in magnitude of effect	**Anti-TNF alpha agents are effective for increasing rates of induction of remission** with effect size estimates ranging from RR 1.66 to RR 3.07 (High certainty)	**Derived range using effect estimates from meta-analyses and range of control group event rates across biologic agents:** Risk estimates were calculated from effect estimates shown to the left and the control group event rate range of 5.3% to 11.7%. Doing this yields a range of 8.8% to 35.9%. (The midpoint of the control group event rate range is 8.5%. The midpoint of the intervention group event rate range is 22.35%.)	**8.8% to 35.9% of people treated with anti-TNF alpha agents have induction of remission.** Rate may vary with drug.
Remission rate at 52 to 54 weeks	**Range of relative effect estimates from sources with High certainty:** Three systematic reviews with analyses combining or splitting three different drugs are consistent in direction and largely consistent in magnitude if disregarding one estimate with Low certainty.	**Anti-TNF alpha agents are effective for increasing rates of remission at 1 year**, with effect size estimates relatively consistent, with RR range of 1.96 to 2.29 (High certainty)	**Range of calculated risk estimates:** Because this outcome was only reported for the anti-TNF alpha agents and we present estimates as a range across the meta-analyses, the concept of a harmonized comparison frame for control group event rates does not apply here. Risk estimates were calculated from effect estimate and control group event rate for each meta-analysis. The control group event rate ranges from 10.4% to 15.4% (disregarding one meta-analysis with Low certainty). Calculated intervention group rates range from 21.1% to 30.2%. (The midpoint of the control group event rate range is 12.9%. The midpoint of the intervention group event rate range is 25.65%.)	**21.1% to 30.2% of people treated with anti-TNF alpha agents have remission at 1 year.** Rate may vary with drug.

Sustained maintenance of remission (remission at 2 months and at 1 year)	**Qualitative statement from sources with Moderate or High certainty:** Both trials directly reporting this outcome found significant differences. Limited data to justify calculating a pooled effect estimate.	**Anti-TNF alpha agents are effective for increasing rates of inducing and sustaining remission at 2 months and 1 year** (High certainty)	**Range of observed risk estimates:** Because this outcome was only reported for the anti-TNF alpha agents and we present estimates as a range across the meta-analyses, the concept of a harmonized comparison frame for control group event rates does not apply here. Risk estimates were directly observed in 2 trials. The control group event rate ranges from 4.1% to 6.6%. The intervention group event rate ranges from 8.5% to 20.5%. (The midpoint of the control group event rate range is 5.35%. The midpoint of the intervention group event rate range is 14.5%.)	**8.5% to 20.5% of people treated with anti-TNF alpha agents may have sustained remission at 2 months and at 1 year.** Rate may vary with drug.

Evidence Synthesis Results – anti-TNF alpha agents

Symptoms of ulcerative colitis include things like pain or cramping in your stomach or intestines, feeling like you suddenly need to move your bowels, having to move your bowels many times during the day, and sometimes losing control of your bowels. Some people also have fever, weight loss, or fatigue.

Out of 100 people who do not take a biologic agent:

- **5 to 12 (5% to 12%) have symptoms under control at 8 weeks.** (About 9 out of 100)
- **10 to 15 (10% to 15%) have symptoms under control at 1 year.** (About 13 out of 100)
- **4 to 7 (4% to 7%) have symptoms under control at 8 weeks and at 1 year.** (About 5 out of 100)

Taking a TNF alpha medicine helps people have a better chance of getting their symptoms under control. Out of 100 people who take a TNF alpha medicine:

- **9 to 36 (9% to 36%) have symptoms under control at 8 weeks.** (About 22 out of 100) (High certainty; based on 3 systematic reviews: Bonovas 2018, Lopez 2015, Singh 2018)
- **21 to 30 (21% to 30%) have symptoms under control at 1 year.** (About 26 out of 100) (High certainty; based on 3 systematic reviews: Bonovas 2018, Lv 2014, Lopez 2015)
- **8 to 21 (8% to 21%) have symptoms under control at 8 weeks and at 1 year.** (About 15 out of 100) (High certainty; based on 2 randomized trials: Rutgeerts 2005, Sandborn 2012)

Effects may vary with the specific drug used.

Vedolizumab

Evidence Review Tables – vedolizumab

Effects of vedolizumab vs. placebo on induction of remission (6 to 10 weeks)

Study	No. of patients (studies)	Intervention group event rate (% with remission)	Control group event rate (% with remission)	Comparative effect estimate (95% CI)	Certainty (reason for downgrade)
Bonovas 2018 (6 weeks; GEMINI 1 trial limited to patients not previously exposed to TNF inhibitors)	206 (1)	23.1% (30/130)	6.6% (5/76)	OR 4.26 (1.58 to 11.52) RR 3.51 (1.52 to 6.81)*	High
Feagan 2013 (GEMINI 1 trial; 6 weeks)	374 (1)	16.9% (38/225)	5.4% (8/149)	Adjusted absolute rate increase 11.5% (4.7% to 18.3%)	Moderate (indirectness)[1]
Motoya 2019 (10 weeks)	246 (1)	18.3% (30/164)	12.2% (10/82)	Absolute rate increase 6.1% (-3.1% to 15.3%)	Low (imprecision, indirectness)[1]

* RR calculated from the reported OR and control group event rate in the standard fashion (was not reported directly by this study)
1 Each of these trials included a substantial proportion of people with prior exposure to TNF inhibitors and thus constitute a less direct match to the population of interest for this evidence report.

Effects of vedolizumab every 8 weeks vs. placebo on remission at 52 to 60 weeks among those who responded to induction therapy

Agent	No. of patients (studies)	Intervention group event rate (% with remission)	Control group event rate (% with remission)	Comparative effect estimate	Certainty (reason for downgrade)
Bonovas 2018 (52 weeks; GEMINI 1 trial limited to patients not previously exposed to TNF inhibitors)*	151 (1)	45.8% (33/72)	19.0% (15/79)	OR 3.61 (1.74 to 7.48) RR 2.41 (1.53 to 3.35)†	High[1]
Feagan 2013 (GEMINI 1 trial; 52 weeks)	248 (1)	41.8% (51/122)	15.9% (20/126)	Adjusted absolute rate increase 26.1% (14.9% to 37.2%)	Moderate (indirectness)[1,2]
Motoya 2019 (60 weeks)	83 (1)	56.1% (23/41)	31.0% (13/42)	Absolute rate increase 25.1% (4.5% to 45.8%)	Moderate (indirectness)[1,2]

* Singh 2018 reported results consistent with Bonovas 2018

† RR calculated from the reported OR and control group event rate in the standard fashion (was not reported directly by this study)

1 In maintenance of remission studies of vedolizumab, only induction responders were eligible and were re-randomized at beginning of maintenance study; the goal of studies using this design was to determine whether remission can be maintained among patients who had previously been treated with the agent and responded. This selective population is considered to less directly match patients who would be using the decision aid (presumably before starting the biologic agent) and would thus warrant a downgrade for indirectness if trying to apply this evidence to all-comers with ulcerative colitis. However, we specified the outcomes are specific to induction responders to convey the group for whom we have higher certainty (i.e., the group for whom this indirectness downgrade would not apply), and the practical clinical reality is that if a patient does not show a response to induction therapy, s/he will not be maintained on the medication anyway.

2 Each of these trials included a substantial proportion of people with prior exposure to TNF inhibitors and thus constitute a less direct match to the population of interest for this evidence report.

Effects of vedolizumab vs. placebo on sustained maintenance of remission (at 6 to 10 weeks and at 52 to 60 weeks)

Study	No. of patients (studies)	Intervention group event rate (%)	Control group event rate (%)	Difference	Certainty (reason for downgrade)
Bonovas 2018 – indirectly derived estimates (GEMINI 1 trial; 6-week remission rate among people not previously exposed to TNF inhibitors x 52-week remission rate among induction responders)	Indirectly derived	23.1% * 45.9% = 10.6%	6.6% * 19.0% = 1.3%	Indirectly derived	Low (very serious indirectness)[1]
Feagan 2013 – indirectly derived estimates (GEMINI 1 trial; 6-week remission rate x 52-week remission rate among induction responders)	Indirectly derived	16.9% * 41.8% = 7.1%	5.4% * 15.9% = 0.9%	Indirectly derived	Very low (extremely serious indirectness)[1,2]
Motoya 2019 – Indirectly derived estimates (10-week remission rate * 60-remission rate among induction responders)	Indirectly derived	18.3% * 56.1% = 10.3%	12.2% * 31.0% = 3.8%	Indirectly derived	Very low (extremely serious indirectness, imprecision)[1,2,3]

1 Indirectly derived and derivation uses estimates downgraded for indirectness based on the population

2 This trial had a substantial proportion of patients with prior exposure to anti-TNF therapy and thus constitutes a less direct match to the population of interest for this evidence report

3 One of the estimates for Motoya 2019 used for this calculation includes a downgrade for imprecision, so we carry it forward here as well

Evidence Synthesis Process – vedolizumab

Outcome	Approach taken and justification: measure of comparative effect	Results: measure of comparative effect	Approach taken and justification: option-specific measure	Results: option-specific measure
Induction of remission	**Use meta-analysis already done:** Bonovas 2018 uses a subset of data from the randomized trial (Feagan 2013, GEMINI 1) that more closely matches the population of interest.	**Vedolizumab is effective for increasing rates of induction of remission** (High certainty) with effect size estimate of RR 3.51 (95% CI 1.52 to 6.81).	**Derived range using effect estimate from meta-analysis and range of control group event rates across biologic agents:** Risk estimates were calculated from effect estimate shown to the left and the control group event rate range of 5.3% to 11.7%. Doing this yields a range of 18.6% to 41.1%. (The midpoint of the control group event rate range is 8.5%. The midpoint of the intervention group event rate range is 29.85%.)	**18.6% to 41.1% of people treated with vedolizumab have induction of remission.**
Remission at 1 year among those with response to induction	**Use meta-analysis already done:** Bonovas 2018 uses a subset of data from the randomized trial (Feagan 2013, GEMINI 1) that more closely matches the population of interest.	**Vedolizumab appears effective for increasing rates of remission at 1 year among those who respond to induction** (High certainty) with effect size estimate of RR 2.41 (95% CI 1.53 to 3.35)	**Derived range using effect estimate from meta-analysis and control group event rates across biologic agents:** Risk estimates were calculated from effect estimate shown to the left and the control group event rate range of 15.9% to 31%, yielding a range of 38.3% to 74.7%. This estimate is limited to induction responders. (The midpoint of the control group event rate range is 23.45%. The midpoint of the intervention group event rate range is 56.5%.)	**38.3% to 74.7% of people treated with vedolizumab who have a good response early on have remission at 1 year.**

Although we also present indirect estimates for sustained remission among all-comers with ulcerative colitis (not just those with a response to induction), we do not consider these estimates sufficiently valid for use in evidence synthesis statements. Additionally, although the directly-available evidence for remission maintenance is specific to those with an induction response, this is also more applicable to the real-world use of these medications, because a patient who does not show a response to induction therapy will not be continued on the medication anyway.

To provide a proper framework for interpreting the outcomes at 1 year, we also present maintenance trial data for the control group. In maintenance trials for vedolizumab and ustekinumab, patients showing a response to induction therapy were randomized to placebo or the biologic agent being studied. Accordingly, those randomized to a placebo offer insight into what might be expected for patients who show an initial response to the biologic agent but then stop taking it. Presenting only the results for patients randomized to the biologic agent would provide an imbalanced frame by virtue of not having a control group risk to "anchor" the intervention group risk. For example, if the risk in the intervention group is 50% and the risk in the control group is 28%, simply presenting 50% for the intervention group risk would likely give an inflated impression of the degree of risk attributable to the intervention (22%).

Evidence Synthesis Results – vedolizumab

Symptoms of ulcerative colitis include things like pain or cramping in your stomach or intestines, feeling like you suddenly need to move your bowels, having to move your bowels many times during the day, and sometimes losing control of your bowels. Some people also have fever, weight loss, or fatigue.

Taking vedolizumab helps people have a better chance of getting their symptoms under control.

Out of 100 people who do not take a biologic agent, 5 to 12 (5% to 12%) have symptoms under control at 8 weeks. (About 9 out of 100)

Out of 100 people who take vedolizumab, 19 to 41 (19% to 41%) have symptoms under control at 8 weeks. (About 30 out of 100)

Out of 100 people who have a good response to vedolizumab early on but then stop taking it, 16 to 31 (16% to 31%) have symptoms under control at 1 year. (About 23 out of 100)

Out of 100 people who have a good response to vedolizumab early on and keep taking it, 38 to 75 (38% to 75%) have symptoms under control at 1 year. (About 57 out of 100)

(High certainty; based on 1 systematic review: Bonovas 2018)

Ustekinumab

Evidence Review Tables – ustekinumab

Effects of ustekinumab vs. placebo on remission (Sands 2019)

Time point	Estimated rate with ustekinumab	Placebo group event rate (% with remission)	Relative risk (95% CI)*	Certainty (reason for downgrade)
8 weeks (induction)	15.6% (100/642)	5.3% (17/319)	2.92 (1.78 to 4.80)	High
44 weeks after re-randomization of induction responders (maintenance of remission at 52 weeks among induction responders)	43.8% (77/176)	24.0% (42/175)	1.82 (1.33 to 2.49)	High[1]
Estimated sustained maintenance of remission (at 8 weeks and at 52 weeks)	15.6% * 43.8% = 6.83%	5.3% * 24.0% = 1.27%	Indirectly derived	Low (very serious indirectness)[2]

* These values were calculated by EBSCO Information Services as a part of Evidence Synthesis (they are not directly reported in Sands 2019).

[1] In the maintenance of remission study of ustekinumb, only induction responders were eligible and were re-randomized at beginning of maintenance study; the goal of studies using this design was to determine whether remission can be maintained among patients who had previously been treated with the agent and responded. This selective population is considered to less directly match patients who would be using the decision aid (presumably before starting the biologic agent) and would thus warrant a downgrade for indirectness if trying to apply this evidence to all-comers with ulcerative colitis. However, we specified the outcome is specific to induction responders to convey the group for whom we have higher certainty (i.e., the group for whom this indirectness downgrade would not apply), and the practical clinical reality is that if a patient does not show a response to induction therapy, s/he will not be maintained on the medication anyway.

[2] Indirectly derived and derivation uses estimates downgraded for indirectness based on the population

Evidence Synthesis Process – ustekinumab

Outcome	Approach taken and justification: measure of comparative effect	Results: measure of comparative effect	Approach taken and justification: option-specific measure	Results: option-specific measure
Induction of remission	**Use only available trial:** The only published trial comparing ustekinumab to placebo is Sands 2019	**Ustekinumab is effective for increasing rates of inducing remission** (High certainty), with relative risk of 2.92 (95% CI 1.78 to 4.80)	**Derived range using effect estimate from meta-analysis and control group event rates across biologic agents:** Risk estimates were calculated from effect estimate shown to the left and the control group event rate range of 5.3% to 11.7%, yielding a range of 15.47% to 34.2%. (The midpoint of the control group event rate range is 8.5%. The midpoint of the intervention group event rate range is 24.84%.)	**15% to 34% of people treated with ustekinumab have induction of remission.**
Remission at 1 year among those with response to induction	**Use only available trial:** The only published trial comparing ustekinumab to placebo is Sands 2019	**Ustekinumab is effective for increasing rates of remission at 1 year among people who respond to induction** (High certainty), with relative risk of 1.82 (95% CI 1.33 to 2.49)	**Derived range using effect estimate from meta-analysis and control group event rates across biologic agents:** Risk estimates were calculated from effect estimate shown to the left and the control group event rate range of 15.9% to 31%, yielding a range of 28.9% to 56.4%. This estimate is limited to induction responders. (The midpoint of the control group event rate range is 23.45%. The midpoint of the intervention group event rate range is 42.65%.)	**28.9% to 56.4% of people treated with ustekinumab who have a good response early on have remission at 1 year.**

Although we also present an indirect estimate for sustained remission among all-comers with ulcerative colitis (not just those with a response to induction), we do not consider this estimate sufficiently valid for use in evidence synthesis statements. Additionally, although the directly-available evidence for remission maintenance is specific to those with an induction response, this is also more applicable to the real-world use of these medications, because a patient who does not show a response to induction therapy will not be continued on the medication anyway.

To provide a proper framework for interpreting the outcomes at 1 year, we also present maintenance trial data for the control group. In maintenance trials for vedolizumab and ustekinumab, patients showing a response to induction therapy were randomized to placebo or the biologic agent being studied. Accordingly, those randomized to a placebo offer insight into what might be expected for patients who show an initial response to the biologic agent but then stop taking it. Presenting only the results for patients randomized to the biologic agent would provide an imbalanced frame by virtue of not having a control group risk to "anchor" the intervention group risk. For example, if the risk in the intervention group is 50% and the risk in the control group is 28%, simply presenting 50% for the intervention group risk would likely give an inflated impression of the degree of risk attributable to the intervention (22%).

Evidence Synthesis Results – ustekinumab

Symptoms of ulcerative colitis include things like pain or cramping in your stomach or intestines, feeling like you suddenly need to move your bowels, having to move your bowels many times during the day, and sometimes losing control of your bowels. Some people also have fever, weight loss, or fatigue.

Taking ustekinumab helps people have a better chance of getting their symptoms under control.

Out of 100 people who do not take a biologic agent, 5 to 12 (5% to 12%) have symptoms under control at 8 weeks. (About 9 out of 100)

Out of 100 people who take ustekinumab, 15 to 34 (15% to 34%) have symptoms under control at 8 weeks. (About 25 out of 100)

Out of 100 people who have a good response to ustekinumab early on but then stop taking it, 16 to 31 (16% to 31%) have symptoms under control at 1 year. (About 23 out of 100)

Out of 100 people who have a good response to ustekinumab early on and keep taking it, about 29 to 56 (29% to 56%) have symptoms under control at 1 year. (About 43 out of 100)

(High certainty; based on 1 trial: Sands 2019)

FAQ 3: Will it improve my quality of life?

Sands 2019V is the only head-to-head trial comparing different biologic agents for ulcerative colitis (specifically, vedolizumab vs. adalimumab). However, despite the trial favoring vedolizumab over adalimumab, because it is a first-of-kind trial and provides data for only 769 patients, we do not consider it possible to make firm inferences from head-to-head data at present. Additionally, there is considerable heterogeneity in the population in consideration and in the control group event rates in the body of evidence for biologic therapy in ulcerative colitis. A harmonized framework for comparing results across biologic agent options requires establishing a common estimate for patients who do not receive a biologic agent (i.e., a common control group event rate). Although one could pool the control group event rates from the various trials informing this evidence report, we consider this less appropriate than presenting a range of plausible control group risks given the population heterogeneity.

Although quality of life can be measured on a number of different scales, the IBDQ is a validated quality of life scale specific to inflammatory bowel disease with 4 categories of questions: bowel symptoms, systemic symptoms, emotional function, and social function. The total score ranges from 32 to 224, with higher scores being better. A clinically-meaningful difference has been most commonly defined as a ≥16-point improvement (LeBlanc 2015). Achieving an IBDQ ≥170 is typically considered having a good or normal (i.e., similar to the general population) quality of life, and is also often referred to as the quality of life consistent with clinical remission (Bickston 2011, Danese 2019, Sandborn 2011, Vogelaar 2009). The evidence sources focused on the total IBDQ score rather than also reporting subdomains of the IBDQ scale (LeBlanc 2015, Feagan 2013, Sands 2019).

For FAQ 3, the range for control group event rates for achieving a clinically-meaningful improvement in quality of life at 6 to 8 weeks (defined as a ≥16-point improvement in IBDQ score from baseline) is 46.2% to 50.1%

For outcomes at 1 year, the actual outcome measured was different for anti-TNF alpha agents, vedolizumab, and ustekinumab such that quantitative harmonization was not possible. The following outcomes are available at 1 year:

- anti-TNF alpha agents: improvement in quality of life (defined as a ≥16-point improvement in IBDQ score from induction baseline) among all-comers (not just induction responders)
- vedolizumab: good quality of life (defined as IBDQ score of ≥170) among induction responders
    - those randomized in this trial had average baseline IBDQ scores of 125 to 126
- ustekinumab: continuous data for IBDQ score among induction responders

Accordingly, for the synthesis of 52-week outcomes, although we provide quantitative summaries for each of the outcomes, we are concerned that quantitative synthesis in the decision aid could be confusing or misleading for clinicians and patients given the disparate outcomes assessed. Therefore, we also provide a harmonized qualitative synthesis statement to establish a fair and common framework for comparative evaluation. Namely, we state each of these agents has evidence of helping people who respond to induction therapy have or maintain a better quality of life at 1 year. To emphasize the qualitative synthesis statements over the quantitative synthesis statements for quality of life at 1 year, we only bold the qualitative synthesis statements.

Anti-TNF alpha agents

Evidence Review Tables – anti-TNF alpha agents

Effects of intervention vs. placebo on clinically meaningful improvement (≥16-point improvement from baseline) on IBDQ (LeBlanc 2015)

Agent(s) and time point	No. of patients (studies)	Estimated rate with intervention	Control group event rate (%)	Risk ratio (95% CI)	Certainty (reason for downgrade)
Anti-TNF alpha agents – 6 or 8 weeks	1,495 (4)	61.0%	46.2% (271/586)	1.32 (1.19 to 1.46)	High
Adalimumab – 52 weeks	767 (2)	26.3%	15.2% (52/342)	1.73 (1.28 to 2.34)	High[1]

[1] Certainty downgraded by Cochrane authors due to sparse data (162 events), but we consider this overly stringent

Evidence Synthesis Process – anti-TNF alpha agents

Outcome	Approach taken and justification: measure of comparative effect	Results: measure of comparative effect	Approach taken and justification: option-specific measure	Results: option-specific measure
Improvement in quality of life (from baseline) at 8 weeks	**Use meta-analysis already done.**	**Anti-TNF alpha agents increase the likelihood of having improvement in quality of life at 8 weeks** (High certainty), with RR 1.32 (1.19 to 1.46).	**Derived range using effect estimate from meta-analysis and control group event rates across biologic agents:** Risk estimates were calculated from effect estimate shown to the left and the control group event rate range of 46.2% to 50.1%, yielding a range of 61% to 66.1%. (The midpoint of the control group event rate range is 48.15%. The midpoint of the intervention group rate range is 63.55%.)	**Likelihood of improvement in quality of life with anti-TNF alpha agents at 8 weeks is 61% to 66.1%.**
Improvement in quality of life (from baseline) at 52 weeks	**Use meta-analysis already done.**	**Anti-TNF alpha agents may increase the likelihood of having improvement in quality of life at 1 year** (Moderate certainty), with RR 1.73 (1.28 to 2.34).	**Provide calculated estimates, but use qualitative synthesis across biologic agents as the primary answer:** Risk estimate (26.3%) was calculated from effect estimate and control group event rate for the meta-analysis (15.2%). Because this outcome was only reported for the anti-TNF alpha agents, the concept of a harmonized comparison frame for control group event rates does not apply here. Qualitative description is provided for better comparisons with other options, and the qualitative description used for other options refers to induction responders. Although we do not have direct evidence for change from maintenance baseline in IBDQ scores among induction responders for TNF medicines, there is evidence for this outcome for the other biologics, and there is no reason to think anti-TNF alpha agents would be substantively different. Due to this additional indirectness, we downgrade our certainty from Moderate to Low.	**People who have a good response to a TNF medicine early on and keep taking it may often still have an improved quality of life at 1 year.**

Evidence Synthesis Results – anti-TNF alpha agents

Out of 100 people who do not take a biologic agent:

- **46 to 50 (46% to 50%) have improvement in quality of life at 8 weeks** (About 48 out of 100)
- 15 (15%) may have improvement in quality of life at 1 year

Out of 100 people who take a TNF medicine:

- **61 to 66 (61% to 66%) have improvement in quality of life at 8 weeks** (About 64 out of 100) (High certainty; based on 1 systematic review: LeBlanc 2015)
- 26 (26%) may have improvement in quality of life at 1 year (Moderate certainty; based on 1 systematic review: LeBlanc 2015)

People who have a good response to a TNF medicine early on and keep taking it may often still have an improved quality of life at 1 year.

People who have a good response to a TNF medicine early on but then stop taking it may often no longer have an improved quality of life at 1 year.

(Low certainty; based on 1 systematic review [LeBlanc 2015] and indirect extrapolation from other biologic agents)

Vedolizumab

Evidence Review Tables – vedolizumab

Effects of vedolizumab vs. placebo on good quality of life (IBDQ score ≥170) (LeBlanc 2015)*

Time point	No. of patients (studies)	Estimated rate with intervention	Control group event rate (%)	Risk ratio (95% CI)	Certainty (reason for downgrade)
6 or 8 weeks	374 (1)	36.9%	22.8% (34/149)	1.62 (1.15 to 2.27)	Moderate (indirectness)[1,2]
52 weeks (specific to induction responders)	373 (1)	63.6%	38.1% (48/126)	1.67 (1.31 to 2.12)	Low (indirectness, risk of bias)[1,2,3,4]

* LeBlanc 2015 reports this as being "Improved IBDQ (≥16 points from baseline)", but the statement of "≥16 points from baseline" is misleading. These figures are actually for the proportion of patients achieving IBDQ score ≥170 (with randomized participants having a baseline IBDQ of 125 to 126). IBDQ score has a possible range of 32 to 224, with higher scores being better. See Critical Appraisal for details.

[1] The trial on which this estimate is based included a substantial proportion of people with prior exposure to TNF inhibitors and thus constitutes a less direct match to the population of interest for this evidence report.

[2] Certainty downgraded by Cochrane authors due to sparse data (117 events at 6 or 8 weeks, 205 events at 52 weeks), but we consider this overly stringent

[3] Study was limited to patients who were induction responders and would thus warrant a downgrade for indirectness if trying to apply this evidence to all-comers with ulcerative colitis. However, we specified the outcome is specific to induction responders to convey the group for whom we have higher certainty (i.e., the group for whom this indirectness downgrade would not apply), and the practical clinical reality is that if a patient does not show a response to induction therapy, s/he will not be maintained on the medication anyway..

[4] The trial on which this outcome is based used last observation carried forward for continuous outcomes for patients who withdrew from the trial prematurely, and the trial had substantial and imbalanced early discontinuation in the maintenance phase (45/122 in the group receiving vedolizumab every 8 weeks, 41/125 in the group receiving vedolizumab every 4 weeks, and 78/126 in the group receiving placebo).

Given the difference in outcome measure used for the evidence for vedolizumab, we do not consider the control group risk of 22.8% in the range of control group risks for a clinically-meaningful improvement in quality of life at 6 to 8 weeks (i.e., achieving a ≥16-point improvement in IBDQ score). Given the much greater threshold for being considered a responder in the evidence for vedolizumab (achieving an IBDQ score of ≥170 compared to an average baseline of 125 to 126 among randomized participants), using the 22.8% control group risk in the range of control group risks could result in seriously underestimating the rate of clinically-meaningful improvement in quality of life.

Effect of vedolizumab vs. placebo on change in quality of life from maintenance baseline among induction responders (Feagan 2013)

Time point, outcome	Intervention group (n = 122)	Placebo group (n = 126)	Certainty (reason for downgrade)
Mean change in quality of life (on IBDQ scale) from maintenance baseline (6 weeks) to 52 weeks*	1-point increase†	20-point decrease†	Low (indirectness, risk of bias)[1,2,3]

*This outcome provides insight into how quality of life might be impacted by staying on vedolizumab after induction vs. discontinuing it. IBDQ is measured on a scale from 32 to 224, with higher scores being better.

†Estimated from Figure 1B, disregarding the every-4-week dosing of vedolizumab for maintenance, as vedolizumab is typically given every 8 weeks for maintenance. Error bars are standard errors (not CIs), so they are not reported here given how these data are incorporated into synthesis.

[1] This trial had a substantial proportion of patients with prior exposure to anti-TNF therapy and thus constitutes a less direct match to the population of interest for this evidence report

[2] This trial was limited to patients who were induction responders and would thus warrant a downgrade for indirectness if trying to apply this evidence to all-comers with ulcerative colitis. However, we specified the outcome is specific to induction responders to convey the group for whom we have higher certainty (i.e., the group for whom an indirectness downgrade would not apply), and the practical clinical reality is that if a patient does not show a response to induction therapy, s/he will not be maintained on the medication anyway.

[3] This trial used last observation carried forward for continuous outcomes for patients who withdrew from the trial prematurely, and the trial had substantial and imbalanced early discontinuation in the maintenance phase (45/122 in the group receiving vedolizumab every 8 weeks, 41/125 in the group receiving vedolizumab every 4 weeks, and 78/126 in the group receiving placebo).

Evidence Synthesis Process – vedolizumab

Outcome	Approach taken and justification: measure of comparative effect	Results: measure of comparative effect	Approach taken and justification: option-specific measure	Results: option-specific measure
Improvement in quality of life at 8 weeks	**Use meta-analysis already done.**	**Vedolizumab may increase the likelihood of having improvement in quality of life by 8 weeks** (Moderate certainty; RR 1.62 [95% CI 1.15 to 2.27]). The outcome actually measured is achieving IBQD ≥170 (compared to a baseline of 125 to 126 among randomized participants), but given this is a more difficult endpoint to achieve than a ≥16-point improvement from baseline (as LeBlanc 2015 label it), we consider it reasonable to assume vedolizumab is at least as effective for achieving a 16-point improvement. If anything, the effect estimate shown would be expected to underestimate the effect estimate for achieving a 16-point improvement.	**Derived range using effect estimate from meta-analysis and control group event rates across biologic agents:** Risk estimates were calculated from effect estimate shown to the left and the control group event rate range of 46.2% to 50.1%, yielding a range of 74.8% to 81.2%. (The midpoint of the control group event rate range is 48.15%. The midpoint of the intervention group rate range is 78%.)	**Likelihood of improvement in quality of life with vedolizumab may be 74.8% to 81.2% at 8 weeks.**

Good quality of life at 52 weeks among those with a response to induction	**Use meta-analysis already done.**	**For people with a good response to vedolizumab early on, vedolizumab may increase the likelihood of having good quality of life at 1 year** (Low certainty; RR 1.67 [95% CI 1.31 to 2.12]).	**Provide calculated estimates, but use qualitative synthesis across biologic agents as the primary answer:** Risk estimate (63.6%) was calculated from effect estimate and control group event rate for the meta-analysis (38.1%). Because this outcome was only reported for vedolizumab, the concept of harmonized comparison frame for control group event rates does not apply here. The mean change in the continuous IBDQ scores from maintenance baseline suggests that people who continue to take vedolizumab often maintain the improvement in quality of life experienced at 6 weeks (mean change of a 1-point increase), whereas those who stop taking it do not (mean change of a 20-point decrease). Qualitative description is provided for better comparisons with other options.	**People who have a good response to vedolizumab early on and keep taking it may often still have an improved quality of life at 1 year.**

To provide a proper framework for interpreting the outcomes at 1 year, we also present maintenance trial data for the control group. In maintenance trials for vedolizumab and ustekinumab, patients showing a response to induction therapy were randomized to placebo or the biologic agent being studied. Accordingly, those randomized to a placebo offer insight into what might be expected for patients who show an initial response to the biologic agent but then stop taking it. Presenting only the results for patients randomized to the biologic agent would provide an imbalanced frame by virtue of not having a control group risk to "anchor" the intervention group risk. For example, if the risk in the intervention group is 50% and the risk in the control group is 28%, simply presenting 50% for the intervention group risk would likely give an inflated impression of the degree of risk attributable to the intervention (22%).

Evidence Synthesis Results – vedolizumab

Out of 100 people who do not take a biologic agent, 46 to 50 (46% to 50%) have improvement in quality of life at 8 weeks. (About 48 out of 100)

Out of 100 people who take vedolizumab, 75 to 81 (75% to 81%) may have improvement in quality of life at 8 weeks. (About 78 out of 100)

(Moderate certainty; based on 1 systematic review [LeBlanc 2015] containing 1 trial for vedolizumab [Feagan 2013])

Out of 100 patients who have a good response to vedolizumab early on but stop taking it, 38 (38%) may have good quality of life at 1 year.

Out of 100 patients who have a good response to vedolizumab early on and keep taking it, 64 (64%) may have good quality of life at 1 year.

(Low certainty; based on 1 systematic review [LeBlanc 2015] containing 1 trial for vedolizumab [Feagan 2013])

People who have a good response to vedolizumab early on and keep taking it may often still have an improved quality of life at 1 year.

People who have a good response to vedolizumab early on but then stop taking it may often no longer have an improved quality of life at 1 year.

(Low certainty; based on 1 trial: Feagan 2013)

Ustekinumab

Evidence Review Tables – ustekinumab

Effects of ustekinumab vs. placebo on quality of life assessed by IBDQ (range of 32 to 224, with higher scores being better) (Sands 2019)

Time point	Mean (SD, n) in ustekinumab group	Mean (SD, n) in placebo group	Mean difference (95% CI)*	Certainty (reason for downgrade)
Score at 8 weeks (induction)	160.6 (36.4, 641)	143.5 (39.96, 319)	17.1 (12.0 to 22.2)	Moderate (imprecision)[1]
8-week change from induction baseline	34.2 (32.18, 637)	16.1 (31.39, 317)	NA	Moderate (imprecision)[1]
Score at 44 weeks after re-rerandomization of induction responders (maintenance therapy among induction responders)	175.3 (37.09, 348)	159.3 (40.67, 174)	16 (9 to 23)	Moderate (imprecision)[1,2]
44-week change from maintenance baseline among induction responders	0.5 (32.36, 346)	-15.1 (35.43, 173)	NA	Moderate (imprecision)[1,2]

* Calculated by EBSCO Information Services, as Sands 2019 only reports mean (SD) at baseline and different follow-up points, along with change from baseline.
1 Although not addressed by Sands 2019, the lower boundary for a clinically meaningful difference in IBDQ is noted elsewhere (LeBlanc 2015) as 15 to 16 points, with most sources citing 16 points.
2 This estimate is limited to patients who were induction responders. This selective population is considered to less directly match patients who would be using the decision aid (presumably before starting the biologic agent) and would thus warrant a downgrade for indirectness if trying to apply this evidence to all-comers with ulcerative colitis. However, we specified the outcome is specific to induction responders to convey the group for whom we have higher certainty (i.e., the group for whom this indirectness downgrade would not apply), and the practical clinical reality is that if a patient does not show a response to induction therapy, s/he will not be maintained on the medication anyway.

Based on the above data, one can use validated methods (Mayer 2019) to convert the continuous IBDQ outcome into a dichotomous IBDQ outcome for the proportion of patients achieving at least a 16-point improvement in IBDQ.

Effects of ustekinumab vs. placebo on achieving at least a 16-point improvement in IBDQ score

Time point	Risk in ustekinumab group	Risk in placebo group	Relative risk (95% CI)	Certainty (reason for downgrade)
8 weeks (induction)	71.4%	50.1%	1.42 (1.26 to 1.61)	Moderate (inconsistency)[1]
44 weeks after re-randomization of induction responders (maintenance therapy among induction responders)	31.6%	19.0%	1.66 (1.18 to 2.35)	Moderate (imprecision)[2,3]

1 As these estimates come from a single trial, we cannot assess replicability and therefore do not consider this to have High certainty
2 95% CI includes differences that would be of questionable clinical relevance (approximate 3.4% absolute risk difference) to substantial differences (approximate 25.7% absolute risk difference). We also downgraded the 8-week estimate because it is based on a single trial without replication, but we do not feel the concern about replicability and the concern about precision constitute enough concern to warrant 2 downgrades in this case.
3 This estimate is limited to patients who were induction responders. This selective population is considered to less directly match patients who would be using the decision aid (presumably before starting the biologic agent) and would thus warrant a downgrade for indirectness if trying to apply this evidence to all-comers with ulcerative colitis. However, we specified the outcome is specific to induction responders to convey the group for whom we have higher certainty (i.e., the group for whom this indirectness downgrade would not apply), and the practical clinical reality is that if a patient does not show a response to induction therapy, s/he will not be maintained on the medication anyway.

Evidence Synthesis Process – ustekinumab

Outcome	Approach taken and justification: measure of comparative effect	Results: measure of comparative effect	Approach taken and justification: option-specific measure	Results: option-specific measure
Improvement in quality of life (from baseline) at 8 weeks	**Use only available trial:** The only published trial comparing ustekinumab to placebo is Sands 2019	**Ustekinumab may improve quality of life** (Moderate certainty), with RR 1.42 (95% CI 1.26 to 1.61)	**Derived range using effect estimate from randomized trial and control group event rates across biologic agents:** Risk estimates were calculated from effect estimate shown to the left and the control group event rate range of 46.2% to 50.1%, yielding a range of 65.6% to 71.1%. (The midpoint of the control group event rate range is 48.15%. The midpoint of the intervention group rate range is 68.35%.)	**Likelihood of improvement in quality of life with ustekinumab may be 65.6% to 71.1% at 8 weeks.**
Quality of life at 44 weeks among those with a response to induction	**Use only available trial.**	**For people with a good response to ustekinumab early on, those who continue to ustekinumab may be more likely on average to have improved quality of life at 1 year.** (Moderate certainty; RR 1.66 [95% CI 1.18 to 2.35] for additional improvement compared to maintenance baseline, MD 16 [95% CI 9 to 23] for IBDQ score at 44 weeks). Estimates are limited to induction responders.	**Provide calculated estimates, but use qualitative synthesis across biologic agents as the primary answer:** Because this outcome was only reported for ustekinumab, the concept of harmonized comparison frame for control group event rates does not apply here. The calculated risk of an additional improvement in quality of life (≥16-point improvement) from maintenance baseline was 19% in the control group and 31.6% in the intervention group. The mean change in the continuous IBDQ scores from maintenance baseline suggest that people who continue to take ustekinumab may often maintain the improvement in quality of life experienced at 8 weeks (mean change 0.5, SD 32.36), whereas those who stop taking it do not (mean change -15.1, SD 35.43). Qualitative description is provided for better comparisons with other options.	**People who have a good response to ustekinumab early on and keep taking it may often still have an improved quality of life at 1 year.**

To provide a proper framework for interpreting the outcomes at 1 year, we also present maintenance trial data for the control group. In maintenance trials for vedolizumab and ustekinumab, patients showing a response to induction therapy were randomized to placebo or the biologic agent being studied. Accordingly, those randomized to a placebo offer insight into what might be expected for patients who show an initial response to the biologic agent but then stop taking it. Presenting only the results for patients randomized to the biologic agent would provide an imbalanced frame by virtue of not having a control group risk to "anchor" the intervention group risk. For example, if the risk in the intervention group is 50% and the risk in the control group is 28%, simply presenting 50% for the intervention group risk would likely give an inflated impression of the degree of risk attributable to the intervention (22%).

Evidence Synthesis Results – ustekinumab

Out of 100 people who do not take a biologic agent, 46 to 50 (46% to 50%) have improvement in quality of life at 8 weeks. (About 48 out of 100)

Out of 100 people who take ustekinumab, 66 to 71 (66% to 71%) have improvement in quality of life at 8 weeks. (About 68 out of 100)

Out of 100 patients who have a good response to ustekinumab early on but stop taking it, 19 (19%) may have an additional improvement in quality of life at 1 year.

Out of 100 patients who have a good response to ustekinumab early on and keep taking it, 32 (32%) may have an additional improvement in quality of life at 1 year.

People who have a good response to ustekinumab early on and keep taking it may often still have an improved quality of life at 1 year.

People who have a good response to ustekinumab early on but then stop taking it may often no longer have an improved quality of life at 1 year.

(Moderate certainty; based on 1 trial [Sands 2019])

FAQ 4: Will it impact my need for surgery?

There is considerable heterogeneity in the population in consideration and in the control group event rates in the body of evidence for biologic therapy in ulcerative colitis. A harmonized framework for comparing results across biologic agent options requires establishing a common estimate for patients who do not receive a biologic agent (i.e., a common control group event rate). Although one could pool the control group event rates from the various trials informing this evidence report, we consider this less appropriate than presenting a range of plausible control group risks given the population heterogeneity.

For FAQ 4 the control group event rates for the outcome of needing colectomy surgery range from 2.3% (with ustekinumab) to 7.6% (with anti-TNF alpha agents as a drug class). We do not consider the estimates for individual anti-TNF alpha agents in developing this range (in accordance with our scoping document indicating we would seek to evaluate anti-TNF alpha agents as a class); additionally, we discount the estimate from Mao 2017 for reasons stated in the section on anti-TNF alpha agents for this FAQ.

Anti-TNF alpha agents

Evidence Review Tables – anti-TNF alpha agents

Effects of intervention vs. placebo on colectomy rate (52 to 54 weeks)

Agent(s) and Study	No. of patients (studies)	Intervention group event rate (%)	Control group event rate (%)	Relative effect estimate (95% CI)	Certainty (reason for downgrade)
Infliximab – Sandborn 2009	728 (2)	9.5% (46/484)	14.8% (36/244)	HR 0.59 (0.38 to 0.91)	Low (imprecision, inconsistency)[1,2]
Adalimumab – Feagan 2014	963 (2)	3.1% (15/480)	3.9% (19/483)	Not reported	Moderate (imprecision)
Anti-TNF alpha agents (infliximab) – Lv 2014	728 (2)	9.5% (46/484)	14.8% (36/244)	RR 0.64 (0.43 to 0.97)	Low (imprecision, inconsistency)[1,2]
Anti-TNF alpha agents (infliximab and adalimumab, based on data from Sandborn 2009 and Feagan 2014) – Mao 2017†	1,691 (4)	5.8%*	8.3% (60/727)	OR 0.69 (0.49 to 0.97)	Low (inconsistency, imprecision)[1]
Meta-analysis by EBSCO Information Services using pooled data from Sandborn 2009 and Feagan 2014 presented above†	1,691 (4)	5.1%*	7.6% (55/727)	RR 0.68 (0.48 to 0.97)	Low (inconsistency, imprecision)[1]

* Estimated from the control group event rate and relative effect estimate in the standard fashion (other intervention group event rates in this column are reported directly from the corresponding publication based on the authors' simple pooling of 2 similar trials, namely ACT 1 and ACT 2 [Sandborn 2009, which is the source for Lv 2014's estimates] or ULTRA 1 and ULTRA 2 [Feagan 2014])

† Because we were unable to confirm where Mao 2017 obtained some of its estimates, we conducted our own meta-analysis based on the data from Sandborn 2009 and Feagan 2014 (the same sources used by Mao 2017, totaling 4 trials). To help establish comparability of the estimates, we used Mao 2017's model specifications for the meta-analysis, but we computed a relative risk instead of an odds ratio.

1 Inconsistency not apparent in the systematic review, but the systematic review reported Sandborn 2009 as if it were a single trial while Sandborn 2009 reports pooled estimates from ACT 1 and ACT 2 and the individual trials had discordant results

2 Although the upper bound of the 95% CI for the relative effect estimate is < 1, assessment of (im)precision should be based on absolute rather than relative effects. Accordingly, the 95% CI for the absolute risk difference from the simple pooling of the data from the ACT 1 and ACT 2 trials (in accordance with Sandborn 2009's approach, which in turn serves as the source for Lv 2014's estimate) is compatible with an absolute risk difference as small as 0.36%. Accordingly, we assign a downgrade for imprecision to this estimate.

Evidence Synthesis Process – anti-TNF alpha agents

Outcome	Approach taken and justification: measure of comparative effect	Results: measure of comparative effect	Approach taken and justification: option-specific measure	Results: option-specific measure
Colectomy	**Conduct meta-analysis.** The larger meta-analysis (Mao 2017) includes all the trials used in the smaller meta-analysis (Lv 2014) and the two trials not otherwise represented in a meta-analysis (Feagan 2014, which captures the data from ULTRA 1 and ULTRA 2), but the data extraction reported in Mao 2017 could not be verified as accurate. Results from the meta-analysis conducted by EBSCO Information Services are comparable to Mao 2017.	**Anti-TNF alpha agents might reduce the rate of colectomy** (Low certainty), with RR 0.68 (95% CI 0.48 to 0.97)	**Derived range using effect estimate from meta-analysis and control group event rates across biologic agents:** Risk estimates were calculated from effect estimate shown to the left and the control group event rate range of 2.3% to 7.6%, yielding a range of 1.6% to 5.2%. (The midpoint of the control group event rate range is 4.95%. The midpoint of the intervention group event rate range is 3.4%.) Although rounding for patient-friendly presentation results in the lower bound of the range being 2% for both the control group and the anti-TNF group, we consider this acceptable given the imprecision in the RR for the anti-TNF alpha agents (with an upper bound for the RR of 0.97, thus including the possibility of very little effect).	**Risk of colectomy over 1 year may be 2% to 5% with an anti-TNF alpha agent**

Evidence Synthesis Results – anti-TNF alpha agents

Out of 100 people who do not use a biologic agent:

- **2 to 8 (2% to 8%) may have their colon removed in the next year** (About 5 out of 100)

Out of 100 people who use a TNF alpha medicine:

- **2 to 5 (2% to 5%) may have their colon removed in the next year** (About 3 out of 100)

Effects may vary with the specific drug used. (Low certainty; based on a meta-analysis of 4 trials [2 each in Sandborn 2009 and Feagan 2014])

Vedolizumab

Evidence Review – vedolizumab

There is insufficient randomized trial evidence found for this outcome (based on 1 systematic review [Mao 2017] and a search for subsequent randomized trials [see Search and Selection]). We found no randomized placebo-controlled trials for this outcome for vedolizumab. Sands 2019V (VARSITY) compared vedolizumab (n = 383) to the anti-TNF alpha agent adalimumab (n = 386) and reported on UC-related bowel resections over the 52-week trial. However, with 0 events in the vedolizumab group and only 3 events in the adalimumab group, we do not consider Sands 2019V/VARSITY to provide sufficient data for any meaningful inference about whether/how vedolizumab might impact the need for surgery/colectomy.

Evidence Synthesis Process – vedolizumab

Describing the synthesis process is not applicable here

Evidence Synthesis Results – vedolizumab

There is not enough research yet to answer this question.

Ustekinumab

Evidence Review Tables – ustekinumab

Effects of ustekinumab vs. placebo on UC-related surgery (Sands 2019)

Time point	Rate with ustekinumab	Placebo group event rate	Relative risk (95% CI)*	Certainty (reason for downgrade)
8 weeks (induction)	0% (0/642)	0.6% (2/319)	Insufficient data	Very low (extremely serious imprecision)
44 weeks after re-randomization (maintenance)	0.6% (2/348)	1.7% (3/175)	0.34 (0.06 to 1.99)	Very low (extremely serious imprecision)

* Calculated by EBSCO Information Services; Sands 2019 only reports proportion and number with event

Based on the above data, one could also estimate a 52-week rate of UC-related surgery in the placebo group of 0.6% + 1.7% = 2.3%. Because the 1.7% comes from a population who showed an induction response to ustekinumab, this may underestimate the true rate of UC-related surgery in the control group, as these patients may be healthier or have less severe UC. However, because we use it as a lower bound for the range of control group risks discussed at the beginning of this FAQ, we consider this a reasonable estimate.

Evidence Synthesis Process – ustekinumab

The randomized trial evidence for ustekinumab vs. placebo in patients with ulcerative colitis is presently limited to Sands 2019/the UNIFI trial. As seen in the evidence review table above, this evidence is not sufficient for any meaningful inference about how ustekinumab might impact the need for surgery/colectomy.

Evidence Synthesis Results – ustekinumab

There is not enough research yet to answer this question.

FAQ 5: Will it impact my risk of having to go into the hospital?

There is considerable heterogeneity in the population in consideration and in the control group event rates in the body of evidence for biologic therapy in ulcerative colitis. A harmonized framework for comparing results across biologic agent options requires establishing a common estimate for patients who do not receive a biologic agent (i.e., a common control group event rate). Although one could pool the control group event rates from the various trials informing this evidence report, we consider this less appropriate than presenting a range of plausible control group risks given the population heterogeneity.

For FAQ 5 the control group event rates for UC-related hospitalization at 1 year range from 10.1% (with ustekinumab) to 17.6% (with anti-TNF alpha agents as a drug class). We do not consider the estimates for individual anti-TNF alpha agents in developing this range (in accordance with our scoping document indicating we would seek to evaluate anti-TNF alpha agents as a class); additionally, we discount the estimate from Mao 2017 for reasons stated in the section on anti-TNF alpha agents for this FAQ. The 10.1% estimate for ustekinumab may underestimate the rate of UC-related hospitalization in the control group for reasons specified in the section for ustekinumab for this FAQ. However, given the estimate of 10.1% is serving as the lower bound of the harmonized range of control group risk, we feel this is reasonable.

Anti-TNF alpha agents

Evidence Review Tables – anti-TNF alpha agents

Effects of intervention vs. placebo on ulcerative colitis-related hospitalization rate (52 to 54 weeks)

Agent(s), Time point and Study	No. of patients (studies)	Intervention group event rate (%)	Control group event rate (%)	Risk ratio or odds ratio (95% CI)	Certainty (reason for downgrade)
Infliximab – Sandborn 2009	728 (2)	15.7% (76/484)	24.6% (60/244)	Not reported	Moderate (inconsistency)[1]
Adalimumab – Feagan 2014	963 (2)	9.8% (47/480)	14.1% (68/483)	RR 0.7 (0.5 to 1.0)	Moderate (imprecision)
Anti-TNF alpha agents (infliximab and adalimumab, based on data from Sandborn 2009 and Feagan 2014) – Mao 2017†	1,691 (4)	16.3%*	25.4% (185/727)	OR 0.57 (0.43 to 0.76)	Moderate (inconsistency)[1]
Meta-analysis by EBSCO Information Services using pooled data from Sandborn 2009 and Feagan 2014 presented above†	1,691 (4)	11.6%*	17.6% (128/727)	RR 0.66 (0.53 to 0.83) OR 0.61 (0.47 to 0.81)	Moderate (inconsistency)[1]

* Estimated from the control group event rate and relative effect estimate in the standard fashion (other intervention group event rates in this column are reported directly from the corresponding publication based on the authors' simple pooling of 2 similar trials, namely ACT 1 and ACT 2 [Sandborn 2009] or ULTRA 1 and ULTRA 2 [Feagan 2014])

† Because we could not confirm data extraction performed by Mao 2017, we conducted our own meta-analysis based on the same underlying data.

1 Inconsistency not apparent in the systematic review, but the systematic review reported Sandborn 2009 as if it were a single trial while Sandborn 2009 reports pooled estimates from ACT 1 and ACT 2 and the individual trials had discordant results for colectomy (uncertain if concordant or discordant for hospitalization because Sandborn 2009 did not report this for hospitalization, but colectomy and hospitalization are correlated so presumed inconsistency for hospitalization)

Evidence Synthesis Process – anti-TNF alpha agents

Outcome	Approach taken and justification: measure of comparative effect	Results: measure of comparative effect	Approach taken and justification: option-specific measure	Results: option-specific measure
UC-related hospitalization	**Conduct meta-analysis.** The larger meta-analysis (Mao 2017) includes all the trials used in the smaller meta-analysis (Lv 2014) and the two trials not otherwise represented in a meta-analysis (Feagan 2014, which captures the data from ULTRA 1 and ULTRA 2), but the data extraction reported in Mao 2017 could not be verified as accurate. Results for the comparative effect from the meta-analysis conducted by EBSCO Information Services are comparable to Mao 2017.	**Anti-TNF alpha agents may reduce the risk of needing to be hospitalized due to ulcerative colitis** (Moderate certainty), with RR 0.66 (95% CI 0.53 to 0.83).	**Derived range using effect estimate from meta-analysis and control group event rates across biologic agents:** Risk estimates were calculated from effect estimate shown to the left and the harmonized control group event rate range of 10.1% to 17.6%, yielding a range of 6.7% to 11.6%. (The midpoint of the control group event rate range is 13.85%. The midpoint of the intervention group event rate range is 9.15%.)	**Risk of being hospitalized due to ulcerative colitis over 1 year may be 6.7% to 11.6% with an anti-TNF alpha agent**

Evidence Synthesis Results – anti-TNF alpha agents

Out of 100 people who do not take a biologic agent, 10 to 18 (10% to 18%) may have to be in the hospital due to their ulcerative colitis within 1 year. (About 14 out of 100)

Out of 100 people who take a TNF alpha medicine, 7 to 12 (7% to 12%) may have to be in the hospital due to their ulcerative colitis within 1 year. (About 9 out of 100)

(Moderate certainty; based on a meta-analysis of 4 trials [2 each in Sandborn 2009 and Feagan 2014])

Vedolizumab

Evidence Review – vedolizumab

We found no randomized, placebo-controlled trial evidence for this outcome (based on 1 systematic review [Mao 2017] and a search for subsequent randomized trials [see Search and Selection]). However, there is randomized trial evidence for this outcome for the comparison of vedolizumab versus adalimumab over 52 weeks (Sands 2019V/VARSITY), where the risk of UC-related hospitalization was reported as 3.9% (15/383) vs. 5.2% (20/386) for vedolizumab vs. adalimumab, respectively. Although no comparative statistics are provided for these data, we calculate the relative risk and absolute risk difference as 0.76 (95% CI 0.39 to 1.45) and -1.3% (95% CI -4.4% to 1.8%), respectively.

Evidence Synthesis Process – vedolizumab

Given the above findings from Sands 2019V/VARSITY, we need further evidence to elucidate how vedolizumab compares to either placebo or (more ideally given their established use) anti-TNF alpha agents. However, in the interim, given the lack of a clear difference between vedolizumab and adalimumab, one might reasonably suggest – with Very low certainty – setting the absolute risk of UC-related hospitalization among people who use vedolizumab as equal to the estimate for those using an anti-TNF alpha agent (downgrades due to concerns about inconsistency, imprecision, and indirectness). As documented above, we estimate this risk at 6.7% to 11.6% (see section on anti-TNF alpha agents for this FAQ). Importantly, using the observed absolute risk for the vedolizumab group from Sands 2019V/VARSITY would be invalid and misleading, as it would constitute using absolute risks from different populations to make direct comparisons (and would likely imply to many that a meaningful benefit may exist for vedolizumab compared to anti-TNF alpha agents, which current evidence can neither confirm nor refute). We also repeat the range for the control group estimate (10.1% to 17.6%) for a frame of reference.

Evidence Synthesis Results – vedolizumab

Out of 100 people who do not take a biologic agent, 10 to 18 (10% to 18%) may have to be in the hospital due to their ulcerative colitis within 1 year. (About 14 out of 100)

Out of 100 people who take vedolizumab, 7 to 12 (7% to 12%) may have to be in the hospital due to their ulcerative colitis within 1 year. (About 9 out of 100)

(Very low certainty; based on one trial comparing vedolizumab and adalimumab [Sands 2019V])

Ustekinumab

Evidence Review Tables – ustekinumab

Effects of ustekinumab vs. placebo on UC-related hospitalization (Sands 2019)

Time point	Rate with ustekinumab	Placebo group event rate	Relative risk (95% CI)*	Certainty (reason for downgrade)
8 weeks (induction)	1.1% (7/642)	4.4% (14/319)	0.25 (0.10 to 0.61)	Moderate (imprecision)[1]
44 weeks after re-randomization (maintenance)	2.0% (7/348)	5.7% (10/175)	0.35 (0.14 to 0.91)	Moderate (imprecision) [1]

* Calculated by EBSCO Information Services; Sands 2019 only reports proportion and number with event
1 few events reported (< 20 total)

Based on the above data, one could also estimate a 52-week rate of UC-related hospitalization in the placebo group of 4.4% + 5.7% = 10.1%. Because the 5.7% comes from a population who showed an induction response to ustekinumab, this may underestimate the true rate of UC-related hospitalization in the control group, as these patients may be healthier or have less severe UC.

Evidence Synthesis Process – ustekinumab

The randomized trial evidence for ustekinumab vs. placebo in patients with ulcerative colitis is presently limited to Sands 2019/the UNIFI trial. Although reported in one publication and referred to as a single trial, Sands 2019 really constitutes 2 trials: An 8-week induction trial and a 44-week maintenance trial. Only those patients who responded to ustekinumab during the induction trial were re-randomized into the maintenance trial. Thus, the 44-week assessment point in the maintenance trial really constitutes a 1-year assessment point among induction responders.

The data suggest a benefit for ustekinumab but suffer from imprecision. Although the RR point estimate for ustekinumab in the 44-week maintenance trial (RR 0.35) might appear to show a larger benefit than the anti-TNF alpha agents at 52 to 54 weeks (RR 0.66; see section on anti-TNF alpha agents for this FAQ), we note:

- the ustekinumab estimate is for people who responded during the 8-week induction trial and were then re-randomized to the 44-week maintenance trial, whereas the estimate for the anti-TNF inhibitors is for people who were randomized to an anti-TNF alpha agent or placebo at time zero and then assessed 52 to 54 weeks later; thus, the RR for ustekinumab may be biased toward showing more of an apparent effect compared to the anti-TNF alpha agents
- even with the above consideration, we also note the 95% CI for the RR for ustekinumab in the 44-week maintenance trial (0.14 to 0.91) is considerably wider than the 95% CI for the RR for the anti-TNF alpha agents at 52 to 54 weeks (0.53 to 0.83); indeed, the 95% CI for ustekinumab captures the entire 95% CI for the anti-TNF alpha agents.

Given the above considerations, rather than computing an absolute estimate for ustekinumab based on the RR of 0.35 (95% CI 0.14 to 0.91), we feel a more reasonable approach is to set the absolute risk as equal to that for the anti-TNF alpha agents (6.7% to 11.6%), as the current evidence satisfactorily demonstrates ustekinumab is more effective than placebo for this outcome but is insufficient to demonstrate whether ustekinumab is actually any different from the anti-TNF alpha agents for this outcome (and thus, we feel any quantitative suggestion of such would be inappropriate). We also repeat the range for the control group estimate (10.1% to 17.6%) for a frame of reference.

Evidence Synthesis Results – ustekinumab

Out of 100 people who do not take a biologic agent, 10 to 18 (10% to 18%) may have to be in the hospital due to their ulcerative colitis within 1 year. (About 14 out of 100)

Out of 100 people who take ustekinumab, 7 to 12 (7% to 12%) may have to be in the hospital due to their ulcerative colitis within 1 year. (About 9 out of 100)

(Moderate certainty; based on 1 randomized trial [Sands 2019])

FAQ 6: What are the risks or side effects?

Evidence synthesis (noted below) does not provide clear evidence for increased risk for malignancy in systematic reviews of randomized trials. The signal for risk is mostly case reports and case series noted through regulatory efforts for drug marketing. Chen 2016 provided an overview of 42 systematic reviews and meta-analyses beyond inflammatory bowel disease (most reviews included patients with rheumatoid arthritis or IBD) and found insufficient evidence to support conclusions of a relationship between TNF inhibitors and increased malignancy risk. However, the data were not sufficient to conclude an absence of risk.

For risks of infection and malignancy, we expanded our search beyond randomized trials/SRMAs to include observational studies. Because we have very serious concern about selective outcome reporting for harms in randomized trials, particularly in drug trials sponsored by the manufacturer, we also searched for reliable cohort studies. To select the highest quality and most relevant cohort studies of biological therapies, we screened the results of our PubMed searches to select studies that met the following criteria:

- nationwide cohort study
- limits to patients with IBD
- included unexposed group as comparator
- evaluated anti-TNF alpha agents as a class (for this option), vedolizumab, or ustekinumab

We preferentially selected nationwide cohort studies because such studies typically include data on the largest cohorts with minimal selection bias. They are also less likely to be influenced by commercial sponsorship compared with studies funded by industry. If an SRMA and relevant national cohort study both reported data on the same harm outcome, we based our conclusion on the result of the national cohort study.

Infections – studies selected for evidence synthesis for anti-TNF alpha agents:
For estimating effects of anti-TNF alpha agents on risks of infection from randomized trials/SRs, we considered an SR source that combined randomized trials of UC *and* CD patients preferable to a source restricting to one or the other condition because (1) including trials of both conditions increases power to detect a risk and (2) we would not expect the specific condition to modify the risk (in fact the evidence from the SR covering both does not show a significant modifier effect of UC vs. CD).

Bonovas 2016 SR was selected as our sole source of SRMA data because it compared biologic agents vs. placebo on infection and malignancy outcomes, included patients with either UC or CD, reported the effects of anti-TNF agents as a class, and is the most current and comprehensive SR identified in our systematic search.

Additional reviews were critically appraised and summarized but because they restricted to UC patients and were considered inadequately powered to evaluate these risks, they were not progressed to Evidence Synthesis (Lopez 2015 SR, Singh 2018 SR, and Bonovas 2018U).

For anti-TNF alpha agents, we identified two eligible national cohort studies evaluating risk of serious infections (Kirchgesner 2018, Nyboe Andersen 2015) and opportunistic infections (Kirchgesner 2018).

Infections – studies selected for evidence synthesis for vedolizumab:

Although Bonavas 2016 reported infection outcomes for vedolizumab, the data on vedolizumab was too sparse for meaningful conclusions. Therefore, we identified two other SRs of randomized trials that reported infection risk (Bye 2017, Colombel 2017) but on examination both reported identical analyses and results and the analytic approach did not allow for a comparative risk of vedolizumab vs. placebo.

Sandborn 2013 (GEMINI 2) was a maintenance therapy trial comparing vedolizumab vs. placebo. Serious infections were reported in 5.5% patients receiving vedolizumab (45/814) vs. 3% receiving placebo (9/301). (Low certainty due to risk of bias and imprecision)

For vedolizumab, we did not identify any eligible national cohort study that provided reliable data on risks of infection. However, we did identify a systematic review of observational evidence that reported a range of rates of serious infection (Schreiber 2018).

Infections – studies selected for evidence synthesis for ustekinumab:

No SRs provided direct placebo-controlled data. For ustekinumab, we summarized the trial that compared ustekinumab vs. placebo in patients with UC (Sands 2019) but its serious infection risk estimates were too imprecise to be considered informative and were therefore not further considered for Evidence Synthesis.

For ustekinumab, we did not identify any eligible national cohort study that provided reliable data on risks of infection.

Malignancy – studies selected for evidence synthesis:

A "malignancy" outcome was pooled in some SRMAs of randomized trials, but there were few events and very wide CIs, resulting in uninformative estimates for all options. This is expected because randomized trials typically have inadequate duration and insufficient power to detect long-term risks such as malignancy. One individual patient data meta-analysis reported an increased risk for non-melanoma skin cancer with anti-TNF agents (Askling 2011, Low certainty). One systematic review of multiple study types (randomized trials, cohort studies and case series) reported an increased risk for non-Hodgkin's lymphoma with anti-TNF agents (Siegel 2009, Very low certainty).

We identified one national cohort study which found anti-TNF agents to be associated with an increase in risk of lymphoma (Lemaitre 2017, Moderate certainty). We identified two other eligible national cohort studies that reported malignancy risks with anti-TNF agents (Kobayashi 2019, Nyboe Andersen 2014); however, the findings of each were too imprecise for meaningful contribution, all results having Very low certainty.
For vedolizumab and ustekinumab, we did not identify any eligible national cohort studies that provided reliable data on risks of malignancy.

Infection

Anti-TNF alpha agents

Evidence Review – anti-TNF alpha agents

Infection outcomes* with anti-TNF alpha agents vs. placebo in patients with IBD at about 6 months (Bonovas 2016 SRMA)

Outcome	No. of patients (studies)	Odds ratio (95% CI)†	Control group event rate (%)	Certainty (reason for downgrade)
serious infection	9,831 (34)	0.90 (0.69 to 1.17)	2.6% (101/3,856)	Very low (very serious risk of bias, imprecision)[1]
opportunistic infection	7,205 (19)	1.89 (1.15 to 3.12)	0.65% (18/2,765)	High for *increased risk*; Low for reported *magnitude of increase* (very serious risk of bias) [1]

*As defined in each study.

[1] Risk of bias double downgrade because of very serious concern about selective outcome reporting which may result in the reported ORs underestimating the true risk, based on substantial evidence that harms are assessed inconsistently and reported inadequately in randomized trials (particularly trials of pharmacological interventions).

Serious infection* in users of anti-TNF alpha agents compared with propensity score-matched non-users (Nyboe Andersen 2015 national cohort study)†

Risk period	Users of anti-TNF alpha agents			Non-users of anti-TNF alpha agents			Hazard ratio (95% CI)	Certainty
	No. of patients	No. of events	incidence rate per 1,000 person-years (95% CI)	No. of patients	No. of events	incidence rate per 1,000 person-years (95% CI)		
90 days	1,543	51	140 (110 to 180)	1,543	33	90 (60 to 130)	1.63 (1.01 to 2.63)	Moderate (downgrade: observational study; upgrade: consistent with risk pattern in other populations, and no evidence of confounding by indication)[1]
365 days	1,543	107	80 (70 to 100)	1,543	78	60 (50 to 70)	1.27 (0.92 to 1.75)	Low (downgrades: observational study, imprecision; upgrade: consistent with risk pattern in other populations, and no evidence of confounding by indication)[1]

* Defined as diagnosis of infection associated with hospital admission.

† Risk estimates were also adjusted for baseline use of azathioprine and oral corticosteroids (these variables were not included in the propensity score).

[1] We have upgraded the certainty for two reasons: First, we believe that the pattern of increase in serious infection in users of anti-TNF alpha agents in patients with rheumatoid arthritis supports that these agents may similarly increase serious infection risk in patients with IBD. Second, Nyboe Andersen 2015 included a supplementary analysis with an active comparator drug as control (ie, azathioprine) which found no evidence of confounding by indication (see table in summary).

Infectious outcomes in users of anti-TNF alpha agents alone compared with IBD patients not treated with anti-TNF alpha agents or thiopurines (Kirchgesner 2018 national cohort study; Moderate certainty)

Outcome*	Users of anti-TNF agents			Non-users of anti-TNF agents†			Hazard ratio (95% CI)
	No. of patients (person-years follow-up)	No. of events	incidence rate per 1,000 person-years	No. of patients (person-years follow-up)	No. of events	incidence rate per 1,000 person-years	
Serious infections, overall	26,255 (57,835)	1,095	18.9	128,285 (719,407)	6,067	8.4	2.26 (2.08 to 2.45)
Opportunistic infections, overall	26,255 (57,835)	119	2.1	128,285 (719,407)	322	0.4	4.01 (3.06 to 5.26)

* serious and opportunistic infections are based on a diagnosis of infection requiring hospitalization (related ICD-10 codes as primary diagnosis)
† includes non-exposure to thiopurines

Evidence Synthesis Process – anti-TNF alpha agents

Outcome	Approach taken and justification	Results
Serious infection (effect estimate)	**Use existing cohort studies with effect estimates derived from larger study.** Because of substantial evidence that harms are assessed inconsistently and reported inadequately in randomized trials, we obtained estimates from two national cohort studies. They were consistent in direction of effect.	**TNF medicines may increase risk for serious infections** (Moderate certainty; hazard ratio 2.26, 95% CI 2.08 to 2.45.
Serious infection within 90 days (risk estimate)	**Use risk estimates from existing cohort study that reported timepoint-based risk estimates.** Serious infections within 90 days in non-users of anti-TNF alpha agents: 33/1,543 = 2.1% Serious infections within 90 days in users of anti-TNF alpha agents: 51/1,543 = 3.3% If instead using the risk in non-users (2.1%) and the point estimate for the HR (2.36), the estimated risk among users of anti-TNF alpha agents is 4.7%.	**90-day risk of serious infections among people treating their symptoms without anti-TNF alpha agents may be 2%** **90-day risk of serious infections among people treating their symptoms with anti-TNF alpha agents may be 3% to 5%**
Serious infection within 365 days (risk estimate)	Serious infections within 1 year in non-users of anti-TNF alpha agents: 78/1,543 = 5.1% Serious infections within 1 year in users of anti-TNF alpha agents: 107/1,543 = 6.9% If instead using the risk in non-users (5.1%) and the point estimate for the HR (2.26), the estimated risk among users of anti-TNF alpha agents is 11.5%.	**1-year risk of serious infections among people treating their symptoms without anti-TNF alpha agents may be 5%** **1-year risk of serious infections among people treating their symptoms with anti-TNF alpha agents may be 7% to 12%**

Opportunistic infections (effect estimate)	**Use existing cohort study.** One national cohort study provides an effect estimate with Moderate certainty.	**TNF medicines may increase risk for opportunistic infections** (Moderate certainty; hazard ratio 4.01, 95% CI 3.06 to 5.26).
Opportunistic infections (about 6 months) (risk estimate)	**Use risk estimate from meta-analysis (which is clearer for timeframe) and effect estimate from cohort study (with higher certainty of evidence).** For opportunistic infections, our only source for a timeframe-specific risk estimate is the Bonavas 2016 SRMA. Although we have High certainty of an increase in risk we have Low certainty for the specific risk estimates which are likely underestimated due to selective outcome reporting, a concern we previously described. The risk for opportunistic infection in placebo group was about 0.65% over 6 months in Bonavas 2016 SRMA. We calculated the absolute risk for opportunistic infection in patients treated with anti-TNF alpha agents using this control group risk and the hazard ratio 4.01 in the standard fashion, yielding an estimated 2.6% risk over 6 months for patients using an anti-TNF alpha agent.	**6-month risk of opportunistic infection among people treating their symptoms without anti-TNF alpha agents might be 0.65%** **6-month risk of opportunistic infection among people treating their symptoms with anti-TNF alpha agents might be 2.6%**

Evidence Synthesis Results – anti-TNF alpha agents

TNF medicines increase your risk for serious infections, but the increase is small.

TNF medicines increase your risk for infections due to a weak immune system, but the risk is low.

Out of 100 people who do not take a TNF medicine:

- **about 2 (2%) may get a serious infection within 3 months**
- **about 5 (5%) may get a serious infection within 1 year**
- **less than 1 (less than 1%) may get an infection due to a weak immune system within 6 months**

Out of 100 people who take a TNF medicine:

- **about 3 to 5 (3% to 5%) may get a serious infection within 3 months** (Moderate certainty; based on 2 national cohort studies: Kirchgesner 2018, Nyboe Andersen 2015)
- **about 7 to 12 (7% to 12%) may get a serious infection within 1 year** (Moderate certainty; based on 2 national cohort studies: Kirchgesner 2018, Nyboe Andersen 2015)
- **about 3 (3%) may get an infection due to a weak immune system within 6 months** (Moderate certainty; based on 1 systematic review and 1 national cohort study: Bonavas 2016, Kirchgesner 2018)

Vedolizumab

Evidence Review

Vedolizumab may increase the risk for serious infections from 3% to 5.5% over 1 year, based on 1 randomized trial (Sandborn 2013, Low certainty). The risk of serious infections with vedolizumab for up to 1 year may range from 4% to 10%, based on a systematic review of observational evidence (Schreiber 2018, Moderate certainty).

Evidence Synthesis Process

Use the range of rates reported in the systematic review of observational evidence.

Evidence Synthesis Results

People who take vedolizumab may have a higher risk of infection compared to people who do not take vedolizumab. (Low certainty; based on 1 randomized trial, Sandborn 2013)

Out of 100 people who take vedolizumab:

- **4 to 10 (4% to 10%) may get a serious infection within 1 year** (Moderate certainty; based on 1 systematic review: Schreiber 2018)

Ustekinumab

Evidence Review

Our evidence review identified no reliable data from randomized trials or observational studies on the risks of infection with ustekinumab.

Evidence Synthesis Process

Describing the synthesis process is not applicable here. However, risk of infection – including serious infection – is a concern for ustekinumab just as it is for the anti-TNF alpha agents. Accordingly, although there may not be sufficient data to quantify the degree of risk with ustekinumab, we feel it is important to indicate this concern despite the insufficiency of currently-available evidence with respect to quantification.

Evidence Synthesis Results

People who take ustekinumab likely have a higher risk of infection compared to people who do not take ustekinumab. There is not enough research yet to use numbers when talking about this risk.

Malignancies

Anti-TNF alpha agents

Evidence Review

One individual patient data meta-analysis reported an increased risk for non-melanoma skin cancer with adalimumab, an anti-TNF agent (Askling 2011, Low certainty). The findings for infliximab were noninformative (Very low certainty). Adalimumab was associated with non-melanoma skin cancer (hazard ratio 2.59, 95% credible interval 1.01 to 7.67) with an observed incidence rate per 1,000 person-years 3.4 without adalimumab and 8.0 with adalimumab.

One systematic review of multiple study types (randomized trials, cohort studies and case series) reported an increased risk for non-Hodgkin's lymphoma with anti-TNF agents with standardized incidence ratio 3.23 (95% CI 1.5-6.9) (Siegel 2009, Very low certainty). Rather than using such a pooled estimate for risk estimation, the largest cohort study contributing the most events was used and reported 6 NHL cases in 13,126 patient-years, or 4.6 per 10,000 patient-years. This is roughly 0.32% at 7 years, consistent with the Moderate certainty results reported from Lemaitre 2017.

Risk of lymphoma with use of anti-TNF alpha agents (Lemaitre 2017 national cohort study)

Comparison	Estimated intervention group risk at 7 years*	Control group risk at 7 years	HR (95% CI)	Certainty
Exposed to anti-TNF monotherapy vs unexposed to thiopurines or anti-TNF alpha agents	0.43%	0.18%	2.41 (1.60 to 3.64)	Moderate (downgrade: observational design; upgrade: large magnitude of effect and no important concerns about risk of bias, imprecision, inconsistency, indirectness, or publication bias)
Exposed to combination therapy vs exposed to thiopurine monotherapy	0.89%	0.38%	2.35 (1.31 to 4.22)	Moderate (downgrade: observational design; upgrade: large magnitude of effect and no important concerns about risk of bias, imprecision, inconsistency, indirectness, or publication bias)

*Calculated from the baseline risk and the HR in the standard fashion

† Events per person-years were transformed into a risk of the outcome at 7 years in the standard fashion. The time point of 7 years was selected given the median duration of follow-up was 6.7 years.

Evidence Synthesis Process – anti-TNF alpha agents

Outcome	Approach taken and justification	Results
Non-melanoma skin cancer	**Use existing meta-analysis and qualitative expression of results.** The limited evidence available (Askling 2011, Low certainty) suggests an increased risk but absolute rates reported as incidence rate per 1,000 person-years is not clear for conversion to useful rates for comparison with other concepts reported in the resulting decision aid.	**TNF medicines might increase the risk for some skin cancers, but the risk is uncertain.** (Low certainty)
Lymphoma within 7 years (effect estimate)	**Use existing cohort study.** Because of substantial evidence that harms are assessed inconsistently and reported inadequately in randomized trials and additionally because available randomized trials have inadequate duration and insufficient power to detect long-term and uncommon risks such as malignancy, we obtained estimates from a robust national cohort study (Lemaitre 2017) for this outcome.	**TNF medicines may increase risk for lymphoma** over 7 years (Moderate certainty) HR 2.41 (1.60 to 3.64) (for patients unexposed to thiopurine) HR 2.35 (1.31 to 4.22) (for patients exposed to thiopurine)
Lymphoma within 7 years (risk estimate)	We use the risks shown in the table above for synthesis, creating a range for each group (from without to with use of thiopurines). Doing this yields an estimated risk among those not using anti-TNF alpha agents of 0.18% to 0.38% (midpoint of this range is 0.28%) and a risk among those using anti-TNF alpha agents of 0.43% to 0.89% (midpoint of this range is 0.66%).	**7-year risk of lymphoma among people who do not use an anti-TNF alpha agent may be 0.18% to 0.38%** **7-year risk of lymphoma among people who use an anti-TNF alpha agent may be 0.43% to 0.89%**

Evidence Synthesis Results – anti-TNF alpha agents

Out of 1,000 people who do not take a TNF medicine, about 2 to 4 (0.18% to 0.38%) may get lymphoma within about 7 years. (About 3 out of 1,000)

Out of 1,000 people who take a TNF medicine, about 4 to 9 (0.43% to 0.89%) may get lymphoma within about 7 years. (About 7 out of 1,000)

(Moderate certainty; based on 1 national cohort study: Lemaitre 2017)

To match "out of 100" phrasing for the rest of the decision aid this can be simplified to:

TNF medicines may increase your risk for lymphoma (a cancer of the blood), but the risk is low.

Out of 100 people who do not take a TNF medicine, less than 1 (less than 1%) may get lymphoma within 7 years

Out of 100 people who take a TNF medicine, about 1 (1%) may get lymphoma within 7 years

TNF medicines may also increase your risk for some skin cancers, but there is not enough research to use numbers to describe the risk. (Low certainty; based on 1 systematic review, Askling 2011)

Vedolizumab

Evidence Review

Our evidence review identified no reliable data from randomized trials or observational studies on the risks of malignancy with vedolizumab.

Evidence Synthesis Process

Describing the synthesis process is not applicable here

Evidence Synthesis Results

There is not enough research yet to answer this question.

Ustekinumab

Evidence Review

Our evidence review identified no reliable data from randomized trials or observational studies on the risks of malignancy with ustekinumab.

Evidence Synthesis Process

Describing the synthesis process is not applicable here

Evidence Synthesis Results

There is not enough research yet to answer this question.

Side effects

Descriptive Summary

Because of the common sources used for descriptive summaries for this FAQ, we present references at the end of this FAQ rather than after each treatment option.

Anti-TNF alpha agents

Descriptive Summary (pre-synthesis and synthesis efforts not applicable for descriptive summaries)

Side effects with anti-TNF alpha agents may include, but are not necessarily limited to:

- Headache
- Nausea and abdominal pain
- Injection site reaction or pain
- Rash
- Cough, nasopharyngitis/pharyngitis, sinusitis, upper respiratory infection, bronchitis
- Urinary tract infection
- Fatigue
- Increased blood pressure
- Dizziness
- Paresthesias

Descriptive Summary Results

Side effects with TNF alpha medicine may include, but are not limited to:

- **Headache**
- **Nausea or stomach pain**
- **Pain, itching, or redness where you get the injection**
- **Rash**
- **Cough, common cold, sore throat, sinus infection, or chest cold**
- **Bladder infection**
- **Feeling tired**
- **Increased blood pressure**
- **Dizziness**

Vedolizumab

Descriptive Summary (pre-synthesis and synthesis efforts not applicable for descriptive summaries)

Side effects with vedolizumab may include, but are not necessarily limited to:

- Nasopharyngitis/pharyngitis, sinus infection, upper respiratory infection, bronchitis
- Arthralgia
- Headache
- Nausea
- Fatigue
- Fever
- Rash
- Pruritus

Descriptive Summary Results

Side effects with vedolizumab may include, but are not limited to:

- **Common cold, sore throat, sinus infection, or chest cold**
- **Joint pain**
- **Headache**
- **Nausea**
- **Feeling tired**
- **Fever**
- **Rash**
- **Itching**

Ustekinumab

Descriptive Summary (pre-synthesis and synthesis efforts not applicable for descriptive summaries)

Side effects with ustekinumab may include, but are not necessarily limited to:

- Headache
- Nausea, vomiting, diarrhea
- Injection site redness
- Pruritus
- Nasopharyngitis/pharyngitis, sinusitis, upper respiratory infection, bronchitis
- Urinary tract infection or vulvovaginal candidiasis
- Fatigue

Descriptive Summary Results

Side effects with ustekinumab may include, but are not limited to:

- **Headache**
- **Nausea, vomiting, or diarrhea**
- **Redness where you get the injection**
- **Itching**
- **Common cold, sore throat, sinus infection, or chest cold**
- **Bladder infection or yeast infection**
- **Feeling tired**

(DynaMed 2018, FDA 2018, FDA 2019)

Evidence report for biologics in ulcerative colitis

Search and Selection

Prepared by EBSCO Information Services

December 20, 2019

Prepared by EBSCO Health Innovations and EBM Development Department:

Brian S. Alper, MD, MSPH, FAAFP, Vice President

Martin Mayer, DMSc, MS, PA-C, Clinical Evidence Synthesizer

Eric Manheimer, PhD, EBM Editor

Methods

First-round searching will consist of searching DynaMed Plus summaries pertinent to the topic. The search starts with DynaMed Plus because DynaMed Plus content is based on a thorough, systematic search and active literature surveillance system.

> Systematic literature surveillance (SLS) has been a cornerstone of creating DynaMed content since its inception. Currently, the SLS team works closely with members of McMaster University's Department of Health Research Methods, Evidence, and Impact to define and refine optimal search strategies, utilizing search terms for methodology and for clinical concepts (especially diagnosis and treatment) for each journal. These filters for PubMed searches are derived from PubMed Clinical Queries, McMaster University Hedges system, and DynaMed search filters and were found to capture >95% of relevant valid articles for use in DynaMed.[1]
> [1]Alper BS, Iorio A. Optimising search filters for active literature surveillance: a concordance study. Global Evidence Summit. Cape Town, South Africa; September 2017.
>
> The SLS team, in collaboration with McMaster University, continually evaluates and improves these filters to keep abreast of the ever-changing medical literature landscape. PubMed searches are performed daily. Each article is assessed by an external screener for clinical relevance, then reviewed by internal staff for both clinical relevance and validity. Any disagreements are settled by the Deputy Editor of the SLS team.
> In addition, the SLS team continually monitors the Journal source list against the list of journals catalogued in MEDLINE and existing DynaMed content to determine the set of journals that provide the highest yield for valid, clinically relevant content. As of November 2018, 507 Journals are systematically searched (see http://dynamed.com/home/content/content-sources). The journal selection threshold leads to routine adjustments to the number of journals selected.

Second-round searching will involve PubMed/MEDLINE® searches for intervention-specific systematic reviews or guidelines that involve a systematic review that are more recent than those identified in first-round searching.

Third-round searching will involve searches for original evidence reports. Such searching will be limited to areas considered insufficiently addressed by earlier searches, such as focused concepts published after search dates in systematic reviews.

Fourth-round searching will involve citation tracing from sources found in the preceding rounds of searching. This may be done to identify additional evidence sources if the results from the preceding rounds of searching are insufficient.

Additional selective searching, such as tracing citations from articles found or seeking related articles, may be done for additional concepts discovered.

Additional evidence updates may also be added continuously from feedback from any source.

FAQ Summary

Results

First-round searching – DynaMed

DynaMed subsection	Number of article citations	Number of unique references included
Ulcerative Colitis in Adults topic, Management section, Medications subsection, Tumor necrosis factor inhibitors (anti-TNF agents) subsection (December 20, 2019)	37	3 (Costa 2013, LeBlanc 2015, Lv 2014)
Ulcerative Colitis in Adults topic, Management section, Medication subsection, Other biologic medications subsection, Anti-integrin agents subsection, Vedolizumab subsection (December 20, 2019)	7	2 (Bickston 2014, Colombel 2017)

Second-round searching – searches for intervention-specific systematic reviews

Database	Search string	Number of search results	Number of unique references included
PubMed December 20, 2019	((infliximab[tiab] OR golimumab[tiab] OR adalimumab[tiab] OR vedolizumab[tiab] OR ustekinumab[tiab]) AND (ulcerative colitis[ti] OR inflammatory bowel disease*[ti]) AND (systematic[sb] OR meta-analysis[ti])) NOT (pediatric[ti] OR child*[ti])	117	19 (Bonovas 2018, Bonovas 2018U, Bonovas 2016, Bye 2017, Chen 2016, Jin 2015, Lin 2015, Lopez 2015, Mao 2017, Moćko 2017, Paschos 2018, Schreiber 2018, Singh 2018, Singh 2019, Song 2015, Trigo-Vicente 2018, Vickers 2016, Wheat 2017, Zhang 2016)

Third-round searching – searches for original evidence reports

Database	Search string	Number of search results	Number of unique references included
PubMed December 28, 2019	((infliximab[tiab] OR golimumab[tiab] OR adalimumab[tiab] OR vedolizumab[tiab] OR ustekinumab[tiab]) AND (ulcerative colitis[ti] OR inflammatory bowel disease*[ti]) AND randomized controlled trial[pt]) AND ("2017/08/01"[PDAT] : "3000/12/31"[PDAT]) NOT (pediatric[ti] OR child*[ti])	11	3 (Motoya 2019, Sands 2019, Sands 2019V)
PubMed January 8, 2020	(ulcerative colitis[ti] OR Crohn*[ti] OR inflammatory bowel disease*[ti]) AND (infection OR malignancy) AND (national OR nationwide OR multicenter OR multicentre OR registry OR registries) NOT (pediatric[ti] OR child*[ti]) AND ((anti-interleukin[tiab] OR anti-IL*[tiab] OR anti-integrin[tiab] OR vedolizumab[tiab] OR ustekinumab[tiab]) OR ((TNF[tiab] OR tumor necrosis factor[tiab] OR adalimumab[tiab] OR infliximab[tiab] OR golimumab[tiab]) AND ("2015/06/01"[PDAT] : "3000/12/31"[PDAT])))	113	3 (Kobayashi 2019, Lemaitre 2017, Nyboe Andersen 2015)

Fourth-round searching – citation tracing

Source	Tracing	Number of unique references included
Lv 2014	Rutgeerts 2005 provided substantial contribution to meta-analysis, obtained to check trial completion rates	1 (Rutgeerts 2005)
Bonovas 2018	Feagan 2013, Sandborn 2012 and Sandborn 2014 provided substantial contribution to meta-analyses, obtained to check trial completion rates	3 (Feagan 2013, Sandborn 2012, Sandborn 2014)
Lopez 2015, Mao 2017	Sandborn 2009 and Feagan 2014 results were not consistent	2 (Feagan 2014, Sandborn 2009)
Nyboe Andersen 2015	Cites Nyboe Andersen 2014, an earlier study regarding cancer (Nyboe Andersen 2015 focused on infection)*	1 (Nyboe Andersen 2014)

*Our search for original cohort studies would not be expected to capture Nyboe Andersen 2014 on using the date cutoff of 1 Jun 2015 based on search dates from systematic reviews addressing the anti-TNF alpha agents.

Fifth-round searching – Evidence from report on biologics in Crohn's disease for FAQ6

We specified we would update this report with any applicable evidence found during our creation of the evidence report for Crohn's disease. Accordingly, in addition to the evidence noted above, the following studies were identified during searches for "Biologics for Crohn's disease" and contributed to FAQ6 responses. Details of these studies can be found in the full report for biologics for Crohn's disease, though they are not included in the counts shown in "Search summary":

Askling 2011
Kirchgesner 2018
Sandborn 2013
Schreiber 2018
Siegel 2009

Secondary screening – systematic reviews

Selected for critical appraisal (12)	**Excluded – not reporting direct comparisons for questions of interest (7)**	**Excluded – no new information compared to later systematic reviews (5)**
Bonovas 2016, Bonovas 2018, Bonovas 2018U, Bye 2017, Colombel 2017, LeBlanc 2015, Lopez 2015, Lv 2014, Mao 2017, Paschos 2018, Schreiber 2018, Singh 2018	Lin 2015, Mocko 2017, Singh 2019, Song 2015, Trigo-Vicente 2018, Vickers 2016, Wheat 2017	Bickston 2014, Chen 2016, Costa 2013, Jin 2015, Zhang 2017

SR identifier	TNF inhibitors	FAQ2 (induc.)	FAQ2 (maint.)	FAQ3 (QoL)	FAQ4 (surgery)	FAQ5 (hosp.)	FAQ6 (infx)	FAQ6 (malig.)
Bickston 2014	no	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Bonovas 2016	only by individual drug	not covered	not covered	not covered	not covered	not covered	direct absolute	direct absolute
Bonovas 2018	only by individual drug	direct absolute	direct absolute	not covered	not covered	not covered	not covered	not covered
Bonovas 2018U	yes	not covered	not covered	not covered	not covered	not covered	direct relative (umbrella)	direct relative (umbrella)
Bye 2017	no	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Chen 2016	only adalimumab	direct absolute	direct absolute	direct absolute	not covered	not covered	not covered	not covered
Colombel 2017	no	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Costa 2013	only infliximab	not covered	not covered	not covered	direct partial absolute	direct partial absolute	not covered	not covered
Jin 2015	no	N/A	N/A	N/A	N/A	N/A	N/A	N/A
LeBlanc 2015	yes	not covered	not covered	direct absolute	not covered	not covered	not covered	not covered
Lin 2015	no	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Lopez 2015	yes	direct absolute	direct absolute	not covered	direct absolute	direct absolute	direct relative	direct relative
Lv 2014	yes	not covered	direct absolute	not covered	direct absolute	not covered	not covered	not covered
Mao 2017	yes	not covered	not covered	not covered	direct absolute	direct absolute	not covered	not covered
Moćko 2017	only by individual drug	not covered	not covered	not covered	not covered	not covered	indirect relative	not covered
Paschos 2018	only by individual drug	not covered	not covered	direct absolute	not covered	not covered	not covered	not covered
Schreiber 2018	no	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Singh 2018	only by individual drug	direct absolute	not in primary article	not covered	not covered	not covered	limited detail	not covered
Singh 2019	yes	not covered	not covered	not covered	not covered	not covered	indirect relative	not covered
Song 2015	yes (but pools placebo-controlled and active treatment-controlled trials for MA)	direct absolute	direct absolute	not covered	indirect relative	not covered	not covered	not covered
Trigo-Vicente 2018	only by individual drug	indirect relative	indirect relative	not covered	not covered	not covered	indirect relative	not covered
Vickers 2016	only by individual drug	indirect relative	indirect relative	not covered	not covered	not covered	not covered	not covered
Wheat 2017	only by individual drug	not covered	not covered	not covered	not covered	not covered	indirect relative	not covered
Zhang 2016	only adalimumab	direct absolute	direct absolute	direct absolute	not covered	not covered	not covered	not covered

SR identifier	Vedolizumab	FAQ2 (induc.)	FAQ2 (maint.)	FAQ3 (QoL)	FAQ4 (surgery)	FAQ5 (hosp.)	FAQ6 (infx)	FAQ6 (malig.)
Bickston 2014	yes	direct absolute	direct absolute	direct absolute	not covered	not covered	not covered	not covered
Bonovas 2016	yes	not covered	not covered	not covered	not covered	not covered	direct absolute	direct absolute
Bonovas 2018	yes	direct absolute	direct absolute	not covered	not covered	not covered	not covered	not covered
Bonovas 2018U	yes	not covered	not covered	not covered	not covered	not covered	direct relative (umbrella)	direct relative (umbrella)
Bye 2017	yes	not covered	not covered	not covered	not covered	not covered	direct absolute	direct absolute
Chen 2016	no	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Colombel 2017	yes	not covered	not covered	not covered	not covered	not covered	direct absolute	direct absolute
Costa 2013	no	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Jin 2015	yes	direct absolute	not covered	not covered	uncontrolled	not covered	uncontrolled	uncontrolled
LeBlanc 2015	yes	not covered	not covered	direct absolute	not covered	not covered	not covered	not covered
Lin 2015	yes	maybe	not covered	not covered	not covered	not covered	not covered	not covered
Lopez 2015	no	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Lv 2014	no	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Mao 2017	yes	not covered	not covered	not covered	direct absolute	direct absolute	not covered	not covered
Moćko 2017	yes	not covered	not covered	not covered	not covered	not covered	indirect relative	not covered
Paschos 2018	yes	not covered	not covered	direct absolute	not covered	not covered	not covered	not covered
Schreiber 2018	yes	uncontrolled	uncontrolled	not covered	uncontrolled	uncontrolled	uncontrolled	not covered
Singh 2018	yes	direct absolute	not in primary article	not covered	not covered	not covered	limited detail	not covered
Singh 2019	yes	not covered	not covered	not covered	not covered	not covered	indirect relative	not covered
Song 2015	no	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Trigo-Vicente 2018	yes	indirect relative	indirect relative	not covered	not covered	not covered	indirect relative	not covered
Vickers 2016	yes	indirect relative	indirect relative	not covered	not covered	not covered	not covered	not covered
Wheat 2017	yes	not covered	not covered	not covered	not covered	not covered	indirect relative	not covered
Zhang 2016	no	N/A	N/A	N/A	N/A	N/A	N/A	N/A

SR identifier	Ustekinumab	FAQ2 (induc.)	FAQ2 (maint.)	FAQ3 (QoL)	FAQ4 (surgery)	FAQ5 (hosp.)	FAQ6 (infx)	FAQ6 (malig.)
Bickston 2014	no	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Bonovas 2016	no	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Bonovas 2018	no	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Bonovas 2018U	no	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Bye 2017	no	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Chen 2016	no	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Colombel 2017	no	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Costa 2013	no	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Jin 2015	no	N/A	N/A	N/A	N/A	N/A	N/A	N/A
LeBlanc 2015	no	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Lin 2015	no	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Lopez 2015	no	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Lv 2014	no	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Mao 2017	no	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Moćko 2017	no	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Paschos 2018	no	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Schreiber 2018	no	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Singh 2018	no	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Singh 2019	yes	not covered	not covered	not covered	not covered	not covered	indirect relative	not covered
Song 2015	no	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Trigo-Vicente 2018	no	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Vickers 2016	no	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Wheat 2017	yes	not covered	not covered	not covered	not covered	not covered	indirect relative	not covered
Zhang 2016	no	N/A	N/A	N/A	N/A	N/A	N/A	N/A

Search summary:

Number of articles screened and selected

	Screened	Selected (first stage)*	Selected (second stage)*
1st-round (DynaMed)	44	5	3
2nd-round (Systematic review searches)	117	19	9
3rd-round (Original article searches)	124	6	6†
4th-round (Citation tracing)	7	7	7†
Total	*292*	*37*	*25*

* Number shown is after deduplication

† Second stage selection not applicable

	Articles selected for evaluation (Author Year)
Systematic reviews	11 (Bonovas 2016, Bonovas 2018, Bye 2017, Colombel 2017, LeBlanc 2015, Lopez 2015, Lv 2014, Mao 2017, Paschos 2018, Schreiber 2018, Singh 2018)
Randomized, controlled trials	9 (Feagan 2013, Feagan 2014, Motoya 2019, Rutgeerts 2015, Sandborn 2009, Sandborn 2012, Sandborn 2014, Sands 2019, Sands 2019V)
Other article types	5: 1 umbrella review (Bonovas 2018U), 4 cohort studies (Kobayashi 2019, Lemaitre 2017, Nyboe Andersen 2014, Nyboe Andersen 2015)

We also specified we would update this report with any applicable evidence found during our creation of the evidence report for Crohn's disease. Accordingly, in addition to the evidence noted above, the following studies were identified during searches for "Biologics for Crohn's disease" and contributed to FAQ6 responses. Details of these studies can be found in the full report for biologics for Crohn's disease, though they are not included in the counts above:

Askling 2011
Kirchgesner 2018
Sandborn 2013
Schreiber 2018
Siegel 2009

Evidence report for biologics in ulcerative colitis

Critical Appraisal

Prepared by EBSCO Information Services

December 28, 2019

Prepared by EBSCO Health Innovations and EBM Development Department:

Brian S. Alper, MD, MSPH, FAAFP, Vice President

Martin Mayer, DMSc, MS, PA-C, Clinical Evidence Synthesizer

Eric Manheimer, PhD, EBM Editor

Methods

For each study selected for critical appraisal, we assessed for criteria needed for Level 1 [likely reliable] evidence ratings in DynaMed's Levels of Evidence criteria in which evidence quality is labeled in 1 of 3 levels:

- **(level 1 [likely reliable] evidence)** for studies with clinical outcomes and minimal risk of bias;
- **(level 2 [mid-level] evidence)** for studies with clinical outcomes and significant methodological or statistical limitations; and
- **(level 3 [lacking direct] evidence)** for reports that do not include scientific analysis of clinical outcomes or for study types that do not include comparisons between groups.

The specific concepts we critically assessed are fully mapped to cover all the criteria used in GRADE. We summarized key concerns identified that reduce the certainty of evidence in categories used for GRADE methods (i.e., risks of bias, indirectness, imprecision, inconsistency, and other considerations if relevant). In the study-level summaries inconsistency assessment was applied to consistency of within-study results – this applies to consistency across related outcomes for both original studies and for systematic reviews, and also applies to consistency across studies when applied to systematic reviews.

FAQ Summary

Results

Characteristics and Results of Critically Appraised Studies/Sources

BONOVAS 2016

Bonovas S, Fiorino G, Allocca M, Lytras T, Nikolopoulos GK, Peyrin-Biroulet L, Danese S. Biologic Therapies and Risk of Infection and Malignancy in Patients With Inflammatory Bowel Disease: A Systematic Review and Network Meta-analysis. Clin Gastroenterol Hepatol. 2016 Oct;14(10):1385-1397.e10. PubMed

Relevant to FAQ6

- **Study design:** systematic review of randomized trials
- **Population:** adults (> 90% of patients > 18 years old) with inflammatory bowel disease (UC or CD)
- **Intervention:** biologic agents approved for treating adults with inflammatory bowel disease
    - anti-TNF agents
        - adalimumab
        - certolizumab
        - golimumab
        - infliximab
    - anti-integrin molecules
        - natalizumab
        - vedolizumab
- **Comparison:** placebo
    - head-to-head trials between biologic agents were also eligible but none were identified
- **Study inclusion criteria:** reported infectious adverse events and malignancies as outcomes
- **Number of studies:** 49
    - agents evaluated (number of trials; patients)
        - anti-TNF agents
            - adalimumab (10; 3,094)
            - certolizumab pegol (7; 2,179)
            - golimumab (3; 1,820)
            - infliximab (16; 2,922)
        - anti-integrin molecules
            - natalizumab (5; 2,170)
            - vedolizumab (8; 2,405)
    - condition of patients (number of trials)
        - UC (16)
        - CD (33)
- **Number of participants:** 14,590
    - 9,003 treatment group
    - 5,587 placebo group
- **Duration of follow-up:** 1 to 24 months range across studies
    - We have estimated duration of follow-up as 6 months based on the following Results text: “The total period of observation was approximately 8000 person-years (6.5 months per patient on average)...”

- **Results and Certainty:**

Effects of anti-TNF inhibitors and vedolizumab on infection outcomes in patients with irritable bowel disease (UC or CD)

Agents(s)	Population	Outcome	No. of patients (studies)	Odds ratio (95% CI)*	Control group event rate (%)	Certainty (reason for downgrade)
Anti-TNF agents	CD and UC combined	serious infections†	9,831 (34)	0.90 (0.69 to 1.17)	2.6% (101/3,856)	Very low (very serious risk of bias, imprecision)[1]
		opportunistic infections	7,205 (19)	1.89 (1.15 to 3.12)	0.65% (18/2,765)	High certainty that anti-TNF agents increase risk; Low certainty in reported magnitude of increase (very serious risk of bias)[2]
		any infection	9,864 (34)	1.21 (1.10 to 1.33)	29.9% (1,164/3,894)	Low (very serious risk of bias)[1]
Vedolizumab	CD and UC combined	serious infections†	2,358 (7)	0.95 (0.52 to 1.74)‡	1.8% (16/904)	Very low (very serious risk of bias, very serious imprecision)[1]
		opportunistic infections	689 (3)	0.91 (0.17 to 4.90)‡	0.44% (1/225)	Insufficient evidence
		any infection	2,405 (8)	1.07 (0.87 to 1.31)‡	27.8% (254/913)	Very low (very serious risk of bias, imprecision)[1]
Any biologic agents	CD and UC combined	opportunistic infections	8,832 (24)	1.90 (1.21 to 3.01) §¶	0.58% (20/3,454)	Low (very serious risk of bias)[2]
	UC only	opportunistic infections	NR	1.32 (0.64 to 2.72)	NR	Not applicable**
	CD only	opportunistic infections	NR	2.39 (1.32 to 4.34)	NR	Not applicable**

* ORs were extracted from Results text in many cases (not reported in forest plots) and appeared to be based on a fixed effects model. Accordingly, we present all ORs in this table from the fixed effects model for consistency, but when the random effects estimate was available, we also extracted it and report it as a footnote.

† As defined by each study.

‡ Vedolizumab random effects ORs: serious infections, OR 0.83 (95% CI 0.38 to 1.80); opportunistic infections, OR 0.72 (95% CI 0.10 to 5.40); any infection, OR 1.08 (95% CI 0.82 to 1.43)

§ Any biologic agent random effects OR for opportunistic infection: 1.65 (95% CI 1.00 to 2.71)

¶ Subgroup analyses (across trials of all biologics) found no significant difference in subgroup of trials with CD patients and trials with UC patients with subgroup test p-value of 0.21 (ORs for each subgroup of trials reported below).

** Extracted only to show that biologic agents have consistent effect on opportunistic infections in patients with UC and in patients with CD.

1 We have double downgraded for risk of bias because of very serious concern about selective outcome reporting which may result in the reported estimates underestimating the true risk. Our assessment is based on the substantial evidence that harms are assessed inconsistently and reported inadequately in randomized trials; under-reporting of harms is especially of concern because these trials were supported by pharmaceutical companies that produce and market these drugs.

2 We have double downgraded the certainty of the reported *magnitude of increase* in opportunistic infections because of very serious concern about risk of bias due to selective outcome reporting which may result in the reported estimates underestimating the true risk. Our assessment is based on the substantial evidence that harms are assessed inconsistently and reported inadequately in randomized trials; under-reporting of harms is especially of concern because these trials were supported by pharmaceutical companies that produce and market these drugs.

Other considerations:

- Outcomes not progressed to synthesis:
  - The "any infections" outcome was not progressed to Evidence Synthesis (for any option) because it would be highly influenced by upper respiratory tract infections, colds etc., and also because it would combine events due to such minor nuisances together with more serious infections, resulting in an uninformative composite estimate.
  - The "malignancy" outcome was not progressed to Evidence Synthesis (for any option) because there were few events and very wide CIs, resulting in uninformative estimates. This is expected because randomized trials typically have inadequate duration and inadequate power to detect long-term risks such as malignancy.
  - For vedolizumab specifically, the "serious infections" and "opportunistic infections" outcomes were not progressed to Evidence Synthesis because evidence for it was Very low certainty (double-downgraded for both very serious risk of bias and very serious imprecision).
- Results for UC only and CD only meta-analyses were not significantly different for opportunistic infections, serious infections, or any infections, so primary results used were based on CD and UC combined
- For malignancies
  - Effect estimate for all biological agents showed pooled OR 0.90 (95% CI 0.54 to 1.50)
  - Effect estimate for vedolizumab showed pooled OR 0.53 (95% CI 0.12 to 2.32)
  - Effect estimate for anti-TNF agents as a class was not reported in Figure or text and we did not calculate a pooled effect estimate at EBSCO Information Services for an anti-TNF class effect because this data source is not adequate for meaningful effect estimates because all estimates for malignancies are limited by nearly all trial arms (drug or placebo) having only 0-2 events

BONOVAS 2018

Bonovas S, Lytras T, Nikolopoulos G, Peyrin-Biroulet L, Danese S. Systematic review with network meta-analysis: comparative assessment of tofacitinib and biological therapies for moderate-to-severe ulcerative colitis. Aliment Pharmacol Ther. 2018 Feb;47(4):454-465. PubMed

Relevant to FAQ2

- **Study design:** systematic review of randomized trials
- **Population:** adults with moderate to severe ulcerative colitis who were not previously exposed to anti-TNF agents

- **Intervention:** anti-TNF agents (adalimumab, golimumab, infliximab), anti-integrin agents (vedolizumab), and small molecules like Janus kinase inhibitors (tofacitinib)
- **Comparison:** placebo or active treatment

- **Study inclusion criteria:**
  - phase 2 trials (in addition to phase 3 trials) were eligible
  - only market-authorized biologics were eligible for inclusion

- **Number of studies:** 19 (reported in 13 articles)
- **Number of participants:** reported below by outcome
- **Duration of follow-up:** 6-8 weeks for induction of remission, 52-54 weeks for remission maintenance

- **Results and Certainty:**

Effects of intervention vs. placebo on induction of remission (6 to 8 weeks)

Agent	No. of patients (studies)	Odds ratio (95% CI)	Control group event rate (% with remission)	Certainty (reason for downgrade)
adalimumab	927 (4)	1.89 (1.19 to 3.00)	9.3% (43/464)	Moderate (inconsistency) [1]
infliximab	776 (4)	3.97 (2.32 to 6.79)	11.6% (45/389)	High
golimumab	644 (3)	2.80 (1.67 to 4.67)	7.2% (23/320)	High
tofacitinib	577 (3)	2.47 (1.41 to 4.34)	13.1% (18/137)	High
vedolizumab	206 (1)	4.26 (1.58 to 11.52)	6.6% (5/76)	High

[1] heterogeneity with one trial (Suzuki 2014) suggesting no effect

Effects of intervention vs. placebo on maintenance of remission (52 to 54 weeks)

Agent	No. of patients (studies)	Odds ratio (95% CI)	Control group event rate (%)	Certainty (reason for downgrade)*
adalimumab	481 (2)	2.31 (1.37 to 3.87)	10.4% (25/241)	High
infliximab	776 (4)	2.37 (1.63 to 3.44)	15.4% (60/389)	High
golimumab – specific to induction responders	368 (2)	4.44 (0.58 to 34.22)	19.5% (36/185)	Low (inconsistency, imprecision)[1,2]
vedolizumab – specific to induction responders	151 (1)	3.61 (1.74 to 7.48)	19.0% (15/79)	High[1]

* Bonovas 2018 rates all trials contributing to its meta-analytic estimates for maintenance of remission as being at high risk of incomplete outcome data; however, full-text review of trials contributing to the estimates in this table revealed that there were very few losses to follow-up. It appears Bonovas 2018 may be counting discontinuations due to lack of efficacy as contributing to incomplete outcome data, but the trials treated such situations as de facto treatment failures and analyzed them as such. Therefore, this conservative approach would not be expected to introduce bias in the effect estimates.

[1] In maintenance studies of golimumab and vedolizumab, only induction responders were eligible and were re-randomized at beginning of maintenance study; the goal of studies using this design was to determine whether remission can be maintained among patients who had previously been treated with the agent and responded. This selective population is considered to less directly match patients who would be using the decision aid (presumably before starting the biologic agent) and would thus warrant a downgrade for indirectness if trying to apply this evidence to all-comers with ulcerative colitis. However, we specified the outcomes are specific to induction responders to convey the group for whom we have higher certainty (i.e., the group for whom this indirectness downgrade would not apply), and the practical clinical reality is that if a patient does not show a response to induction therapy, s/he will not be maintained on the medication anyway.

[2] Two trials had different effect sizes (odds ratio 1.80 and 14.5) with very little overlap of confidence intervals.

BONOVAS 2018U

Bonovas S, Pantavou K, Evripidou D, Bastiampillai AJ, Nikolopoulos GK, Peyrin-Biroulet L, Danese S. Safety of biological therapies in ulcerative colitis: An umbrella review of meta-analyses. Best Pract Res Clin Gastroenterol. 2018 Feb - Apr;32-33:43-47. PubMed

Relevant to FAQ6

- **Study design:** umbrella review of systematic reviews of randomized trials that have evaluated potential harms of biological agents
    - descriptive review of meta-analyses, with no statistical analysis performed
- **Population:** patients with ulcerative colitis
- **Intervention:** adalimumab, golimumab, infliximab, and vedolizumab
- **Comparison:** placebo

- **Study inclusion criteria:** reported ≥ 1 of following outcomes: any infections, serious infections, opportunistic infections, tuberculosis, and malignancies

- **Number of studies:** 10 SRMAs included

- **Results:**
  - infection-related outcomes
    - any infections – statistically significant increases in some meta-analyses, but not in others; differences not attributable to specific drugs used
    - serious infections – not statistically significant in any meta-analysis reported
    - opportunistic infections – reported in 4 meta-analyses, point estimates consistent with increased risk in all 4 meta-analyses (effect size 1.32 to 1.87) but not statistically significant with wide confidence intervals
  - malignancy – reported in 3 meta-analyses; very wide confidence intervals do not support meaningful conclusions
- **Other considerations**
  - Infection and malignancy outcomes from Bonovas 2018U were not progressed to Evidence Synthesis because this umbrella review includes only SRMAs that restrict to UC patients. We considered the Bonovas 2016 SRMA of risks that combined randomized trials of UC and CD patients preferable to any source restricting to UC or CD patients only because (1) including trials in both patients with UC and patients with CD increases power to detect an increase in risk and (2) we would not expect the specific condition to modify the risk (which was supported by consistency in point estimates for serious infection outcome between Lopez 2015 [which limited to UC patients] and Bonovas 2016). Although this umbrella review is non-informative with respect to risk of infections or malignancies with these agents, it was useful to confirm identification of relevant SRMAs and to support that UC-limited SRMAs are not an optimal source for risks.

BYE 2017

Bye WA, Jairath V, Travis SPL. Systematic review: the safety of vedolizumab for the treatment of inflammatory bowel disease. Aliment Pharmacol Ther. 2017 Jul;46(1):3-15. doi: 10.1111/apt.14075. PubMed

Relevant to FAQ6

Among 2,830 patients exposed to vedolizumab during "registration trials" during drug development:

- Rate of any infection 63.5 per 100 person-years, but many of these were upper respiratory infections
- Rate of enteric infections 7.4 per 100 person-years
- Rate of serious infections 4.3 per 100 person-years; serious infections or infestations reported in 199 patients (7%)
- 18 patients had malignancy

Among 1,049 patients exposed to vedolizumab during post-marketing cohort studies:

- 82 (8%) had any infection (details not clear)
- 21 (2%) had enteric infection
- One study suggested increased risk of surgical site infection with perioperative vedolizumab

Overall rate of opportunistic infections not reported

- Other considerations
  - The "registration trials" consisted of 6 double-blind or open-label trials in patients with UC or CD. However, on examination, we found that patients randomized to placebo in

the placebo-controlled trials and then enrolled in an open-label study could contribute to events in either the placebo or vedolizumab group depending on when they experienced the adverse event; statistical comparisons between the treatment and placebo groups were not performed; and most patients (97%) received ≥ 1 dose of vedolizumab. For these reasons, we did not consider this analysis helpful to test whether vedolizumab increases risks of infections compared to no vedolizumab. This analysis was originally reported in Colombel 2017 and repeated in Bye 2017 with similar methods and results reported.

COLOMBEL 2017
Colombel JF, Sands BE, Rutgeerts P, Sandborn W, Danese S, D'Haens G, Panaccione R, Loftus EV Jr, Sankoh S, Fox I, Parikh A, Milch C, Abhyankar B, Feagan BG. The safety of vedolizumab for ulcerative colitis and Crohn's disease. Gut. 2017 May;66(5):839-851. PubMed

Relevant to FAQ6

Results included in Bye 2017

FEAGAN 2013
Feagan BG, Rutgeerts P, Sands BE, et al; GEMINI 1 Study Group. Vedolizumab as induction and maintenance therapy for ulcerative colitis. N Engl J Med. 2013 Aug 22;369(8):699-710. PubMed

Relevant to FAQ2

- **Study design:** randomized controlled trial
  - induction phase (6 weeks)
    - cohort 1 – 374 patients randomized to vedolizumab vs. placebo
    - cohort 2 – 521 patients received open-label vedolizumab
  - maintenance phase (46 weeks)
    - 373 patients in either cohort 1 or 2 who had response to vedolizumab at week 6 were randomized to vedolizumab (every 4-week and every 8-week arms) vs. placebo for up to 52 weeks total (46 weeks after re-randomization)
    - for the maintenance phase, we limited to patients in every 8-week arm because this is the approved dosing frequency
  - high drug discontinuation rates but these were mostly for "lack of efficacy" so dropouts/loss to follow-up were essentially < 10%; treatment was considered to have failed among those who withdrew from the study prematurely
- **Population:** adults with moderate to severe active ulcerative colitis
- **Intervention:** vedolizumab
- **Comparison:** placebo

- **Duration of follow-up:** 52 weeks

Effects of vedolizumab vs. placebo on induction on multiple outcomes

Time point, outcome	Intervention group	Control group	Absolute difference (95% CI)	Certainty (reason for downgrade)
6 weeks, proportion with induction of remission	16.9% (38/225)	5.4% (8/149)	Adjusted absolute rate increase 11.5% (4.7% to 18.3%)	Moderate (indirectness)[1]
52 weeks, proportion of induction responders with maintenance of remission	41.8% (51/122)	15.9% (20/126)	Adjusted absolute rate increase 26.1% (14.9% to 37.2%)	Moderate (indirectness)[1,2]
Estimated sustained maintenance of remission (at 6 weeks and at 52 weeks)	16.9% * 41.8% = 7.1%	5.4% * 15.9% = 0.86%	Estimated absolute rate increase 6.24%	Very low (extremely serious indirectness)[1,3]
Mean change in quality of life (on IBDQ scale) from maintenance baseline among induction responders (6 weeks) to 52 weeks*	1-point increase† (n = 122)	20-point decrease† (n = 126)	Not applicable†	Low (indirectness, risk of bias)[1,2,4]

*This outcome provides insight into how quality of life might be impacted by staying on vedolizumab after induction vs. discontinuing it. IBDQ is measured on a scale from 32 to 224, with higher scores being better.

†Estimated from Figure 1B, disregarding the every-4-week dosing of vedolizumab for maintenance, as vedolizumab is typically given every 8 weeks for maintenance. Error bars are standard errors (not CIs), so they are not reported here given how these data are incorporated into synthesis.

[1] This trial had a substantial proportion of patients with prior exposure to anti-TNF therapy and thus constitutes a less direct match to the population of interest for this evidence report

[2] In maintenance of remission studies of vedolizumab, only induction responders were eligible and were re-randomized at beginning of maintenance study; the goal of studies using this design was to determine whether remission can be maintained among patients who had previously been treated with the agent and responded. This selective population is considered to less directly match patients who would be using the decision aid (presumably before starting the biologic agent) and would thus warrant a downgrade for indirectness if trying to apply this evidence to all-comers with ulcerative colitis. However, we specified the outcomes are specific to induction responders to convey the group for whom we have higher certainty (i.e., the group for whom this indirectness downgrade would not apply), and the practical clinical reality is that if a patient does not show a response to induction therapy, s/he will not be maintained on the medication anyway.

[3] Indirectly derived and derivation uses estimates downgraded for indirectness based on the population

[4] This trial used last observation carried forward for continuous outcomes for patients who withdrew from the trial prematurely, and the trial had substantial and imbalanced early discontinuation in the maintenance phase (45/122 in the group receiving vedolizumab every 8 weeks, 41/125 in the group receiving vedolizumab every 4 weeks, and 78/126 in the group receiving placebo).

FEAGAN 2014
Feagan BG, Sandborn WJ, Lazar A, et al. Adalimumab therapy is associated with reduced risk of hospitalization in patients with ulcerative colitis. Gastroenterology. 2014 Jan;146(1):110-118.e3. PubMed

Relevant to FAQ5

- **Study design:** pooled results of 2 randomized trials ULTRA 1 and ULTRA 2
  - ULTRA 1
    - 8-week, double-blind, placebo-controlled induction trial of adalimumab
    - open-label extension for total of 52 weeks
  - ULTRA 2
    - 52-week, double-blind, placebo-controlled induction and maintenance trial of adalimumab
    - starting at week 10, patients who met criteria for inadequate response could be switched to open-label adalimumab
- **Population:** adults with moderate to severe ulcerative colitis
- **Intervention:** adalimumab
- **Comparison:** placebo

- **Number of studies:** 2
- **Number of participants:** 963
- **Duration of follow-up:** 52 weeks with additional 70-day follow-up or extension study

- **Results and Certainty:**

Adalimumab vs. placebo on hospitalization and colectomy in all patients from ULTRA 1 and ULTRA 2 during first 8 weeks of therapy

Outcome	Proportion with outcome (Number/Total)		P-value comparing groups	Certainty
	adalimumab	placebo		
all-cause hospitalization	4.6% (22/480)	7.7% (37/483)	0.046	Moderate (imprecision)[1]
colectomy	1.0% (5/480)	1.2% (6/483)	0.77	Moderate (imprecision) [2]

1 Certainty downgraded because between confidence interval approaches no effect (borderline statistical significance)
2 Certainty downgraded due to sparse data (< 20 events per group)

Adalimumab vs. placebo on all-cause hospitalization, UC-related hospitalization, and colectomy in all patients from ULTRA 1 and ULTRA 2 during 52-week period

Outcome	Analysis approach*	Proportion (Number/person-years at risk, incidence rate)		Risk ratio (95% CI)	P-value comparing groups	Certainty
		Adalimumab	Placebo (n =			

		(n = 480)	**483)**			
all-cause hospitalization	Intention to treat	14.4% (69/387.5, 0.18)	18.4% (89/377.7, 0.24)	0.8 (0.6 to 1.0)	0.08	Moderate (imprecision)[1]
	As treated	14.4% (69/387.5, 0.18)	12.0% (58/222.3, 0.26)	0.7 (0.5 to 1.0)	0.03	Low (imprecision, risk of bias) [1,2]
UC-related hospitalization	Intention to treat	9.8% (47/398.1, 0.12)	14.1% (68/384.2, 0.18)	0.7 (0.5 to 1.0)	0.03	Moderate (imprecision)[1]
	As treated	9.8% (47/398.1, 0.12)	10.1% (49/223.6, 0.22)	0.5 (0.4 to 0.8)	0.002	Moderate (risk of bias)[2]
colectomy	Intention to treat	3.1% (15/408.1, 0.04)	3.9% (19/400.0, 0.05)	NR	NR	Moderate (imprecision)[3]
	As treated	3.1% (15/408.1, 0.04)	2.3% (11/231.7, 0.05)	NR	NR	Low (imprecision, risk of bias)[2,3]

*Intention to treat analysis evaluated all patients according to original randomized assignment. As treated analysis excluded original placebo group patients 70 days after receiving open-label adalimumab.

1 Certainty downgraded because wide CIs

2 Certainty downgraded because patients not analyzed as randomized

3 Certainty downgraded due to sparse data (< 20 events per group)

KOBAYASHI 2019

Kobayashi T, Uda A, Udagawa E, Hibi T. Lack of Increased Risk of Lymphoma by Thiopurines or Biologics in Japanese Patients with Inflammatory Bowel Disease: A Large-Scale Administrative Database Analysis. J Crohns Colitis. 2019 Dec 23. Epub ahead of print. PubMed

This study was identified through our PubMed search. The abstract only indicated that anti-TNF users showed "...no notable differences in non-Hodgkin lymphoma incidence relative to the total population..." We obtained the full-text report to evaluate the findings more fully and specifically to determine whether its findings would modify our interpretation of the findings of Lemaitre 2017 which showed an increased risk of lymphoma associated with anti-TNF agents. As further detailed in the 'Other considerations' bullet of Lemaitre 2017 summary, because of the small number of events and the wide CIs in this study, we did not consider the results of Kobayashi 2019 to modify our interpretation of the effects reported in Lemaitre 2017.

LEBLANC 2015

LeBlanc K, Mosli MH, Parker CE, MacDonald JK. The impact of biological interventions for ulcerative colitis on health-related quality of life. Cochrane Database Syst Rev. 2015 Sep 22;(9):CD008655. PubMed

Relevant to FAQ3

- **Study design:** systematic review of randomized trials

- **Population:** ulcerative colitis patients
- **Intervention:** biologic therapy
- **Comparison:** placebo
- **Study inclusion criteria:**
  - reported on health-related quality of life using the Inflammatory Bowel Disease Questionnaire (IBDQ), the SF-36, or the EQ-5D
  - studies published up to September 2015
- **Number of studies:** 11
  - 7 trials evaluated anti-TNF alpha agents (infliximab, n = 3; adalimumab, n = 3; golimumab, n = 1)
  - 2 trials evaluated vedolizumab
  - rituximab and interferon-ß-1a evaluated in 1 study each
- **Number of participants:** 4,143
- **Duration of follow-up:** up to 52 weeks
- **Results and Certainty:**

Effects of interventions vs. placebo on clinically meaningful improvement on IBDQ (range of 32 to 224, with higher scores better)

Time point	Intervention	No. of patients (studies)	Risk ratio (95% CI)	Control group event rate (%)	Certainty (reason for downgrade)
6 or 8 weeks	anti-TNF alpha agents	1,495 (4)	1.32 (1.19 to 1.46)	46.2% (271/586)	High
	vedolizumab*	374 (1)	1.62 (1.15 to 2.27)	22.8% (34/149)	Moderate (indirectness)[1,2]
52 weeks	anti-TNF alpha agents (adalimumab)	767 (2)	1.73 (1.28 to 2.34)	15.2% (52/342)	High[2]
	vedolizumab (specific to induction responders)*	373 (1)	1.67 (1.31 to 2.12)	38.1% (48/126)	Low (indirectness, risk of bias)[1,2,3,4]

* LeBlanc 2015 report this as being "Improved IBDQ (≥16 points from baseline)", but the statement "≥16 points from baseline" is misleading. Feagan 2013 does not report on this outcome in the main publication, but dichotomous results for IBDQ score ≥170 are available from one of the abstracts LeBlanc 2015 cites in association with Feagan 2013 (Feagan 2014, *Gastroenterology*;146(5 Suppl 1):S-590), and the numbers reported in this abstract match those used for this (purported) analysis of ≥16-point improvement from baseline. For achieving an IBDQ score ≥170, Feagan 2014 report the following data: 37% in the vedolizumab group vs. 23% in the placebo group at 6 weeks (out of a total of 225 and 149 people in the groups, respectively, per Feagan 2013); and 68% (with every-4-weeks dosing) and 59% (with every-8-weeks dosing) in the vedolizumab groups vs. 38% in the placebo group (out of 125, 122, and 126 people in the groups, respectively, per Feagan 2013) at 52 weeks. Per the data in Feagan 2013, IBDQ scores at baseline were between 125 and 126 among randomized participants. Consequently, LeBlanc 2015's suggestion of measuring IBDQ score improvement of ≥16 points from baseline is misleading.

1 The trial on which this estimate is based included a substantial proportion of people with prior exposure to TNF inhibitors and thus constitutes a less direct match to the population of interest for this evidence report
2 Certainty downgraded by Cochrane authors due to sparse data (162 events at 6 weeks, 2015 events at 52 weeks), but we consider this overly stringent
3 Maintenance of remission study for vedolizumab was limited to patients who were induction responders and would thus warrant a downgrade for indirectness if trying to apply this evidence to all-comers with ulcerative colitis. However, we specified the outcome is specific to induction responders to convey the group for whom we have higher certainty (i.e., the group for whom this indirectness downgrade would not apply), and the practical clinical reality is that if a patient does not show a response to induction therapy, s/he will not be maintained on the medication anyway.
4 The trial on which this outcome is based used last observation carried forward (LOCF) for continuous outcomes for patients who withdrew from the trial prematurely. There were a relative minority of withdrawals in the 6-week induction phase (7/225 and 14/149 in the vedolizumab and placebo groups, respectively), and although there were more withdrawals in the placebo group, we do not consider this enough to warrant a downgrade from Moderate to Low (this outcome is presented in the row for vedolizumab at 6 to 8 weeks). However, for the 46-week maintenance phase (totaling 52 weeks of vedolizumab therapy), there were a large number of withdrawals (45/122 in the group receiving vedolizumab every 8 weeks, 41/125 in the group receiving vedolizumab every 4 weeks, and 78/126 in the group receiving placebo). Using LOCF here puts the results at substantial risk of bias, especially if being compared to other agents where LOCF was not used (e.g., ustekinumab/Sands 2019).

- **Other considerations**
  - Consistent effects were seen in analyses reporting IBDQ as continuous outcome (Analyses 4.2 and 7.1) and in analyses measuring health-related quality of life using questionnaires other than IBDQ.
  - 3 included placebo-controlled trials evaluating anti-TNF alpha agents did not contribute to health-related quality of life dichotomous results in table above for following reasons:
    - Reinisch 2011 (n = 576) was a 3-armed trial that compared adalimumab (at two separate doses) vs. placebo at 8 weeks and reported IBDQ as continuous measure but for which outcome data was not extracted for review because no standard deviations were reported; the narrative description of results indicated that only the higher dose group had significantly improved IBDQ scores vs. placebo.
    - Probert 2003 (n = 81) compared infliximab vs. placebo at 8 weeks and reported IBDQ as continuous measure only; although its result was not significant on this outcome, its magnitude of effect was consistent with those of the larger trials included in the analysis of IBDQ as continuous measure at weeks 6 or 8, all of which showed a significant benefit (Analysis 7.1 – Rutgeerts 2005 [ACT 1 and ACT 2 combined]; Sandborn 2012; Sandborn 2014).
    - Sandborn 2014 (n = 504) compared golimumab vs. placebo at 8 weeks and reported IBDQ as continuous measure only, finding a significant benefit consistent with those of the larger trials included in the analysis of IBDQ as continuous measure at weeks 6 or 8.
  - Rituximab (an anti-CD20 antibody) was also included in this review but not found to be effective

LEMAITRE 2017
Lemaitre M, Kirchgesner J, Rudnichi A, Carrat F, Zureik M, Carbonnel F, Dray-Spira R. Association Between Use of Thiopurines or Tumor Necrosis Factor Antagonists Alone or in Combination and Risk of

Lymphoma in Patients With Inflammatory Bowel Disease. JAMA. 2017 Nov 7;318(17):1679-1686. PubMed

Relevant to FAQ6

- **Study design:** observational study
  - nationwide cohort study (based on French National Health Insurance database which include all medical prescriptions and hospital stays for IBD in France)
- **Population:** adults with inflammatory bowel disease
- **Intervention:** thiopurines and anti-TNF agents (infliximab or adalimumab) used alone or in combination
- **Comparison:** not exposed to either thiopurines or anti-TNF agents
  - for the evaluation of anti-TNF agents as an adjunct to thiopurines, thiopurines used alone was comparison group

- **Study inclusion criteria:** eligible patients were included from January 1, 2009 through December 31, 2013

- **Number of participants:** 189,289
- **Duration of follow-up:** median of 6.7 years (up until December 31, 2015)

- **Results and Certainty:**

Results:

Incidence of lymphoma based on exposure group

Unexposed to thiopurines or anti-TNF agents (838,611 person-years)		**Exposed to thiopurine monotherapy (129,743 person-years)**		**Exposed to anti-TNF monotherapy (77,229 person-years)**		**Exposed to combination therapy (14,753 person-years)**	
no. of events	incidence rate per 1,000 person-years (95% CI)	no. of events	incidence rate per 1,000 person-years (95% CI)	no. of events	incidence rate per 1,000 person-years (95% CI)	no. of events	incidence rate per 1,000 person-years (95% CI)
220	0.26 (0.23 to 0.29)	70	0.54 (0.41 to 0.67)	32	0.41 (0.27 to 0.55)	14	0.95 (0.45 to 1.45)

Adjusted hazard ratios (HRs) for lymphoma comparing exposure groups*†

Comparison	HR (95% CI)	Certainty
Exposed to thiopurine monotherapy vs unexposed to thiopurines or anti-TNF agents	2.60 (1.96 to 3.44)	Moderate (downgrade: observational design; upgrade: large magnitude of effect and no important concerns about risk of bias, imprecision, inconsistency, indirectness, or publication bias) [1]
Exposed to anti-TNF monotherapy vs unexposed to thiopurines or anti-TNF agents	2.41 (1.60 to 3.64)	Moderate (downgrade: observational design; upgrade: large magnitude of effect and no important concerns about risk of bias, imprecision, inconsistency, indirectness, or publication bias) [1]
Exposed to combination therapy vs unexposed to thiopurines or anti-TNF agents	6.11 (3.46 to 10.8)	Moderate (downgrade: observational design; upgrade: large magnitude of effect and no important concerns about risk of bias, imprecision, inconsistency, indirectness, or publication bias) [1]
Exposed to combination therapy vs exposed to thiopurine monotherapy	2.35 (1.31 to 4.22)	Moderate (downgrade: observational design; upgrade: large magnitude of effect and no important concerns about risk of bias, imprecision, inconsistency, indirectness, or publication bias) [1]

* Among patients exposed to anti-TNF agents, the risk of lymphoma did not statistically differ between adalimumab and infliximab

† Consistent effects found when restricting analysis to the first-line of IBD treatment, which thus considers only anti-TNF agents occurring in absence of previous exposure to thiopurines

[1] We upgraded our certainty due to the moderate to large magnitude of effect and no important concerns about risk of bias (beyond observational nature), directness, precision, or publication bias.

- **Other considerations:**
  - Because the events in Lemaitre 2017 were reported per person-years of follow-up rather than per number of people (see table "Incidence of lymphoma based on exposure group), we transformed these estimates into risks over 7 years for an individual person in the standard fashion (7 years was selected given the median follow-up was 6.7 years). Doing so yields the following results, which are no different if one uses a linear or exponential method:
    - unexposed to thiopurines or anti-TNF agents: 0.18%
    - exposed to thiopurine monotherapy: 0.38%
    - exposed to anti-TNF monotherapy: 0.29%
    - exposed to combination therapy: 0.66%
  - Our searches identified two other national cohort studies that compared risk of lymphoma in IBD patients who were users of anti-TNF agents vs. non-users but the

findings of each were too imprecise to modify the estimates from the Lemaitre 2017 study:

- Nyboe Andersen 2014 reported effects on multiple site-specific cancers, none of which showed a significant increase in risk and all of which had wide CIs; for the site-specific cancer of hematopoietic and lymphoid tissue the rate ratio was 0.90 (95% CI 0.42 to 1.91) (see summary for additional detail)
- Kobayashi 2019 reported effects on non-Hodgkin lymphoma as well as non-melanoma skin cancers, neither of which showed significant increase with anti-TNF agents:
    - for non-Hodgkin lymphoma, the incidence rate was 4.08 events per 100,000 person-years in patients exposed to anti-TNF agents and the incident rate ratio vs. unexposed patients was 0.97 (95% CI 0.42 to 1.90) (from Figure 2)
        - 103 cases of non-Hodgkin lymphoma were seen in 75,673 patients overall
            - 8 cases of non-Hodgkin lymphoma were seen in 6,062 patients receiving anti-TNF agents (without thiopurine) (Supplementary Table 3)
                - because of the small number of events and the wide CIs, we did not consider the results of Kobayashi 2019 to modify our interpretation of the effects reported in Lemaitre 2017
        - Supplementary Table 3 reports slightly different estimate (ie, 0.99, 95% CI 0.43 to 1.95 and Results text also reports point estimate as 0.99 [instead of 0.97])
    - for non-melanoma skin cancers, there were zero events so the incidence rate ratio was reported as 0

LOPEZ 2015

Lopez A, Ford AC, Colombel JF, Reinisch W, Sandborn WJ, Peyrin-Biroulet L. Efficacy of tumour necrosis factor antagonists on remission, colectomy and hospitalisations in ulcerative colitis: Meta-analysis of placebo-controlled trials. Dig Liver Dis. 2015 May;47(5):356-64. PubMed

Relevant to FAQ2, FAQ4, FAQ5, FAQ6

- **Study design:** systematic review of randomized trials
- **Population:** adults with moderate to severe ulcerative colitis who were either treatment-naive or previously exposed to anti-TNF agents
- **Intervention:** biologic therapy with anti-TNF agents (infliximab, adalimumab, golimumab)
- **Comparison:** placebo
- **Study inclusion criteria:**
    - phase 3 trials
- **Number of studies:** 6
- **Number of participants:** 3,654
- **Duration of follow-up:** 6-8 weeks for induction of remission; 52-54 weeks for remission maintenance, hospitalizations, colectomy

- **Results and Certainty:**

Effects of anti-TNF alpha agents (infliximab, adalimumab, golimumab) vs. placebo

Outcome	No. of patients (studies)	Risk ratio (95% CI)	Control group event rate (%)	Certainty (reason for downgrade)
induction of remission (at 6 to 8 weeks)	2,808 (5)	0.85 (95% CI 0.81 to 0.90) for non-remission	91.9% (1,964/2,138) for non-remission	Moderate (inconsistency)[1]
maintenance of remission (52 to 54 weeks)	858 (2)	0.85 (95% CI 0.74 to 0.98) for non-remission	88.8% (326/367) for non-remission	Moderate (imprecision)
ulcerative colitis-related hospitalizations (52 to 54 weeks)	1,691 (2)	0.71 (95% CI 0.56 to 0.90)	16.6% (121/727)	INVALID[2]
colectomy (52 to 54 weeks)	1,691 (2)	0.87 (95% CI 0.42 to 1.81)	6.5% (47/727)	INVALID[3]
malignancies	3,654 (6)	0.81 (95% CI 0.22 to 2.98)	NR	Low (serious imprecision)
serious infections	3,654 (6)	0.95 (95% CI 0.47 to 1.91)	NR	Low (serious imprecision)

NR not reported

[1] heterogeneity with one trial arm (lower-dose adalimumab) suggesting no effect

[2] Lopez 2015 included rates of 1 hospitalization rather than rates of any hospitalization in their extracted data so missed patients with 2 or more hospitalizations

[3] Lopez 2015 included "Feagan 2013" as data for colectomy rates with risk ratio 1.37 favoring placebo over adalimumab (963 patients), but Feagan 2014 (the appropriate citation) favors adalimumab over placebo

- Other considerations
    - Harm outcomes (ie, malignancies and serious infections) from Lopez 2015 were not progressed to Evidence Synthesis because we considered the Bonovas 2016 SRMA that combined randomized trials of UC and CD patients preferable to a source restricting to UC or CD patients only because (1) we would not expect the specific condition to modify the risk and (2) including trials in both patients with UC and patients with CD increases power to detect an increased risk. Although not progressed to Evidence Synthesis, its effect estimates for serious infection comparing anti-TNF alpha agents vs. placebo in patients with UC are consistent with those reported in patients with UC or CD from Bonovas 2016 (ie, RR 0.95, 95% CI 0.47 to 1.91 in analysis of 6 trials with 3,654 patients with UC in Lopez 2015; OR 0.90, 95% CI 0.69 to 1.17 in analysis of 34 trials with 9,831 patients with either UC or CD in Bonovas 2016).

LV 2014

Lv R, Qiao W, Wu Z, Wang Y, Dai S, Liu Q, Zheng X. Tumor necrosis factor alpha blocking agents as treatment for ulcerative colitis intolerant or refractory to conventional medical therapy: a meta-analysis. PLoS One. 2014 Jan 27;9(1):e86692. PubMed

Relevant to FAQ2, FAQ4

- **Study design:** systematic review of randomized trials
- **Population:** ulcerative colitis patients who had previously failed therapy of corticosteroids and/or immunosuppressive agents
- **Intervention:** anti-TNF alpha agents
- **Comparison:** placebo or other intervention

- **Study inclusion criteria:**
  - duration of follow-up ≥ 12 weeks after initial dose
  - ≥ 2 infusions of anti-TNF alpha agents
  - published in English

- **Number of studies:** 7
  - 3 placebo-controlled trials (ACT [Active Ulcerative Colitis Trial] 1, ACT 2, ULTRA 2)
  - 4 trials compared anti-TNF alpha agents vs. other intervention
    - 3 compared infliximab vs. corticosteroid
    - 1 compared infliximab vs. cyclosporine
- **Number of participants:** 1,922
  - 2,122 was total number of patients in all 7 trials as reported in abstract. However, it was not clear how this number was arrived at and it was only reported in the abstract. The numbers in 'Case (n)' column of Table 1 add up to 1,922.
- **Duration of follow-up:** not reported in Lv 2014; range from 30 weeks to 54 weeks across 3 placebo-controlled trials (ACT 1, ACT 2, ULTRA 2)

- **Results and Certainty**

Effects of anti-TNF alpha agents (infliximab or adalimumab) vs. placebo at longest follow-up (30 to 54 weeks)

Outcome	No. of patients (studies)	Risk ratio (95% CI)	Control group event rate (%)	Certainty (reason for downgrade)
clinical remission	1,222 (3)	2.29 (1.73 to 3.03)	11.02% (54/490)	High[1]
colectomy	728 (2)*	0.64 (0.43 to 0.97)	14.75% (36/244)†	Low (imprecision, inconsistency)[2,3]

* Two trials (ACT 1 and ACT 2) reported together as one via simple pooling (Sandborn 2009)
† Intervention group event rate in Sandborn 2009 was 9.5% (46/484)
[1] Lv 2014 reported risk of bias with unclear blinding and unclear allocation concealment in ULTRA 2 (Sandborn 2012) but our evaluation of the original trial found clear blinding and clear allocation concealment
[2] Lv 2014 reported risk of bias with unclear blinding in Sandborn 2009 but our evaluation of the original trial found clear blinding
[3] Lv 2014 reported Sandborn 2009 as if it were a single trial but Sandborn 2009 reports pooled estimates from ACT 1 and ACT 2 and the individual trials had discordant results

MAO 2017
Mao EJ, Hazlewood GS, Kaplan GG, Peyrin-Biroulet L, Ananthakrishnan AN. Systematic review with meta-analysis: comparative efficacy of immunosuppressants and biologics for reducing hospitalisation and surgery in Crohn's disease and ulcerative colitis. Aliment Pharmacol Ther. 2017 Jan;45(1):3-13. PubMed

Relevant to FAQ4, FAQ5

- **Study design:** systematic review of randomized trials
- **Population:** patients with Crohn's disease or ulcerative colitis
- **Intervention:** biological or immunomodulator therapy
- **Comparison:** placebo or other intervention

- **Study inclusion criteria:**
  - irritable bowel disease-related hospitalization and/or surgery reported as outcome

- **Number of studies:** 7
  - 2 in patients with ulcerative colitis, both placebo-controlled
    - Sandborn 2009 compared infliximab vs. placebo in anti-TNF naive patients
    - Feagan 2014 compared adalimumab vs. placebo in mix of anti-TNF naive and exposed patients
  - 5 in patients with Crohn's disease
- **Number of participants:** 1,691 (in 2 trials in ulcerative colitis)
- **Duration of follow-up:** 52 to 54 weeks

- **Results and Certainty:**

Effects of anti-TNF alpha agents (infliximab or adalimumab) vs. placebo on ulcerative colitis-related hospitalization and surgery

Outcome	No. of patients (studies)	Odds ratio (95% CI)	Control group event rate (%)*	Estimated intervention group event rate (%)	Certainty (reason for downgrade)
ulcerative colitis-related hospitalization	1,691 (4)	0.57 (95% CI 0.43 to 0.76)	25.4% (185/727)	16.3%	Moderate (inconsistency)[1]
ulcerative colitis-related surgery (colectomy)	1,691 (4)	0.69 (95% CI 0.49 to 0.97)	8.3% (60/727)	5.8%	Low (imprecision, inconsistency)[1]

* Calculated from Table 1; Mao 2017 also reports a "pooled proportion" for the control group for these outcomes (23% and 7%, respectively; pp 8 and 9), but it is not clear how these estimates are obtained, and they do not correspond to the numbers presented in Table 1.
1 Mao 2017 reported Sandborn 2009 as if it were a single trial but Sandborn 2009 reports pooled estimates from ACT 1 and ACT 2 and the individual trials had discordant results for colectomy, Sandborn 2009 did not report hospitalization outcomes by individual trial so consistency cannot be confirmed;

likewise, Mao 2017 reported Feagan 2014 as one trial, but Feagan 2014 pooled ULTRA 1 and ULTRA 2 trials

MOTOYA 2019

Motoya S, Watanabe K, Ogata H, et al. Vedolizumab in Japanese patients with ulcerative colitis: A Phase 3, randomized, double-blind, placebo-controlled study. PLoS One. 2019 Feb 26;14(2):e0212989. PubMed

Relevant to FAQ2

- **Study design:** randomized controlled trial
  - induction phase (10 weeks)
    - cohort 1 – 246 patients randomized to vedolizumab vs. placebo
    - cohort 2 – 46 patients received open-label vedolizumab
  - maintenance phase (60 weeks)
    - 83 patients in either induction cohort 1 or 2 who had clinical response to vedolizumab at week 10 were randomized to vedolizumab vs. placebo and followed for up to 60 weeks
- **Population:** adults with moderate to severe ulcerative colitis
  - TNF inhibitors were noted to have failed in approximately 50% of patients
- **Intervention:** vedolizumab
- **Comparison:** placebo

- **Duration of follow-up:** 60 weeks
- **Results and Certainty:**

Effects of vedolizumab vs. placebo on induction of remission at 10 weeks, maintenance of remission at 60 weeks, and estimated sustained maintenance of remission (at 10 weeks and at 60 weeks)

Time point	Rate with intervention	Control group event rate (% with remission)	Absolute difference (95% CI)	Certainty (reason for downgrade)
10 weeks	18.3% (30/164)	12.2% (10/82)	6.1% (-3.1% to 15.3%) (not significant)	Low (imprecision, indirectness)[1]
60 weeks (specific to induction responders)	56.1% (23/41)	31.0% (13/42)	25.1% (4.5% to 45.8%) (p = 0.021)	Low (indirectness)[1,2]
Estimated sustained maintenance of remission (at 10 weeks and at 60 weeks)	18.3% * 56.1% = 10.3%	12.2% * 31.0% = 3.8%	Estimated absolute rate increase 6.5%	Very low (extremely serious indirectness, imprecision) [1,3]

[1] This trial had a substantial proportion of patients with prior exposure to anti-TNF agents and thus constitutes a less direct match to the population of interest for this evidence report

[2] In maintenance of remission studies of vedolizumab, only induction responders were eligible and were re-randomized at beginning of maintenance study; the goal of studies using this design was to determine whether remission can be maintained among patients who had previously been treated with the agent and responded. This selective population is considered to less directly match patients who would be using the decision aid (presumably before starting the biologic agent) and would thus warrant a downgrade for indirectness if trying to apply this evidence to all-comers with ulcerative colitis. However, we specified the outcome is specific to induction responders to convey the group for whom we have higher certainty (i.e., the group for whom this indirectness downgrade would not apply), and the practical clinical reality is that if a patient does not show a response to induction therapy, s/he will not be maintained on the medication anyway.
[3] Indirectly derived and derivation uses estimates downgraded for indirectness based on the population and imprecision in estimates

NYBOE ANDERSEN 2014
Nyboe Andersen N, Pasternak B, Basit S, Andersson M, Svanström H, Caspersen S, Munkholm P, Hviid A, Jess T. Association between tumor necrosis factor-α antagonists and risk of cancer in patients with inflammatory bowel disease. JAMA. 2014 Jun 18;311(23):2406-13. PubMed

Relevant to FAQ6

- **Study design:** observational study
  - nationwide register-based cohort study in Denmark with propensity score adjustment to limit effects of confounding
- **Population:** patients in Denmark with inflammatory bowel disease aged 15 years or older
- **Intervention:** patients treated with anti-TNF agents
- **Comparison:** patients not treated with anti-TNF agents

- **Study inclusion criteria:** 1999 to 2012

- **Number of participants:** 56,146
  - 4,553 (8.1%) were exposed to anti-TNF agents

- **Duration of follow-up:** median of 3.7 years for patients exposed to anti-TNF agents after study entry
  - median of 9.3 years for overall study cohort

- **Results:**

Rate ratios for incident overall cancer and site-specific cancers (skin and hematopoietic/lymphoid tissue)* among patients with IBD exposed and unexposed to anti-TNF agents†

	anti-TNF exposed		anti-TNF unexposed				
	person-years	cases	person-years	cases	crude‡	adjusted§	adjusted¶
Total	18,440	81	469,874	3,465	1.07 (0.86 to 1.33)	1.25 (1.00 to 1.58)	1.07 (0.85 to 1.36)
Site-specific							
Hematopoietic and lymphoid tissue	18,440	8	469,874	260	1.36 (0.67 to 2.76)	1.06 (0.50 to 2.22)	0.90 (0.42 to 1.91)
Skin**	18,440	12	469,874	315	1.43 (0.80	1.45 (0.79	1.02 (0.55 to

					to 2.56)	to 2.67)	1.89)

* Article also reported rate ratios for multiple other site-specific cancers; none showed significant increase associated with anti-TNF exposure but all had wide CIs. Skin and hematopoietic/lymphoid tissue were selected for presentation in summary because their risks in IBD and the relation to medical treatment has been debated. Risk of hematopoietic/lymphoid tissue was also selected because another national cohort study in Denmark published later found a significant increase in lymphoma in patients using anti-TNF agents (Lemaitre 2017 – summarized above).
† Analyses were restricted to > 3 months following first anti-TNF agent exposure
‡ Adjusted for age
§ Adjusted for age, calendar year, disease duration, baseline propensity scores, and use of 5-aminosalicylates/sulphasalazine, local and systemic corticosteroids, and methotrexate/cyclosporine/cyclophosphamide
¶ Additionally adjusted for use of azathioprine. There was no evidence of an increased overall cancer risk associated with anti-TNF agent exposure in this model that also adjusted for azathioprine use, thus suggesting the (borderline) significant association observed among anti-TNF agent users in other adjusted model was almost fully explained by concomitant use of azathioprine (which has been associated with increased cancer risk in earlier research summarized in Discussion).
** Excludes basel cell carcinomas

- **Certainty:**
  - *overall cancer* – Very low certainty
    - Downgrades
      - observational study design
      - indirectness
        - median follow-up of 3.7 years cannot detect whether there is an increased risk of malignancy in the long term
        - overall cancer measure can obscure risks if increase in cancers of any specific sites
      - imprecision
  - *site-specific cancers* - Very low certainty
    - Downgrades
      - observational study design
      - indirectness
        - median follow-up of 3.7 years cannot detect whether there is an increased risk of malignancy in the long term
      - imprecision
        - imprecision was very serious – rate ratio 95% CI upper limit was close to or greater than 2 for all cancer sites

NYBOE ANDERSEN 2015
Nyboe Andersen N, Pasternak B, Friis-Møller N, Andersson M, Jess T. Association between tumour necrosis factor-α inhibitors and risk of serious infections in people with inflammatory bowel disease: nationwide Danish cohort study. BMJ. 2015 Jun 5;350:h2809. PubMed

Relevant to FAQ6

- **Study design:** observational study
  - nationwide register-based propensity score-matched cohort study (based on database which includes data on the entire Danish population with inflammatory bowel disease)
- **Population:** patients in Denmark with inflammatory bowel disease
  - background cohort eligible for matching consisted of 52,392 IBD patients aged 15 to 75 years, of whom 4300 were treated with TNF-α inhibitors
- **Intervention:** patients treated with anti-TNF agents (including infliximab, adalimumab, and certolizumab pegol)
- **Comparison:** patients not treated with anti-TNF agents

- **Study inclusion criteria:** 2002 to 2012

- **Number of participants:** 3,086 propensity-score matched patients
  - 1,543 treated with anti-TNF agents
  - 1,543 not treated with anti-TNF agents
- **Duration of follow-up:** 365 days

- **Results:**

Hazard ratios for any serious infection (defined as diagnosis of infection associated with hospital admission) in users of anti-TNF agents compared with propensity score-matched non-users within 90 days and 365 days risk periods*

Risk period	Users of anti-TNF agents			Non-users of anti-TNF agents			Hazard ratio (95% CI)	Certainty
	No. of patients	No. of events	incidence rate per 1,000 person-years (95% CI)	No. of patients	No. of events	incidence rate per 1,000 person-years (95% CI)		
90 days	1,543	51	140 (110 to 180)	1,543	33	90 (60 to 130)	1.63 (1.01 to 2.63)	Moderate (downgrade: observational study; upgrade: consistent with risk pattern in other populations, and no evidence of confounding by indication)[1]
365 days†	1,543	107	80 (70 to 100)	1,543	78	60 (50 to 70)	1.27 (0.92 to 1.75)	Low (downgrades: observational study, imprecision; upgrade: consistent with risk pattern in other populations, and no evidence of confounding by indication)[1]

* Risk estimates were also adjusted for baseline use of azathioprine and oral corticosteroids (these variables were not included in the propensity score).
† Hazard ratios of site-specific serious infections were obtained only for the 365 days risk period and on analyses of site-specific infections, the HR was > 2 for several of the subgroups but only showed statistically significant increase for skin and soft tissue infections (HR 2.51, 95% CI 1.23 to 5.12).
[1] We have upgraded the Certainty for two reasons: First, we believe that the increase in serious infection in users of anti-TNF agents in patients with rheumatoid arthritis supports that these agents may similarly increase serious infection risk in patients with IBD (ie, authors reported in their Introduction section that "Studies assessing the risk of serious infections in people treated with TNF-α inhibitors for rheumatoid arthritis have gradually revealed a largely coherent pattern of a moderately increased risk of serious infections in the initial phase of treatment and a subsequent decline in risk."). Second, a supplementary analysis with an active comparator drug as control (ie, azathioprine) found no evidence of confounding by indication (see table below in this summary).

Hazard ratios for any serious infection in patients who started anti-TNF agents compared with patients who started azathioprine*

Risk period	Users of anti-TNF agents		Users of azathioprine		Hazard ratio (95% CI)
	No. of	No. of	No. of	No. of	

	patients	events	patients	events	
90 days	268	12	268	7	2.17 (0.85 to 5.52)
365 days	268	18	268	11	2.05 (0.97 to 4.36)

* Analyses only included patients who started monotherapy with the respective drug and had no history of use of the other drug—that is, patients starting anti-TNF agents had no history of azathioprine use and vice versa. These supplementary analyses with an active comparator drug as control were done to test for confounding by indication.

PASCHOS 2018

Paschos P, Katsoula A, Salanti G, Giouleme O, Athanasiadou E, Tsapas A. Systematic review with network meta-analysis: the impact of medical interventions for moderate-to-severe ulcerative colitis on health-related quality of life. Aliment Pharmacol Ther. 2018 Dec;48(11-12):1174-1185. PubMed

Relevant to FAQ3

This systematic review does not provide substantially different results from the Cochrane review (LeBlanc 2015) and does not provide absolute effect estimates so was not appraised further.

RUTGEERTS 2005

Rutgeerts P, Sandborn WJ, Feagan BG, Reinisch W, Olson A, Johanns J, Travers S, Rachmilewitz D, Hanauer SB, Lichtenstein GR, de Villiers WJ, Present D, Sands BE, Colombel JF. Infliximab for induction and maintenance therapy for ulcerative colitis. N Engl J Med. 2005 Dec 8;353(23):2462-76. PubMed

Relevant to FAQ2

- **Study design:** 2 randomized, double-blind, placebo-controlled trials (ACT 1 and ACT 2)
    - study infusions prematurely discontinued at substantially higher rate in placebo group vs. either intervention group
        - more than twice as many discontinuations in placebo group vs. each of the other 2 groups in ACT 2
        - treatment was treated as having failed in patients who discontinued, so we did not consider the between group differences in discontinuations an important risk of bias
    - only design differences between ACT 1 and ACT 2 were duration of follow-up (see below) and specification of concurrent therapy that had to be insufficiently controlling the patient's UC (assessed by the Mayo Score and endoscopic disease activity) to be eligible for enrollment (corticosteroids alone or in combination with azathioprine or mercaptopurine in ACT 1, corticosteroids alone or in combination with azathioprine or mercaptopurine and medications with 5-ASA compounds in ACT 2)
- **Population:** adults with moderate-to-severe active ulcerative colitis not responding adequately to the aforementioned therapies
- **Intervention:** infliximab – 2 arms
    - 5 mg per kilogram of body weight
    - 10 mg per kilogram of body weight
- **Comparison:** placebo

- **Number of studies:** 2
- **Number of participants:** 364 patients randomized in each of 2 trials for a combined total of 728 patients

- **Duration of follow-up:**
  - 54 weeks in ACT 1
  - 30 weeks in ACT 2

Proportion of patients with clinical remission, infliximab vs. placebo

Trial	Time point	Infliximab group event rate		Placebo group event rate	Absolute difference (vs. placebo)		Certainty (reason for downgrade)
		5 mg	10 mg		5 mg	10 mg	
ACT 1	8 weeks	38.8% (47/121)	32% (39/122)	14.9% (18/121)	23.9% p < 0.001	17.1% p = 0.002	High
	30 weeks	33.9% (41/121)	36.9% (45/122)	15.7% (19/121)	18.2% p = 0.001	21.2% p < 0.001	High
	54 weeks	34.7% (42/121)	34.4% (42/122)	16.5% (20/121)	18.2% p = 0.001	17.9% p = 0.001	High
	clinical remission at 8 and 30 weeks	23.1%	26.2%	8.3%	14.8% p = 0.001	17.9% p < 0.001	High
	clinical remission at 8, 30, and 54 weeks	19.8%	20.5%	6.6%	13.2% p = 0.002	13.9% p = 0.002	High
ACT 2	8 weeks	33.9% (41/121)	27.5% (33/120)	5.7% (7/123)	28.2% p < 0.001	21.8% p < 0.001	High
	30 weeks	25.6% (31/121)	35.8% (43/120)	10.6% (13/123)	15.0% p = 0.003	25.2% p < 0.001	High
	clinical remission at 8 weeks and 30 weeks	14.9%	22.5%	2.4%	12.5% p < 0.001	20.1% p < 0.001	High

SANDBORN 2009

Sandborn WJ, Rutgeerts P, Feagan BG, Reinisch W, Olson A, Johanns J, Lu J, Horgan K, Rachmilewitz D, Hanauer SB, Lichtenstein GR, de Villiers WJ, Present D, Sands BE, Colombel JF. Colectomy rate comparison after treatment of ulcerative colitis with placebo or infliximab. Gastroenterology. 2009 Oct;137(4):1250-60. PubMed

Relevant to FAQ4, FAQ5

- **Study design:** 2 randomized controlled trials
- **Study design:** pooled results of 2 randomized trials ACT-1 and ACT-2
  - ACT-1
    - 54-week, double-blind, placebo-controlled trial of infliximab
  - ACT-2
    - 30-week, double-blind, placebo-controlled trial of infliximab
    - starting at week 30, patients who completed ACT-2 and were judged by investigator to benefit from continued treatment were eligible to continue the same blinded treatment in study extension through week 54
- **Population:** adults with moderate to severe ulcerative colitis

- **Intervention:** infliximab
- **Comparison:** placebo

- **Number of studies:** 2
- **Number of participants:** 728
- **Duration of follow-up:** 54 weeks
    - 87% (630/728) of randomized patients had complete colectomy follow-up data through 54 weeks

- **Results and Certainty:**

Infliximab vs. placebo on ulcerative colitis-related hospitalization and colectomy through 54 weeks

Outcome	Proportion with outcome (Number/Total)		P-value comparing groups	Hazard ratio (95% CI)	Certainty
	infliximab	placebo			
colectomy (ACT-1 plus ACT-2)	9.5% (46/484)	14.8% (36/244)	0.02	0.59 (95% CI 0.38 to 0.91)	Low (imprecision, inconsistency)[1,2]
colectomy (ACT-1)	10.3%	10.7%	> 0.05	0.89 (95% CI 0.46 to 1.75)	
colectomy (ACT-2)	8.7%	18.7%	< 0.05	0.41 (95% CI 0.23 to 0.75)	
ulcerative colitis-related hospitalization (ACT-1 plus ACT-2)	15.7% (76/484)	24.6% (60/244)	0.03	NR	Moderate (inconsistency)[3]

1 Certainty downgraded for inconsistency because of different results in ACT-1 and ACT-2; only ACT-2 showed a significant benefit and interaction p-value comparing results in ACT-1 and ACT-2 was borderline significant (p = 0.09).
2 Although the upper bound of the 95% CI for the relative effect estimate is < 1, assessment of (im)precision should be based on absolute rather than relative effects. Accordingly, the 95% CI for the absolute risk difference from the simple pooling of the data from the ACT 1 and ACT 2 trials (in accordance with Sandborn 2009's approach, which in turn serves as the source for Lv 2014's estimate [see corresponding summary for Lv 2014]) is compatible with an absolute risk difference as small as 0.36%. Accordingly, we assign a downgrade for imprecision to this estimate.
3 Certainty downgraded because of inability to assess consistency between ACT-1 and ACT-2 because only pooled results of ACT-1 and ACT-2 were reported and because of concern about inconsistency based on the colectomy results and the correlation between the two outcomes.

SANDBORN 2012
Sandborn WJ, van Assche G, Reinisch W, Colombel JF, D'Haens G, Wolf DC, Kron M, Tighe MB, Lazar A, Thakkar RB. Adalimumab induces and maintains clinical remission in patients with moderate-to-severe ulcerative colitis. Gastroenterology. 2012 Feb;142(2):257-65.e1-3. PubMed

Relevant to FAQ2

- **Study design:** randomized placebo-controlled induction and maintenance trial (ULTRA 2)
    - starting at week 12, patients who met criteria for inadequate response could be switched to open-label adalimumab
    - Lv 2014 reported risk of bias with unclear blinding and unclear allocation concealment in ULTRA 2
        - it is uncertain why Lv 2014 assessed blinding as unclear because the trial reported using a double-blind, placebo-controlled method for at least the first 12 weeks, but it may have been because Sandborn 2012 permitted patients to switch to open-label adalimumab starting at week 12
        - it is uncertain why Lv 2014 assessed allocation concealment as unclear because Sandborn 2012 reported that "randomization was performed centrally" in their multi-center trial
- **Population:** adults with moderate to severe active ulcerative colitis
    - 75% were currently receiving steroids and/or azathioprine/6-mercaptopurine
        - remaining 25% had previously failed and discontinued one or both of these agents
    - 40% had previously received and discontinued an anti-TNF agent
- **Intervention:** adalimumab
- **Comparison:** placebo

- **Number of studies:** 1
- **Number of participants:** 494
    - total 518 randomized (260 to placebo, 258 to adalimumab) but 24 excluded for site noncompliance (14 in placebo group, 10 in adalimumab group)
- **Duration of follow-up:** 52 weeks

- **Results and Certainty**

Effects of adalimumab vs. placebo on clinical remission at week 8 and at week 52, and on clinical remission at both week 8 and week 52

Time point	Estimated rate with adalimumab (% with remission)	Estimated rate with placebo (% with remission)	Absolute difference (95% CI); p-value	Certainty (reason for downgrade)
8 weeks	16.5%	9.3%	7.2% (95% CI 1.2% to 12.9%); p = 0.019	Moderate (imprecision)
52 weeks	17.3%	8.5%	8.8% (2.8% to 14.5%); p = 0.004	Moderate (imprecision)
clinical remission at 8 weeks and 52 weeks	8.5% (21/248)	4.1% (10/246)	4.4% (0.1% to 8.9%)*; p = 0.047	Moderate (imprecision)

* EBSCO Information Services calculated this confidence interval (it is not reported by Sandborn 2012).

SANDBORN 2014
Sandborn WJ, Feagan BG, Marano C, et al; PURSUIT-Maintenance Study Group. Subcutaneous golimumab maintains clinical response in patients with moderate-to-severe ulcerative colitis. Gastroenterology. 2014 Jan;146(1):96-109.e1. PubMed

Relevant to FAQ2

- **Study design:** randomized controlled maintenance trial
  - (PURSUIT M) 464 patients who had response to golimumab in induction trial (reported separately – PURSUIT – SC trial) were randomized to golimumab vs. placebo for up to 52 weeks
  - "treatment failure rules were applied" for analysis, in which patients were considered treatment failures if they did not achieve the respective endpoint because of, for example, discontinuation due to lack of therapeutic effect or missing data
  - on loss of response during maintenance trial, patients were eligible for dose adjustment as follows
    - placebo patients received 100 mg golimumab every 4 weeks
      - treatment was recorded as failing for these patients, and they were effectively censored at that time (but they still contributed to the denominator, consistent with the principles of intent-to-treat analysis)
    - 50 mg golimumab patients were rerandomized to 50 mg or 100 mg golimumab every 4 weeks
    - 100 mg golimumab patients were initially re-randomized to receive 100 mg or 200 mg every 4 weeks
      - following protocol amendment, dose adjustment to 200 mg was discontinued and patients initially randomized to 100 mg continued to receive 100 mg, and patients who already had their dose increased to golimumab 200 mg were decreased to golimumab 100 mg

- **Population:** adults with moderate to severe active ulcerative colitis
- **Intervention:** golimumab
- **Comparison:** placebo

- **Number of studies:** 1
- **Number of participants:** 464
- **Duration of follow-up:** up to 54 weeks

- **Results and Certainty**

Effects of golimumab (50 mg and 100 mg) vs. placebo on clinical remission at week 30, week 54, and both week 30 and week 54

Time point	Estimated rate with golimumab (% with remission)		Estimated rate with placebo (% with remission)	p-value vs. placebo		Certainty (reason for downgrade)*
	50 mg	100 mg		50 mg	100 mg	
week 30	35.9%	40.9%	22.4% (35/156)	0.009	< 0.001	High

	(55/153)	(63/154)				
week 54	33.3% (51/153)	34.4% (53/154)	22.4% (35/156)	0.071	0.010	50 mg: Moderate (imprecision) 100 mg: Moderate (imprecision)[1]
at both week 30 and week 54	23.5% (36/153)	28.6% (44/154)	15.4% (24/156)	0.091	0.003	50 mg: Moderate (imprecision) 100 mg: High

* Those who responded in the induction trial who were receiving placebo in the maintenance trial could be switched to golimumab if they lost remission. However, if this occurred, the therapy was counted as a failure for that patient and the patient was effectively censored at that time (though s/he still contributed to the denominator, consistent with the principle of intent-to-treat analysis). Therefore, we do not consider this design to introduce bias.
1 Lower bound of the calculated 95% CI for the absolute risk difference is 1.9% (upper bound is 21.7%)

SANDS 2019
Sands BE, Sandborn WJ, Panaccione R, et al; UNIFI Study Group. Ustekinumab as induction and maintenance therapy for ulcerative colitis. N Engl J Med. 2019 Sep 26;381(13):1201-1214. PubMed

Relevant to FAQ2

- **Study design:** 2 randomized controlled trials
  - induction trial (8 weeks)
    - 961 patients randomized to ustekinumab at set dose (130 mg) vs. ustekinumab at dose based on body weight vs. placebo
      - the two ustekinumab arms had nearly identical results for clinical remission (15.6% for set dose and 15.5% for dose based on body weight) and were pooled for reporting in table below; we also pool results for all other outcomes other than infectious outcomes
  - maintenance phase (44 weeks)
    - 523 patients who had response to ustekinumab at week 8 in induction trial were randomized to ustekinumab every 8 weeks (n = 176) vs. ustekinumab every 12 weeks (n = 172) vs. placebo (n = 175)
      - because adult dosing of ustekinumab is every 8 weeks, we limit to the results from this trial arm
- **Population:** patients with moderate to severe ulcerative colitis
  - 51% of randomized patients had previous treatment failure with biologic agents
- **Intervention:** ustekinumab
- **Comparison:** placebo

- **Duration of follow-up:** 52 weeks total, with 8 weeks for induction phase and 44 weeks for maintenance phase

- **Results and Certainty:**

Effects of ustekinumab vs. placebo on induction of remission at 8 weeks, maintenance of remission at 44 weeks, and estimated sustained maintenance of remission (at 8 weeks and at 44 weeks)

Time point	Rate with ustekinumab	Placebo group event rate	Absolute difference (95% CI)	Certainty (reason for downgrade)
8 weeks (induction)	15.6% (100/642)	5.3% (17/319)	10.3% (p < 0.001)*	High
44 weeks after re-randomization of induction responders (maintenance of remission at 52 weeks among induction responders)	43.8% (77/176)	24.0% (42/175)	19.8% (p < 0.001)	High[1]
Estimated sustained maintenance of remission (at 8 weeks and at 44 weeks)	15.6% * 43.8% = 6.83%	5.3% * 24.0% = 1.27%	5.56%	Low (very serious indirectness)[2]

* Effects of each arm vs. placebo was reported as p < 0.001. The two arms had nearly identical 8-week clinical remission results and therefore we combined them for the comparison vs. placebo. Although the p-value for this comparison was not reported or calculated, it would be expected to also be < 0.001.

[1] In maintenance of remission studies of ustekinumab, only induction responders were eligible and were re-randomized at beginning of maintenance study; the goal of studies using this design was to determine whether remission can be maintained among patients who had previously been treated with the agent and responded. This selective population is considered to less directly match patients who would be using the decision aid (presumably before starting the biologic agent) and would thus warrant a downgrade for indirectness if trying to apply this evidence to all-comers with ulcerative colitis. However, we specified the outcome is specific to induction responders to convey the group for whom we have higher certainty (i.e., the group for whom this indirectness downgrade would not apply), and the practical clinical reality is that if a patient does not show a response to induction therapy, s/he will not be maintained on the medication anyway.

[2] Indirectly derived and derivation uses estimates downgraded for indirectness based on the population

Effects of ustekinumab vs. placebo on quality of life assessed by IBDQ (range of 32 to 224, with higher scores being better) (Sands 2019)

Time point	Mean (SD, n) in ustekinumab group	Mean (SD, n) in placebo group	Mean difference (95% CI)*	Certainty (reason for downgrade)
Score at 8 weeks (induction)	160.6 (36.4, 641)	143.5 (39.96, 319)	17.1 (12.0 to 22.2)	Moderate (imprecision)[1]
8-week change from induction baseline	34.2 (32.18, 637)	16.1 (31.39, 317)	NA	Moderate (imprecision)[1]
Score at 44 weeks after	175.3 (37.09, 348)	159.3 (40.67, 174)	16 (9 to 23)	Moderate

re-rerandomization of induction responders (maintenance therapy among induction responders)				(imprecision)[1,2]
44-week change from maintenance baseline among induction responders	0.5 (32.36, 346)	-15.1 (35.43, 173)	NA	Moderate (imprecision)[1,2]

* Calculated by EBSCO Information Services, as Sands 2019 only reports mean (SD) at baseline and different follow-up points, along with change from baseline.
1 Although not addressed by Sands 2019, the lower boundary for a clinically meaningful difference in IBDQ is noted elsewhere (LeBlanc 2015) as 15 to 16 points, with most sources citing 16 points.
2 This estimate is limited to patients who were induction responders. This selective population is considered to less directly match patients who would be using the decision aid (presumably before starting the biologic agent) and would thus warrant a downgrade for indirectness if trying to apply this evidence to all-comers with ulcerative colitis. However, we specified the outcome is specific to induction responders to convey the group for whom we have higher certainty (i.e., the group for whom this indirectness downgrade would not apply), and the practical clinical reality is that if a patient does not show a response to induction therapy, s/he will not be maintained on the medication anyway..

Effects of ustekinumab vs. placebo on UC-related surgery and hospitalization

Time point	Rate with ustekinumab	Placebo group event rate	Relative risk (95% CI)*	Absolute risk difference (95% CI)*	Certainty (reason for downgrade)
UC-related hospitalization					
8 weeks (induction)	1.1% (7/642)	4.4% (14/319)	0.25 (0.10 to 0.61)	-3.3% (-1.2% to -6.2%)	Moderate (imprecision)
44 weeks after re-randomization (maintenance)	2.0% (7/348)	5.7% (10/175)	0.35 (0.14 to 0.91)	-3.7% (-0.4% to -8.3%)	Moderate (imprecision)
UC-related surgery†					
8 weeks (induction)	0% (0/642)	0.6% (2/319)	Insufficient data	Not calculated	Very low (extremely serious imprecision)
44 weeks after re-randomization (maintenance)	0.6% (2/348)	1.7% (3/175)	0.34 (0.06 to 1.99)	Not calculated	Very low (extremely serious imprecision)

* Calculated by EBSCO Information Services; Sands 2019 only reports proportion and number with event
† Based on these data, one could also estimate a 52-week rate of UC-related surgery in the placebo group of 0.6% + 1.7% = 2.3%. Additionally, the estimate of 2.3% is for UC-related surgery whereas evidence for other biologic agents (e.g., the anti-TNF agents) is specific to colectomy. Although the outcome of UC-related surgery may include surgeries other than colectomy, the expected effect of this would be to possibly increase the estimated risk for that outcome (as opposed to an outcome focused solely on colectomy). However, the 2.3% estimate for ustekinumab may also underestimate the rate of

UC-related surgery in the control group, as the 1.7% estimate (which is then added to the 0.6% estimate to yield 2.3%) comes from a population who showed an induction response to ustekinumab, and these patients may be healthier or have less severe UC. Given the estimate of 2.3% is serving as the lower bound of the range of control group risks we use in Evidence Synthesis (further discussed in Evidence Synthesis), we feel it is reasonable to use this estimate.

Effects of ustekinumab on infection outcomes* in patients with UC (Sands 2019 – maintenance trial randomized population)

Outcome	Placebo (N = 175)	ustekinumab, 90 mg/12 week (N = 172)	ustekinumab, 90 mg/8 week (N = 176)	Certainty (reason for downgrade)
serious infections	2.3% (4/175)	3.5% (6/172)	1.7% (3/176)	Very low (very serious risk of bias, very serious imprecision) [1,2]
any infection	46.3% (81/175)	33.7% (58/172)	48.9% (86/176)	Very low (very serious risk of bias, imprecision)[1]

* Authors reported that 4 patients who received ustekinumab presented with potential opportunistic infections, in 3 patients during maintenance trial and 1 patient during induction trial. However, because of the trial design and the fact that all patients in the maintenance phase had responded to ustekinumab during induction trial, it was not possible to compare the risk of opportunistic infection in patients receiving ustekinumab vs. no ustekinumab. In addition, it was not always clear whether patients who had an opportunistic infection during maintenance trial were assigned to placebo or ustekinumab during maintenance trial. For example, as described on pg 44 of Supplement, an opportunistic infection of Legionella pneumonia was reported for a patient in the placebo → 6 mg/kg induction group who was subsequently randomized for inclusion in the maintenance trial but it was not stated if the patient was randomized to intervention or placebo for maintenance trial.

1 Certainty double downgraded for risk of bias because of very serious concern about selective outcome reporting which may result in the reported estimates underestimating the true risk of the intervention based on the substantial evidence that harms are assessed inconsistently and reported inadequately in randomized trials, particularly those sponsored by pharmaceutical companies.

2 Certainty double downgraded for imprecision because the 95% CI for difference in risk ranged from a 3% higher risk in serious infections to a 3% lower risk with ustekinumab. (Not reported in article and calculated by EBSCO Information Services.)

- Outcomes not progressed to Evidence Synthesis:
    - "any infections" because it would be highly influenced by upper respiratory tract infections, colds etc., and also because it would combine events due to such minor nuisances together with more serious infections, resulting in an uninformative composite estimate
    - "serious infections" because the estimates were of Very low certainty and considered uninformative

SANDS 2019V

Sands BE, Pevrin-Biroulet L, Loftus EV Jr, et al; VARSITY Study Group. Vedolizumab versus Adalimumab for Moderate-to-Severe Ulcerative Colitis. N Engl J Med. 2019 Sep 26;381(13):1215-1226. PubMed

Relevant to FAQ2

- **Study design:** randomized controlled trial
  - double-blind, double-dummy design
  - missing values for remission and other binary outcomes were imputed as nonresponses
- **Population:** adults with moderately to severely active ulcerative colitis
- **Intervention:** vedolizumab
- **Comparison:** adalimumab

- **Study inclusion criteria:** previous exposure to tumor necrosis factor inhibitor other than adalimumab allowed in ≤ 25% of patients

- **Number of participants:** 769
  - number of patients who were randomized and received ≥ 1 dose of vedolizumab or adalimumab
- **Duration of follow-up:** 52 weeks
  - for clinical remission
- **Results and Certainty**

Effects of vedolizumab vs. adalimumab on clinical remission at week 14 and at week 52, and on clinical remission at both week 14 and week 52

Time point	Estimated rate with vedolizumab (% with remission)	Estimated rate with adalimumab (% with remission)	Absolute difference (95% CI)	Certainty (reason for downgrade)
14 weeks	26.6% (102/383)	21.2% (82/386)	5.3% (-0.7% to 11.4%)	Moderate (Imprecision)
52 weeks	31.3% (120/383)	22.5% (87/386)	8.8% (2.5% to 15.0%)	Moderate (Imprecision)
clinical remission at 14 weeks and 52 weeks*	18.3% (70/383)	11.9% (46/386)	6.3% (1.3% to 11.3%)	Moderate (Imprecision)

* Defined in publication as “durable clinical remission”

Sands 2019V also report on UC-related bowel resections and hospitalizations during the 52-week trial. For UC-related bowel resections, there were 0 events in the vedolizumab group (n = 383) and 3 events in the adalimumab group (n = 386; 0.78%). For UC-related hospitalizations, rates were 3.9% (15/383) vs. 5.2% (20/386) for vedolizumab vs. adalimumab, respectively; although no comparative statistics are provided for these data, we calculate the relative risk and absolute risk difference as 0.76 (95% CI 0.39 to 1.45) and -1.3% (95% CI -4.4% to 1.8%), respectively.

SCHREIBER 2018

Schreiber S, Dignass A, Peyrin-Biroulet L, Hather G, Demuth D, Mosli M, Curtis R, Khalid JM, Loftus EV Jr. Systematic review with meta-analysis: real-world effectiveness and safety of vedolizumab in patients with inflammatory bowel disease. J Gastroenterol. 2018 Sep;53(9):1048-1064. doi: 10.1007/s00535-018-1480-0. Epub 2018 Jun 4. PubMed

Relevant to FAQ6

We prepared a brief summary of this systematic review for its possible contribution to the safety of vedolizumab. It also reports on efficacy outcomes, but given it uses observational data for these outcomes, we do not consider any of its efficacy outcomes.

Over a follow-up period of 2 weeks to 12 months, 46 studies in patients with CD, UC, or unspecified IBD reported a safety outcome of some kind (total N not reported). However, many of these studies only contributed to outcomes we consider too broad to be meaningful (e.g., "overall adverse events"), and we do not consider such outcomes in this evidence report.

The authors also report a range for infections and serious infections based on 12 and 3 studies totaling 1,176 and 832 patients, respectively. For infections, the range is 5 to 24%, and for serious infections, the range is 4 to 10%. However, much as with an outcome like "overall adverse events", the outcome of any infection is not as meaningful as serious infection, especially in the absence of a control / placebo group risk, which this study does not provide. Therefore, we only progress the outcome of serious infection for further consideration in Evidence Synthesis. We consider the range for serious infection to have Moderate certainty as a univariate estimate (downgrade due to insufficient data to assess risk of bias) and insufficient for any consideration about how vedolizumab might compare to a control / placebo group (these data are not sufficient for any such claim).

SINGH 2018
Singh S, Fumery M, Sandborn WJ, Murad MH. Systematic review with network meta-analysis: first- and second-line pharmacotherapy for moderate-severe ulcerative colitis. Aliment Pharmacol Ther. 2018 Jan;47(2):162-175. PubMed

Relevant to FAQ2, FAQ6

- **Study design:** systematic review of randomized trials
- **Population:** adults with moderate to severe ulcerative colitis who were either treatment-naive or previously exposed to anti-TNF agents
- **Intervention:** anti-TNF agents (adalimumab, golimumab, infliximab), anti-integrin agents (vedolizumab), and small molecules like janus kinase inhibitors (tofacitinib)
- **Comparison:** placebo, biologic agent, small molecule

- **Study inclusion criteria:**
  - phase 2 trials (in addition to phase 3 trials) were eligible
  - duration $\geq$ 14 days
  - authors excluded trials of novel agents in development with only phase II randomized trial data (without phase III data) including etrolizumab or ozanimod

- **Number of studies:** 14
  - 12 in treatment-naive patients
  - 4 in patients previously exposed to anti-TNF agents (each was subgroup analysis)
- **Number of participants:** 4,212
- **Duration of follow-up:** 6-8 weeks for induction of remission

- **Results and Certainty:**

Effects of intervention vs. placebo on induction of remission (6 to 8 weeks)

Agent	No. of patients (studies)	Odds ratio (95% CI)	Control group event rate (%)	Certainty (reason for downgrade)
adalimumab	741 (3)	1.80 (1.18 to 2.76)	10.5% (39/371)	Moderate (inconsistency) [1]
infliximab	667 (4)	4.22 (2.80 to 6.35)	11.7% (39/334)	High
golimumab	644 (2)	2.81 (1.69 to 4.69)	7.2% (23/320)	High
tofacitinib	520 (2)	2.17 (1.16 to 4.06)	12.6% (13/103)	High
vedolizumab	206 (1)	4.26 (1.58 to 11.52)	6.6% (5/76)	High

[1] heterogeneity with one trial (Suzuki 2014) suggesting no effect

- **Outcomes with limited reporting in the primary article:**
  - Maintenance of remission
    - In patients initially randomized for induction therapy - adalimumab and infliximab reported to be superior to placebo and comparable to each other
    - In induction responders - vedolizumab, tofacitinib and golimumab were superior to placebo and comparable to each other
  - Serious infections
    - median rate of serious infections in induction trials with active intervention was reported to be 1.3% (interquartile range, 0.3% to 2.1%)
    - range of serious infection rates (or single rate when only 1 study available)
      - with TNF inhibitors
        - infliximab: 0% in NCT01551290 to 2.5% in ACT 1 trial
        - adalimumab: 1.6% in ULTRA 2 to 4.5% in Suzuki 2014
        - golimumab: 3.2% in PURSUIT-M
      - with vedolizumab: 2.5% in GEMINI 1
- Other considerations
  - Serious infections outcome from Singh 2018 were not progressed to Evidence Synthesis because we considered the Bonovas 2016 SRMA that combined randomized trials of UC and CD patients preferable to a source restricting to UC or CD patients only because (1) we would not expect the specific condition to modify the risk (supported by consistency in results for serious infection outcome between Lopez 2015 [which limited to UC patients] and Bonovas 2016) and (2) including trials in both patients with UC and patients with CD increases power to detect an increase in risk. Additionally, Singh 2018 reported the serious infection outcome in a way that was not useful for our purposes (eg, no comparison vs. placebo, with only univariate risks reported for specific agents rather than comparative estimates reported for anti-TNF alpha agents as a class).

Evidence report for biologics in ulcerative colitis

Reference list

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