Evidence report for biologics in Crohn's disease

Prepared by EBSCO Health Innovations and EBM Development Department:

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

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

Eric Manheimer, PhD, EBM Editor

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Evidence report for biologics in Crohn's disease

Scoping

Prepared by EBSCO Information Services

December 17, 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

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

CD – Crohn's disease/Crohn disease/Morbus Crohn
EQ-5D – EuroQol 5 Dimensions (a quality of life scale)
IBDQ – Inflammatory Bowel Disease Questionnaire (a disease-specific quality of life scale)
IL – interleukin
QoL/QOL – quality of life
SF-36 – 36-Item Short Form Survey (a quality of life scale)
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 Crohn's disease/Morbus Crohn (CD) has not responded well to standard treatment (such as corticosteroids for induction of remission) or specific non-biologic treatments (such as immunosuppressants / immunomodulators like azathioprine / 6-mercaptopurine, or methotrexate for maintenance of remission), 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, it appears systematic reviews of RCTs investigating ustekinumab in CD may not consider the use of ustekinumab for induction of remission, but rather, only maintenance of remission. For instance, the very recent Cochrane review (Davies 2019) only considers patients with quiescent CD, and accordingly, only assesses maintenance of remission. However, this focus omits evidence pertaining to the use of ustekinumab for induction of remission, as was studied in the UNITI-IM-UNITI (Feagan 2016) and CERTIFI (Sandborn 2012) trial programs. Accordingly, although we specify we will seek evidence from systematic reviews of RCTs for FAQ 2 ("Will it help my symptoms?"), if systematic reviews of RCTs for ustekinumab do not include induction of remission as an outcome, it should be understood we will consider UNITI-IM-UNITI and CERTIFI for the outcome of induction of remission 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 (e.g., Crohn's Disease Activity Index) 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. 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 CD (e.g., some might measure using the SF-36). 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 CD-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 (Lamb 2019) and product monographs.

Davies SC, Nguyen TM, Parker CE, MacDonald JK, Jairath V, Khanna R. Anti-IL-12/23p40 antibodies for maintenance of remission in Crohn's disease. Cochrane Database Syst Rev. 2019 Dec 12;12:CD012804. doi: 10.1002/14651858.CD012804.pub2. Review. PubMed

Feagan BG, Sandborn WJ, Gasink C, Jacobstein D, Lang Y, Friedman JR, Blank MA, Johanns J, Gao LL, Miao Y, Adedokun OJ, Sands BE, Hanauer SB, Vermeire S, Targan S, Ghosh S, de Villiers WJ, Colombel JF, Tulassay Z, Seidler U, Salzberg BA, Desreumaux P, Lee SD, Loftus EV Jr, Dieleman LA, Katz S, Rutgeerts P; UNITI–IM-UNITI Study Group. Ustekinumab as Induction and Maintenance Therapy for Crohn's Disease. N Engl J Med. 2016 Nov 17;375(20):1946-1960. 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

Sandborn WJ, Gasink C, Gao LL, Blank MA, Johanns J, Guzzo C, Sands BE, Hanauer SB, Targan S, Rutgeerts P, Ghosh S, de Villiers WJ, Panaccione R, Greenberg G, Schreiber S, Lichtiger S, Feagan BG; CERTIFI Study Group. Ustekinumab induction and maintenance therapy in refractory Crohn's disease. N Engl J Med. 2012 Oct 18;367(16):1519-28. doi: 10.1056/NEJMoa1203572. PubMed

Evidence report for biologics in Crohn's disease

Evidence Synthesis

Prepared by EBSCO Information Services

February 13, 2020

Prepared by EBSCO Health Innovations and EBM Development Department:

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

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

Eric Manheimer, PhD, EBM Editor

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. 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 while you take the medicine. 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 while you take the medicine. You will also be monitored for signs of an allergic reaction when you are getting the medicine in your vein. Sometimes the allergic reaction can 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 while you take the medicine. 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, Lamb 2019

FAQ 2: Will it help my symptoms?

Anti-TNF alpha agents

Symptoms of Crohn's disease 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. In the key evidence sources contributing to answering this FAQ, control of symptoms was typically operationalized as achieving a Crohn's Disease Activity Index [CDAI] < 150.

Out of 100 people who do not take a biologic agent, 10 to 28 (10% to 28%) have symptoms under control at 2 months. (About 19 out of 100)

Out of 100 people who take a TNF alpha medicine, 27 to 74 (27% to 74%) have symptoms under control at 2 months. (About 51 out of 100)

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

Out of 100 people who have a good response to a TNF alpha medicine early on but then stop taking it, 13 to 33 (13% to 33%) have symptoms under control at 1 year. (About 23 out of 100)

Out of 100 people who have a good response to a TNF alpha medicine early on and keep taking it, about 33 to 83 (33% to 83%) have symptoms under control at 1 year. (About 58 out of 100)

(Moderate certainty; based on 1 systematic review: Singh 2018)

Effects may vary with the specific drug used.

Vedolizumab

Symptoms of Crohn's disease 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, 10 to 28 (10% to 28%) have symptoms under control at 2 months. (About 19 out of 100)

Out of 100 people who take vedolizumab, 23 to 38 (23% to 38%) have symptoms under control at 2 months. (About 30 out of 100)

(High certainty; based on 1 systematic review: Chandar 2015)

Out of 100 people who have a good response to vedolizumab early on but then stop taking it, 13 to 33 (13% to 33%) 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, about 24 to 59 (24% to 59%) have symptoms under control at 1 year. (About 42 out of 100)

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

Ustekinumab

Symptoms of Crohn's disease 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, 10 to 28 (10% to 28%) have symptoms under control at 2 months. (About 19 out of 100)

Out of 100 people who take ustekinumab, 21 to 57 (21% to 57%) have symptoms under control at 2 months. (About 39 out of 100)

(Moderate certainty; based on 1 systematic review: Singh 2018)

Out of 100 people who have a good response to ustekinumab early on but then stop taking it, 13 to 33 (13% to 33%) 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 20 to 50 (20% to 50%) have symptoms under control at 1 year. (About 35 out of 100)

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

FAQ 3: Will it improve my quality of life?

Anti-TNF alpha agents

Starting a TNF medicine may improve quality of life for people with active Crohn's disease. (Moderate certainty; based on 1 systematic review: Abbass 2019)

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 [Dretzke 2011] and indirect extrapolation from other biologic agents)

Vedolizumab

Starting vedolizumab may improve quality of life for people with active Crohn's disease.

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.

(Very low certainty; based on 1 randomized trial [Sandborn 2013] and indirect extrapolation from other biologic agents)

Ustekinumab

Starting ustekinumab may improve quality of life for people with active Crohn's disease.

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.

(High certainty; based on 1 randomized trial [Sands 2018])

FAQ 4: Will it impact my need for surgery?

Anti-TNF alpha agents

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

- 4 to 13 (4% to 13%) may have surgery to treat Crohn's disease in the next year (About 8 out of 100)

Out of 100 people who use a TNF alpha medicine:

- 1 to 3 (1% to 3%) may have surgery to treat Crohn's disease in the next year (About 2 out of 100)

Effects may vary with the specific drug used. (Moderate certainty; based on 1 systematic review: Mao 2017)

Vedolizumab

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

- 4 to 13 (4% to 13%) may have surgery to treat Crohn's disease in the next year (About 8 out of 100)

Out of 100 people who use vedolizumab:

- 2 to 6 (2% to 6%) may have surgery to treat Crohn's disease in the next year (About 4 out of 100)

(Moderate certainty; based on 1 randomized trial: Feagan 2008 as reported in Mao 2017)

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, 15 to 38 (15% to 38%) may have to be in the hospital due to their Crohn's disease within 1 year. (About 27 out of 100)

Out of 100 people who take a TNF alpha medicine, 8 to 20 (8% to 20%) may have to be in the hospital due to their Crohn's disease within 1 year. (About 14 out of 100)

(Moderate certainty; based on a 1 systematic review: Mao 2017)

Vedolizumab

There is not enough research yet to answer this question.

Ustekinumab

There is not enough research yet to answer this question.

FAQ 6: What are the risks or side effects? – What is the risk of 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 biologic agent:

- 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 a biologic agent. (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 may have a higher risk of infection compared to people who do not take a biologic agent. There is not enough research yet to use numbers when talking about this risk.

FAQ 6: What are the risks or side effects? – What is the risk of cancer?

Anti-TNF alpha agents

Out of 1,000 people who do not take a biologic agent, 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 biologic agent, 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.

FAQ 6: What are the risks or side effects? – What are other risks and 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*
1st-round (DynaMed)	130	11
2nd-round (Systematic review searches)	127	13
3rd-round (Original article searches)	155	3
4th-round (Citation tracing)	5	2
Total	*417*	*29*

* Number shown is after deduplication

	Articles selected for evaluation (Author Year)
Systematic reviews (21)	Abbass 2019, Askling 2011, Bonovas 2016, Bye 2017, Chandar 2015, Colombel 2017, Costa 2013, Dassopoulos 2013, Davies 2019, Dretzke 2011, Ford 2013, Hazlewood 2015, Lin 2015, MacDonald 2016, Mao 2017, Moćko 2016, Schreiber 2018, Siegel 2009, Singh 2014, Singh 2018, Stidham 2014
Randomized, controlled trials (3)	Sandborn 2013, Sands 2018, Watanabe 2012
Other article types (5)	National cohort studies (Kirchgesner 2018, Kobayashi 2019, Lemaitre 2017, Nyboe Andersen 2014, Nyboe Andersen 2015)

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
  - Hazlewood 2015 includes data for induction and maintenance of remission
  - Singh 2018 includes data for induction and maintenance of remission
  - Singh 2014 includes data for induction and maintenance of remission
  - Stidham 2014 includes data for induction and maintenance of remission
- Etanercept – an anti-TNF alpha and anti-TNF beta agent
  - Asklin 2011 includes data on malignancies
- Natalizumab – an anti-integrin agent
  - Bonovas 2016 includes data for infections and malignancies
  - Chandar 2015 includes data for induction and maintenance of remission, quality of life, infections, and malignancy
  - Singh 2014 includes data for induction and maintenance of remission

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)

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. The second dose occurs 2 weeks after the first dose. Thereafter, doses are given every other week (i.e., every 2 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. 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 while you take the medicine. 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 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 while you take the medicine. You will also be monitored for signs of an allergic reaction when you are getting the medicine in your vein. Sometimes the allergic reaction can 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 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 while you take the medicine. 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.

(DynaMed 2018, Lamb 2019)

FAQ 2: Will it help my symptoms?

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 Crohn's disease. 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 – derived from the various control group estimates from the applicable evidence – given the population heterogeneity.

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

- for the outcome of induction of remission (defined as Crohn's Disease Activity Index [CDAI] < 150) – 10.2% to 28% (Singh 2018)
- for the outcome of remission maintenance at 1 year among induction responders – 13.1% to 32.8% (Hazlewood 2015, Singh 2018)

Anti-TNF alpha agents

Evidence Review Tables – anti-TNF alpha agents

Effects of intervention vs. placebo on induction of remission (CDAI < 150) in treatment-naive patients (6 to 10 weeks)

Agent and SR	No. of patients (studies)	Control group event rate (% with remission)	Risk ratio or odds ratio (95% CI)	Certainty (reason for downgrade)
Adalimumab				
Singh 2018	174 (2) Hanauer 2006/CLASSIC I* Watanabe 2012	13.1% (11/84)	OR 3.80 (1.76 to 8.18) RR 2.78 (1.60 to 4.22)**	High
Singh 2014	263 (2) Hanauer 2006/CLASSIC I* Watanabe 2012	13.1% (11/84)	RR 2.30 (1.27 to 4.16)	High
Infliximab				
Singh 2018	166 (2) Lemann 2006 Targan 1997***	28% (23/82)	OR 6.35 (3.04 to 13.28) RR 2.54 (1.93 to 2.99)**	High
Singh 2014	219 (2) Lémann 2006 Targan 1997***	27.2% (22/81)	RR 3.11 (0.72 to 13.45)	Moderate (imprecision)

*Hanauer 2006/CLASSIC 1 had 3 intervention groups, Singh 2018 MA included only 160 mg group, Singh 2014 MA used 160 mg and 80 mg groups, Hazlewood 2015 used all 3 groups (Hazlewood 2015 not reported here because it did not limit to anti-TNF agent naïve patients)

**RR not reported by authors, so it was estimated from the OR and control group risk in the standard fashion.

***Targan 1997 had 3 intervention groups, Singh 2018 MA included only 5 mg/kg group, Singh 2014 MA included all 3 groups.

Effects of intervention vs. placebo on maintenance of remission at 52 to 54 weeks (among clinical responders at 6 weeks)

Agent(s) and Study	No. of patients (studies)	Control group event rate (% with remission)	Risk ratio or odds ratio (95% CI)	Certainty (reason for downgrade)
Adalimumab				
Singh 2018	422 (3) Colombel 2007/CHARM* Sandborn 2007/CLASSIC 2* Watanabe 2012	14.3% (30/210)	OR 4.43 (2.69 to 7.29) RR 2.97 (2.17 to 3.84)**	Moderate (risk of bias)[1]
Singh 2014	597 (3) Colombel 2007/CHARM* Sandborn 2007/CLASSIC 2* Watanabe 2012	14.3% (30/210)	RR 2.65 (1.63 to 4.32)	Moderate (risk of bias)[1]
Hazlewood 2015	726 (4) Colombel 2007/CHARM* Sandborn 2007/CLASSIC 2* Rutgeerts 2012/EXTEND 2012*** Watanabe 2012	13.1% (36/275)	OR 4.88 (3.22 to 7.40)	Moderate (risk of bias)[1]
Infliximab				
Singh 2018	296 (2) Hanauer 2002/ACCENT 1* Rutgeerts 1999	20.5% (30/146)	OR 2.87 (1.72 to 4.80) RR 2.07 (1.50 to 2.70)**	Moderate (risk of bias)[2]
Singh 2014	408 (2) Hanauer 2002/ACCENT 1* Rutgeerts 1999	20.5% (30/146)	RR 2.15 (1.52 to 3.05)	Moderate (risk of bias)[2]
Hazlewood 2015	408 (2) Hanauer 2002/ACCENT 1* Rutgeerts 1999	20.5% (30/146)	OR 2.36 (1.22 to 4.55)	Moderate (risk of bias)[2]

* For all of these trials (Colombel 2007/CHARM, Sandborn 2007/CLASSIC II, Hanauer 2002/ACCENT 1) they each had 2 intervention groups, Singh 2018 MA and Chandar 2015 included only 1 intervention group, Singh 2014 MA and Hazlewood 2015 MA used both intervention groups

**RR not reported by authors, so it was estimated from the OR and control group risk in the standard fashion

*** Rutgeerts 2012/EXTEND 2012 was the only treat-through trial; all other trials were limited to patients who had clinical response to the agent being evaluated for maintenance therapy

[1] Colombel 2007/CHARM contributed > 50% weight to meta-analyses and was rated as unclear risk of bias related to equal use of co-interventions in treatment and placebo groups

[2] Hanauer 2002/ACCENT-I contributed > 50% weight to meta-analyses and was rated as unclear risk of bias related to equal use of co-interventions in treatment and placebo groups

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	**Use meta-analysis already done but report separately for adalimumab and infliximab:** Singh 2018 is most recent and limited to patients naïve to biologic therapies. Drug-specific estimates were consistent (upon converting odds ratios to relative risks) so RR estimates were averaged for drug class effect.	**Adalimumab is effective for increasing rates of inducing remission** (High certainty), with RR 2.78 (95% CI 1.60 to 4.22). **Infliximab is effective for increasing rates of inducing remission** (High certainty), with RR 2.54 (95% CI 1.93 to 2.99). Average RR 2.66.	**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 10.2% to 28%, yielding a range of 27.1% to 74.48% with anti-TNF alpha agents. (The midpoint of the control group event rate range is 19.1%. The midpoint of the intervention group event rate range is 50.8%.)	**27% to 74% of people treated with anti-TNF alpha agents have induction of remission.**
Remission at 1 year among those with response to induction	**Use meta-analysis already done:** Singh 2018 is most recent and comprehensive and limited to doses approved for use. Drug-specific estimates were somewhat consistent (upon converting odds ratios to relative risks) so RR estimates were averaged for drug class effect.	**Adalimumab may be effective for increasing rates of remission at 1 year among people who respond to induction** (Moderate certainty), with RR 2.97 (95% CI 2.17 to 3.84). **Infliximab may be effective for increasing rates of remission at 1 year among people who respond to induction** (Moderate certainty), with RR 2.07 (95% CI 1.50 to 2.70). Average RR 2.52	**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 13.1% to 32.8%, yielding a range of 33.0% to 82.7% with anti-TNF alpha agents. These estimates are limited to induction responders. (The midpoint of the control group event rate range is 23% (22.95%). The midpoint of the intervention group event rate range is 57.8%.)	**33% to 83% of people treated with anti-TNF alpha agents who have a good response early on may have remission at 1 year.**

Evidence Synthesis Results – anti-TNF alpha agents

Out of 100 people who do not take a biologic agent, 10 to 28 (10% to 28%) have symptoms under control at 2 months. (About 19 out of 100)

Out of 100 people who take a TNF alpha medicine, 27 to 74 (27% to 74%) have symptoms under control at 2 months. (About 51 out of 100)

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

Out of 100 people who have a good response to a TNF alpha medicine early on but then stop taking it, 13 to 33 (13% to 33%) have symptoms under control at 1 year. (About 23 out of 100)

Out of 100 people who have a good response to a TNF alpha medicine early on and keep taking it, about 33 to 83 (33% to 83%) have symptoms under control at 1 year. (About 58 out of 100)

(Moderate certainty; based on 1 systematic review: Singh 2018)

Effects may vary with the specific drug used.

Vedolizumab

Evidence Review Tables – vedolizumab

Effects of vedolizumab vs. placebo on induction of remission in treatment-naive patients (6 to 10 weeks)

Study (SR)	No. of patients (studies)	Control group event rate (% with remission)	Risk ratio or odds ratio (95% CI)	Certainty (reason for downgrade)
Singh 2018	294 (2) Sandborn 2013/GEMINI II (6 weeks) Sands 2014/GEMINI III	10.2% (13/128)	OR 2.68 (1.35 to 5.31)	Moderate (risk of bias)[1]
Singh 2014	378 (2) Feagan 2008 Sandborn 2013/GEMINI II (6 weeks)	14.0% (19/136)	RR 1.76 (1.11 to 2.78)	High
Chandar 2015	479 (3) Feagan 2008 Sandborn 2013/GEMINI 2 (10 weeks) Sands 2014/GEMINI 3	14.5% (27/186)	RR 0.86 (0.79 to 0.94) for failure of induction of remission	High

[1] Unclear why Feagan 2008 was not included in systematic search and selection.

Effects of vedolizumab vs. placebo on maintenance of remission at 52 to 54 weeks (among clinical responders at 6 weeks)

Study (SR)	No. of patients (studies)	Control group event rate (% with remission)	Risk ratio or odds ratio (95% CI)	Certainty (reason for downgrade)
Singh 2018	307 (1) Sandborn 2013/GEMINI II*	21.6% (33/153)	OR 2.32 (1.4 to 3.84) RR 1.81 (1.29 to 2.38)**	High
Singh 2014	461 (1) Sandborn 2013/GEMINI II*	21.6% (33/153)	RR 1.75 (1.25 to 2.44)	High
Hazlewood 2015	461 (1) Sandborn 2013/GEMINI 2b*	21.6% (33/153)	OR 2.20 (1.40 to 3.44)	High
Chandar 2015	307 (1) Sandborn 2013/GEMINI 2b*	21.6% (33/153)	Not reported (but same data as Singh 2018)	High

*Sandborn 2013/GEMINI 2 had 2 intervention groups, Singh 2018 MA and Chandar 2015 included only 1 intervention group, Singh 2014 MA and Hazlewood 2015 MA used both intervention groups

**RR not reported by authors, so it was estimated from the OR and control group risk in the standard fashion.

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:** Chandar 2015 is most comprehensive and limited to patients naïve to biologic therapies.	**Vedolizumab is effective for increasing rates of induction of remission** (High certainty) with RR 0.86 (95% CI 0.79 to 0.94) for failure of induction of remission.	**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 10.2% to 28%, yielding a range of 22.8% to 38.1%. (The midpoint of the control group event rate range is 19.1%. The midpoint of the intervention group event rate range is 30.4%.)	**23% to 38% of people treated with vedolizumab have induction of remission.**
Remission at 1 year among those with response to induction	**Use meta-analysis already done:** Singh 2018 is most recent and limited to doses approved for use.	**Vedolizumab appears effective for increasing rates of remission at 1 year among those who respond to induction** (High certainty) with RR 1.81 (95% CI 1.29 to 2.38) for maintenance of remission	**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 13.1% to 32.8%, yielding a range of 23.7% to 59.4%. This estimate is limited to induction responders. (The midpoint of the control group event rate range is 23% (22.95%). The midpoint of the intervention group event rate range is 41.54%.)	**24% to 59% of people treated with vedolizumab who have a good response early on have remission at 1 year.**

Evidence Synthesis Results – vedolizumab

Out of 100 people who do not take a biologic agent, 10 to 28 (10% to 28%) have symptoms under control at 2 months. (About 19 out of 100)

Out of 100 people who take vedolizumab, 23 to 38 (23% to 38%) have symptoms under control at 2 months. (About 30 out of 100)

(High certainty; based on 1 systematic review: Chandar 2015)

Out of 100 people who have a good response to vedolizumab early on but then stop taking it, 13 to 33 (13% to 33%) 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, about 24 to 59 (24% to 59%) have symptoms under control at 1 year. (About 42 out of 100)

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

Ustekinumab

Evidence Review Tables – ustekinumab

Effects of ustekinumab vs. placebo on induction of remission in treatment-naive patients (6 to 10 weeks)

Study (SR)	No. of patients (studies)	Control group event rate (% with remission)	Risk ratio or odds ratio (95% CI)	Certainty (reason for downgrade)
Ustekinumab				
Singh 2018	400 (1) Feagan 2016/UNITI–2	19.5% (39/200)	OR 2.75 (1.76 to 4.32) RR 2.05 (1.53 to 2.62)*	Moderate (inconsistency)[1]
Singh 2014	52 (1) Sandborn 2008	53.8% (14/26)	RR 0.79 (0.44 to 1.39)	Very low (very serious imprecision, indirectness)[2]

*RR not reported by authors, so it was estimated from the OR and control group risk in the standard fashion.

[1] Inconsistency a serious concern with Singh 2018. Although there was only 1 trial included (Feagan 2016) an earlier SR by Singh 2014 included a different trial (Sandborn 2008) and had inconsistent findings.

[2] Sandborn 2008 had such a high control group event rate it does not appear to reflect the population of interest. We do not consider the control group risk reliable enough to be included in the range of control group risks noted at the beginning of this section.

Effects of ustekinumab vs. placebo on maintenance of remission at 52 to 54 weeks (among clinical responders at 6 weeks)

Study (SR)	No. of patients (studies)	Control group event rate (% with remission)	Risk ratio or odds ratio (95% CI)	Certainty (reason for downgrade)
Singh 2018	404 (2) Sandborn 2012/CERTIFI Feagan 2016/IM-UNITI	32.8% (67/204)	OR 2.02 (1.35 to 3.30) RR 1.51 (1.21 to 1.88)*	High
Singh 2014	145 (1) Sandborn 2012/CERTIFI	27.4% (20/73)	RR 1.52 (0.96 to 2.42)	Moderate (imprecision)

*RR not reported by authors, so it was estimated from the OR and control group risk in the standard fashion.

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 meta-analysis already done:** Singh 2018 is most recent and limited to patients naïve to biologic therapies.	**Ustekinumab appears effective for increasing rates of inducing remission** (Moderate certainty), with RR 2.05 (95% CI 1.53 to 2.62)	**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 10.2% to 28%, yielding a range of 20.9% to 57.4%. (The midpoint of the control group event rate range is 19.1%. The midpoint of the intervention group event rate range is 39.2%.)	**21% to 57% of people treated with ustekinumab may have induction of remission.**
Remission at 1 year among those with response to induction	**Use meta-analysis already done:** Singh 2018 is most recent and comprehensive and limited to doses approved for use.	**Ustekinumab is effective for increasing rates of remission at 1 year among people who respond to induction** (High certainty), with RR 1.51 (95% CI 1.21 to 1.88)	**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 13.1% to 32.8%, yielding a range of 19.8% to 49.53%. This estimate is limited to induction responders. (The midpoint of the control group event rate range is 23% (22.95%). The midpoint of the intervention group event rate range is 34.7%.)	**20% to 50% of people treated with ustekinumab who have a good response early on have remission at 1 year.**

Evidence Synthesis Results – ustekinumab

Out of 100 people who do not take a biologic agent, 10 to 28 (10% to 28%) have symptoms under control at 2 months. (About 19 out of 100)

Out of 100 people who take ustekinumab, 21 to 57 (21% to 57%) have symptoms under control at 2 months. (About 39 out of 100)

(Moderate certainty; based on 1 systematic review: Singh 2018)

Out of 100 people who have a good response to ustekinumab early on but then stop taking it, 13 to 33 (13% to 33%) 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 20 to 50 (20% to 50%) have symptoms under control at 1 year. (About 35 out of 100)

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

FAQ 3: Will it improve my quality of life?

There were limited quantitative data reported across the set of biologic agents. We are concerned that quantitative synthesis in the decision aid could be confusing or misleading for clinicians and patients. Additionally, results were sometimes only reported narratively as "significant" differences; this raises serious difficulty in interpretation, as achieving the conventional frequentist threshold for statistical significance does not by itself give any indication of clinical relevance. To assess clinical relevance, one must know the magnitude of the effect and some measure of precision of the estimated effect (e.g., a point estimate may suggest clinical relevance, but the confidence interval may include the possibility of a trivial difference). Therefore, considering all these factors, we 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. Despite one agent (ustekinumab) having higher certainty evidence with more quantitative data there is no evidence to suggest that ustekinumab is specifically more effective than other biologic agents, so we suggest not representing one option more favorably in the summary results.

Anti-TNF alpha agents

Evidence Review Details – anti-TNF alpha agents

Adalimumab was associated with significantly higher quality of life compared to placebo in 3 induction trials described narratively in a systematic review (Abbass 2019; Moderate certainty due to imprecision)

Adalimumab and infliximab were associated with maintenance of quality of life scores similar to baseline in placebo-controlled trials among patients who were clinical responders, while drug cessation was associated with reduced quality of life (Dretzke 2011; Low certainty due to risk of bias and imprecision)

Evidence Synthesis Process – anti-TNF alpha agents

See note above about providing a harmonized qualitative synthesis statement.

Evidence Synthesis Results – anti-TNF alpha agents

Starting a TNF medicine may improve quality of life for people with active Crohn's disease.
(Moderate certainty; based on 1 systematic review: Abbass 2019)

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 [Dretzke 2011] and indirect extrapolation from other biologic agents)

Vedolizumab

Evidence Review Tables – vedolizumab

In one maintenance trial among patients who were clinical responders, vedolizumab was associated with small but positive adjusted mean changes in quality of life scores while placebo was associated with small but negative adjusted mean changes in quality of life scores (Sandborn 2013; Very low certainty due to risk of bias, imprecision and indirectness)

Evidence Synthesis Process – vedolizumab

See note above about providing a harmonized qualitative synthesis statement.

Evidence Synthesis Results – vedolizumab

Starting vedolizumab may improve quality of life for people with active Crohn's disease.

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.

(Very low certainty; based on 1 randomized trial [Sandborn 2013] and indirect extrapolation from other biologic agents)

Ustekinumab

Evidence Review Tables – ustekinumab

Sands 2018 reported a randomized trial evaluating ustekinumab for induction of remission in patients with active CD unresponsive to conventional therapy (UNITI-2). A meaningful improvement in quality of life (defined as at least 16-point improvement in IBDQ score from baseline to 8 weeks) was reported in 41.1% of 207 patients treated with placebo, 58.7% of 208 patients treated with ustekinumab 130 mg IV ($p < 0.001$ vs. placebo), and 68.1% of 207 patients treated with ustekinumab weight-based dosing with about 6 mg/kg IV ($p < 0.001$ vs. placebo). Consistent results were reported with other measures of quality of life. (High certainty)

Sands 2018 reported a randomized trial evaluating ustekinumab for maintenance of remission in patients who had clinical response to ustekinumab in one of two induction trials (IM-UNITI). The other induction trial (UNITI-1) included patients who had been unresponsive to anti-TNF therapy. A meaningful improvement in quality of life (defined as at least 16-point improvement in IBDQ score from baseline of induction trial to 52 weeks [ie, 44 weeks of maintenance trial]) was reported in 50.4% of 119 patients treated with placebo, 61.3% of 119 patients treated with ustekinumab 90 mg subcutaneously every 12 weeks (not significant vs. placebo), and 67.9% of 112 patients treated with ustekinumab 90 mg subcutaneously every 8 weeks ($p = 0.014$ vs. placebo). All groups had lower mean IBDQ scores at 44 weeks compared to baseline but the reductions in IBDQ scores were greater with placebo (mean change -21.5) than ustekinumab every 12 weeks (mean change -8.9) or ustekinumab every 8 weeks (mean change -9.9). Consistent results were reported with other measures of quality of life. (High certainty)

Evidence Synthesis Process – ustekinumab

See note above about providing a harmonized qualitative synthesis statement.

Evidence Synthesis Results – ustekinumab

Starting ustekinumab may improve quality of life for people with active Crohn's disease.

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.

(High certainty; based on 1 randomized trial [Sands 2018])

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 Crohn's disease. 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 3.8% to 12.6%. (Mao 2017)

Anti-TNF alpha agents

Evidence Review Tables – anti-TNF alpha agents

Effects of intervention vs. placebo on surgery rate (54 to 56 weeks)

Agent(s) and Study	No. of patients (studies)	Control group event rate (%)	Risk ratio or odds ratio (95% CI)	Certainty (reason for downgrade)
Anti-TNF alpha agents (infliximab and adalimumab) – Mao 2017	1,633 (3)	Range from 3.8% to 12.6%	OR 0.23 (0.13 to 0.42) RR 0.24 (0.14 to 0.44)*	Moderate (risk of bias)[1]

*RR not reported by authors, so it was estimated from the OR and pooled control group risk (42/592 ≈ 7.1%) in the standard fashion.
[1]Unclear risk of bias due to crossovers and potential contamination, not fully assessed in critical appraisal by Mao 2017

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	**Use meta-analysis already done.** (Mao 2017)	**Anti-TNF alpha agents may reduce the rate of surgery** (Moderate certainty), with RR 0.24 (95% CI 0.14 to 0.44)	**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 3.8% to 12.6%, yielding a range of 0.9% to 3.0%. (The midpoint of the control group event rate range is 8.2%. The midpoint of the intervention group event rate range is 2.0%.)	**Risk of surgery over 1 year may be 1% to 3% with an anti-TNF alpha agent**

Evidence Synthesis Results – anti-TNF alpha agents

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

- **4 to 13 (4% to 13%) may have surgery to treat Crohn's disease in the next year** (About 8 out of 100)

Out of 100 people who use a TNF alpha medicine:

- **1 to 3 (1% to 3%) may have surgery to treat Crohn's disease in the next year** (About 2 out of 100)

Effects may vary with the specific drug used. (Moderate certainty; based on 1 systematic review: Mao 2017)

Vedolizumab

Evidence Review – vedolizumab

Effects of vedolizumab vs. placebo on surgery rate (54 to 56 weeks)

Study	No. of patients (studies)	Control group event rate (%)	Risk ratio or odds ratio (95% CI)	Certainty (reason for downgrade)
Feagan 2008 – as reported in Mao 2017	185 (1)	10.3% (6/58)	RR 0.46 (0.15 to 1.36)*	Moderate (imprecision)

*Calculated from numerators and denominators reported in Mao 2017

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
Colectomy	**Calculate effect estimate from data available from single trial.** (Feagan 2008 as reported in Mao 2017)	**Vedolizumab may reduce the rate of surgery** (Moderate certainty), with RR 0.46 (95% CI 0.15 to 1.36)	**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 3.8% to 12.6%, yielding a range of 1.7% to 5.8%. (The midpoint of the control group event rate range is 8.2%. The midpoint of the intervention group event rate range is 3.8%.)	**Risk of surgery over 1 year may be 2% to 6% with vedolizumab**

Evidence Synthesis Results – vedolizumab

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

- **4 to 13 (4% to 13%) may have surgery to treat Crohn's disease in the next year** (About 8 out of 100)

Out of 100 people who use vedolizumab:

- **2 to 6 (2% to 6%) may have surgery to treat Crohn's disease in the next year** (About 4 out of 100)

(Moderate certainty; based on 1 randomized trial: Feagan 2008 as reported in Mao 2017)

Ustekinumab

Evidence Review Tables – ustekinumab

No evidence identified.

Evidence Synthesis Process – ustekinumab

No evidence identified.

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 Crohn's disease. 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 CD-related hospitalization at 1 year range from 15.3% to 37.8%. (Mao 2017)

Anti-TNF alpha agents

Evidence Review Tables – anti-TNF alpha agents

Effects of intervention vs. placebo on Crohn's disease-related hospitalization rate (54 to 56 weeks)

Agent(s) and Study	No. of patients (studies)	Control group event rate (%)	Risk ratio or odds ratio (95% CI)	Certainty (reason for downgrade)
Anti-TNF alpha agents (infliximab and adalimumab) – Mao 2017	1,633 (3)	Range from 15.3% to 37.8%	OR 0.46 (0.36 to 0.60) RR 0.54 (0.43 to 0.67)*	Moderate (risk of bias)[1]

*RR not reported by authors, so it was estimated from the OR and pooled control group risk (156/592 ≈ 26.4%) in the standard fashion.

[1]Unclear risk of bias due to crossovers and potential contamination, not fully assessed in critical appraisal by Mao 2017

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
CD-related hospitalization	**Use meta-analysis already done.** (Mao 2017)	**Anti-TNF alpha agents may reduce the risk of needing to be hospitalized due to Crohn's disease** (Moderate certainty), with RR 0.54 (95% CI 0.43 to 0.67).	**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 15.3% to 37.8%, yielding a range of 8.3% to 20.4%. (The midpoint of the control group event rate range is 26.55%. The midpoint of the intervention group event rate range is 14.3%.)	**Risk of being hospitalized due to Crohn's disease over 1 year may be 8% to 20% with an anti-TNF alpha agent**

Evidence Synthesis Results – anti-TNF alpha agents

Out of 100 people who do not take a biologic agent, 15 to 38 (15% to 38%) may have to be in the hospital due to their Crohn's disease within 1 year. (About 27 out of 100)

Out of 100 people who take a TNF alpha medicine, 8 to 20 (8% to 20%) may have to be in the hospital due to their Crohn's disease within 1 year. (About 14 out of 100)

(Moderate certainty; based on a 1 systematic review: Mao 2017)

Vedolizumab

Evidence Review – vedolizumab

We found no randomized, placebo-controlled trial evidence found for this outcome (based on 1 systematic review [Mao 2017] and a search for subsequent randomized trials [see Search and Selection]).

Evidence Synthesis Process – vedolizumab

No evidence identified.

Evidence Synthesis Results – vedolizumab

There is not enough research yet to answer this question.

Ustekinumab

Evidence Review Tables – ustekinumab

No evidence identified.

Evidence Synthesis Process – ustekinumab

No evidence identified.

Evidence Synthesis Results – ustekinumab

There is not enough research yet to answer this question.

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.

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 previously 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 (2.26), 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 of 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 biologic agent:

- **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 a biologic agent. (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 may have a higher risk of infection compared to people who do not take a biologic agent. 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 rare.** (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

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

Out of 1,000 people who do not take a biologic agent, 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 biologic agent, 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 Crohn's disease

Search and Selection

Prepared by EBSCO Information Services

December 20, 2019
Updated February 10, 2020

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
Crohn Disease in Adults topic, Management section, Medications subsection, Tumor necrosis factor inhibitors (anti-TNF therapy) subsection, Anti-TNF therapy for induction of remission subsection (February 8, 2020)	49	1 (Dassopoulos 2013)
Crohn Disease in Adults topic, Management section, Medications subsection, Tumor necrosis factor inhibitors (anti-TNF therapy) subsection, Anti-TNF therapy for maintenance therapy or prevention of relapse subsection (February 8, 2020)	41	2 (Costa 2013, Dretzke 2011)
Crohn Disease in Adults topic, Management section, Medications subsection, Tumor necrosis factor inhibitors (anti-TNF therapy) subsection, Adverse effects of anti-TNF therapy subsection, Infection risk subsection (February 8, 2020)	9	2 (Ford 2013, Kirchgesner 2018)
Crohn Disease in Adults topic, Management section, Medications subsection, Tumor necrosis factor inhibitors (anti-TNF therapy) subsection, Adverse effects of anti-TNF therapy subsection, Malignancy subsection (February 8, 2020)	11	3 (Askling 2011, Lemaitre 2017, Siegel 2009)
Crohn Disease in Adults topic, Management section, Medications subsection, Nontumor necrosis factor inhibitor biologic therapies subsection, Integrin agents subsection (February 8, 2020)	14	2 (Colombel 2017, Sandborn 2013)
Crohn Disease in Adults topic, Management section, Medications subsection, Nontumor necrosis factor inhibitor biologic therapies subsection, Interleukin antibodies subsection (February 8, 2020)	6	1 (MacDonald 2016)

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

Database	Search string	Number of search results	Number of unique references included
PubMed February 8, 2020	(infliximab[tiab] OR golimumab[tiab] OR adalimumab[tiab] OR vedolizumab[tiab] OR ustekinumab[tiab]) AND (Crohn*[ti] OR inflammatory bowel disease*[ti]) AND (systematic[sb] OR meta-analysis[ti]) AND ("2011/12/02"[PDAT] : "3000/01/01"[PDAT]) NOT (pediatric[ti] OR child*[ti])	127	13 (Abbass 2019, Bonovas 2016, Bye 2017, Chandar 2015, Davies 2019, Hazlewood 2015, Lin 2015, Mao 2017, Moćko 2016, Schreiber 2018, Singh 2014, Singh 2018, Stidham 2014)

Third-round searching – searches for original evidence reports

Database	Search string	Number of search results	Number of unique references included
PubMed January 29, 2020	((infliximab OR golimumab OR adalimumab OR vedolizumab OR ustekinumab) AND (crohn*[ti]) AND randomized controlled trial[pt]) AND ("2017/02/01"[PDAT] : "3000/12/31"[PDAT]) NOT (pediatric[ti] OR child*[ti])	26	1 (Sands 2018)*
PubMed February 10, 2020	(vedolizumab[tiab] OR ustekinumab[tiab]) AND Crohn*[ti] AND quality of life[tiab] NOT (pediatric[ti] OR child*[ti])	14	0
PubMed February 10, 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])))	115	2 (Kobayashi 2019, Nyboe Andersen 2015)

* We conducted this search to determine whether additional trials had been published since the closure of the search window for Singh 2018. This yielded 2 sources that appeared to possibly be long-term follow-ups of the trial programs for ustekinumab and vedolizumab (Sandborn 2018 and Vermeire 2017, respectively). However, on review of the full text for these publications, it became clear this was not the case. Both were extension studies were all patients were on the biologic agent of interest: Vermeire 2017 describes its methods as a "single-arm, open-label phase 3 extension study", and Sandborn 2018 notes "Because placebo patients discontinued the study after treatment assignments were unblinded to the investigative sites … direct comparisons and/or statistical comparisons of efficacy results between placebo and ustekinumab treatment groups through the extension were not possible". Therefore, these studies were not considered further in Critical Appraisal.

Fourth-round searching – citation tracing

Source	Tracing	Number of unique references included
Chandar 2015	Tracing trials of vedolizumab (other than Sandborn 2013) to see if any reported quality of life outcomes for vedolizumab	0
Singh 2018	Tracing maintenance trials of anti-TNF alpha agents to see if any reported quality of life had been published since Dretzke 2011	1 (Watanabe 2012)
Singh 2018	Tracing trials of vedolizumab to see if any reported quality of life had been published since Chandar 2015	0
Singh 2018	Tracing trials of ustekinumab to see if any reported quality of life that had not been included in Sands 2018	0
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.

Search summary:

Number of articles screened and selected

	Screened	Selected*
1st-round (DynaMed)	130	11
2nd-round (Systematic review searches)	127	13
3rd-round (Original article searches)	155	3
4th-round (Citation tracing)	5	2
Total	*417*	*29*

* Number shown is after deduplication

	Articles selected for evaluation (Author Year)
Systematic reviews (21)	Abbass 2019, Askling 2011, Bonovas 2016, Bye 2017, Chandar 2015, Colombel 2017, Costa 2013, Dassopoulos 2013, Davies 2019, Dretzke 2011, Ford 2013, Hazlewood 2015, Lin 2015, MacDonald 2016, Mao 2017, Moćko 2016, Schreiber 2018, Siegel 2009, Singh 2014, Singh 2018, Stidham 2014
Randomized, controlled trials (3)	Sandborn 2013, Sands 2018, Watanabe 2012
Other article types (5)	National cohort studies (Kirchgesner 2018, Kobayashi 2019, Lemaitre 2017, Nyboe Andersen 2014, Nyboe Andersen 2015)

Evidence report for biologics in Crohn's disease

Critical Appraisal

Prepared by EBSCO Information Services

February 13, 2020

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

ABBASS 2019

Abbass M, Cepek J, Parker CE, Nguyen TM, MacDonald JK, Feagan BG, Khanna R, Jairath V. Adalimumab for induction of remission in Crohn's disease. Cochrane Database Syst Rev. 2019 Nov 14;2019(11):CD012878. PubMed

Relevant to FAQ3

Note: This systematic review was consulted only for quality of life data for the anti-TNF agents (see "Other considerations" below for more detail).

- **Study design:** systematic review of randomized trials
- **Population:** patients of any age with active CD
- **Intervention:** adalimumab
- **Comparison:** placebo
  - although an active comparator was eligible as a comparator group, we only extracted data pertaining to a biologic agent vs. placebo
- **Study inclusion criteria:** trials reporting induction of remission as an outcome
  - must have been published by 16 April 2019 (search window closure)
- **Number of studies:** 3
- **Number of participants:** 714
- **Duration of follow-up:** 4 weeks
- **Results and certainty:**
  - Results for this outcome were described narratively, as the authors noted meta-analysis was not possible due to lack of necessary data (e.g., means and/or SDs not reported)

No. studies (no. participants)	Key findings at 4 weeks	Certainty
3 (714)	• Hanauer 2006 (n = 299) ○ adalimumab 160 mg/80 mg (n =76), 80 mg/40 mg (n = 75), or 40 mg/20 mg (n = 74) vs. placebo (n = 74) ○ "significantly higher" IBDQ in adalimumab 160/80 mg and 80 mg/40 mg vs. placebo; numerical results not reported • Sandborn 2007 (n = 325) ○ adalimumab 160 mg/80 mg (n = 159) vs. placebo (n = 166) ○ mean IBDQ 150 vs. 139, respectively; p < 0.001 • Watanabe 2012 (n = 90) ○ adalimumab 160 mg/80mg (n = 33) or 80 mg/40 mg (n = 34) vs. placebo (n = 23) ○ "significantly higher" SF-36 scores for adalimumab 160 mg/80 mg and 80 mg/40 mg vs. placebo; numerical results not reported ○ IBDQ scores were "higher" in adalimumab 160 mg/80 mg vs. placebo, but difference was not statistically significant; numerical results not reported	Moderate (imprecision)[1]

1 Downgraded for imprecision due to inability to fully assess precision of the results

- **Other considerations:**

- Abbass 2019 reported only two relevant outcomes: induction of remission and quality of life. For induction of remission, Abbass 2019 included the same 3 trials of adalimumab vs. placebo (ie, Hanauer 2006/CLASSIC I, Watanabe 2012, Sandborn 2007/GAIN) as 3 other SRs we summarized (Hazlewood 2015, Singh 2014, Singh 2018). Also, the pooled results were consistent between Abbass 2019 and the other 3 SRs; all SRs showed a significant benefit of adalimumab. One difference between Abbass 2019 and the other 3 SRs is that Abbass 2019 used a different definition for 'operationalizing' the induction of remission outcome: Abbass 2019 operationalized their outcome as 'Failure to achieve clinical remission at 4 weeks' whereas the other 3 SRs operationalized their outcome as achieving induction of clinical remission and used later time points for measurement.
- Abbass 2019 limited its scope to induction trials, thus providing information on early/short-term effects on QoL. Accordingly, we consulted additional SRs for evidence pertaining to the longer-term effects of anti-TNF alpha agents on QoL, and Dretzke 2011 was the most current SR providing information on this outcome.

CHANDAR 2015

Chandar AK, Singh S, Murad MH, Peyrin-Biroulet L, Loftus EV Jr. Efficacy and Safety of Natalizumab and Vedolizumab for the Management of Crohn's Disease: A Systematic Review and Meta-analysis. Inflamm Bowel Dis. 2015 Jul;21(7):1695-708. PubMed

Relevant to FAQ2, FAQ3, FAQ6

- **Study design:** systematic review of randomized trials
- **Population:** adults with Crohn's disease (CD)
- **Intervention:** vedolizumab
  - additional agent included but not relevant to scoping: natalizumab
- **Comparison:** placebo
  - although an alternative active intervention was eligible as a comparison group, all included trials used placebo control
- **Study inclusion criteria:**
  - search window close July 2014
  - minimum duration of therapy of 14 days in trials reporting induction of remission in active disease
  - minimum duration of therapy of 22 weeks in trials reporting maintenance of remission (prevention of relapse in patients with clinical remission to induction therapy)
  - outcome—induction of clinical remission (Crohn's Disease Activity Index [CDAI] score <150), and maintenance of medically induced remission (among patients with clinical response to induction therapy)
- **Number of studies:** 8 RCTs (5 natalizumab and 3 vedolizumab trials)
  - focus is on the 3 vedolizumab trials examining induction of remission, maintenance of remission, serious infections, malignancy, and quality of life (QoL)
- **Number of participants:** reported per outcomes/comparison (see table below)
- **Duration of follow-up:**
  - 6 to 10 weeks for induction of remission
    - Sandborn 2013, 6 weeks

  - Feagan 2008, 8 weeks
  - Sands 2014, 10 weeks
- 52 weeks for maintenance of remission (Sandborn 2013, starting from 6 weeks)

- **Results and Certainty:**

Effects of vedolizumab vs. placebo

Outcome	Studies included	No. of patients (studies)	Risk ratio (95% CI)	Intervention group event rate (%)	Control group event rate (%)	Certainty (reason for downgrade)
induction of remission in anti-TNF naïve patients	Sandborn 2013 (GEMINI 2) Feagan 2008 Sands 2014 (GEMINI 3)	479 (3)	0.86 (0.79 to 0.94)	72.0% (211/293)	85.5% failure of induction of remission (159/186)	High
maintenance of remission at week 52 (among clinical responders)	Sandborn 2013	307 (1)		38.9% (60/154)	21.6% (33/153)	High
Serious infections (induction)	Sandborn 2013 (GEMINI 2) Feagan 2008 Sands 2014 (GEMINI 3)	1,069 (3)		0.45% (1/220) 0.44% (1/227) 0.95% (2/209)	1.35% (2/148) 1.7% (1/58) 0% (0/207)	Very low (risk of bias, extremely serious imprecision)[1,2]
Serious infections (maintenance)	Sandborn 2013 (GEMINI 2)	1,115 (1)		5.5% (45/814)	3.0% (9/301)	Low (risk of bias, imprecision)[1]
Malignancy (induction)	Sandborn 2013 (GEMINI 2) Feagan 2008 Sands 2014 (GEMINI 3)	1,069 (3)		0 0 0	0 0 0	Not informative
Malignancy (maintenance)	Sandborn 2013 (GEMINI 2)	1,115 (1)		0.5% (4/814)	0.3% (1/301)	Very low (extremely serious imprecision)[2]

1 Selective outcome reporting may limit interpretation of infectious outcomes
2 Extremely serious imprecision with only 0-4 events per trial arm

Other considerations:

Chandar 2015 did not provide clear quality of life information. In reporting on IBDQ for Sandborn 2013, Chandar 2015 indicated (page 1700) that there were 185 patients and reported a statistically significant improvement in IBDQ that was less than the minimum clinically important difference (mean difference 5.46, 95% CI 5.28–5.64).

COSTA 2013
Costa J, Magro F, Caldeira D, Alarcão J, Sousa R, Vaz-Carneiro A. Infliximab reduces hospitalizations and surgery interventions in patients with inflammatory bowel disease: a systematic review and meta-analysis. Inflamm Bowel Dis. 2013 Sep;19 (10):2098-110. PubMed

Relevant to FAQ4, FAQ5

This systematic review did not provide much additional data beyond the later systematic review (Mao 2017). Costa 2013 included Targan 1997 and Lemann 2006 (which were not included in Mao 2017) but the added information was limited. Targan 1997 had a sample size of 108 patients total (but only about 20 patients per trial arm) and had so few events that it only contributed 0.8% weight to the meta-analysis. Targan 1997 had follow-up limited to 12 weeks. Lemann 2006 had no event data. Therefore this Costa 2013 was not progressed to Evidence Synthesis.

DASSOPOULOS 2013
Dassopoulos T, Sultan S, Falck-Ytter YT, Inadomi JM, Hanauer SB. American Gastroenterological Association Institute technical review on the use of thiopurines, methotrexate, and anti-TNF-α biologic drugs for the induction and maintenance of remission in inflammatory Crohn's disease. Gastroenterology. 2013 Dec;145(6):1464-78. e1-5. PubMed

Relevant to FAQ2, FAQ6

- **Study design:** a technical review to support a guideline
  - utilized a systematic approach for literature evidence searching
  - three separate literature searches were conducted
    - one for evidence summaries (systematic reviews, meta-analyses, and health technology assessments)
    - one for RCTs for the outcomes of efficacy, infection, and lymphoma
    - one for observational evidence to supplement data on infection and lymphoma
- **Population:** adult patients with moderate-to-severe CD
- **Intervention:** anti-TNF alpha agent
  - review also includes information on methotrexate and thiopurines, but we limit our focus per Scoping to anti-TNF alpha agents
- **Comparison:** placebo
  - review also includes information on anti-TNF alpha agent monotherapy vs. other immunomodulator monotherapy, but we limit our focus per Scoping to placebo as the comparator
- **Study inclusion criteria:**
  - literature search to 2012
  - for studies of induction, researchers included studies with at least 12 weeks of therapy but evaluated remission prior to 26 weeks
  - for studies evaluating maintenance, only medically induced (rather than surgically induced) remission was evaluated
- **Number of studies:** 1 systematic review and meta-analysis including 15 RCTs
  - the authors cite the 15 RCTs as separate publications, but when presenting results, they utilized the results from the Ford 2011 systematic review and meta-analysis (Am J Gastroenterol 2011;106:644–659)

  - 10 RCTs for induction of remission
    - authors say they include 11 RCTs, but only present data for 10
    - certolizumab vs placebo (n=4) (outside of scope)
    - infliximab vs placebo (n=3)
    - adalimumab vs placebo (n=3)
  - 5 RCTs for maintenance of remission
    - certolizumab vs placebo (n=1) (outside of scope)
    - infliximab vs placebo (n=2)
    - adalimumab vs placebo (n=2)
- **Number of participants:** reported by outcome; see tables below
  - of note, the results include data for certolizumab pegol, and it is not clear from the authors' reporting to what degree these data might have influenced the results; as an example, however, in checking the trials contributing to the outcome of induction of remission, slightly over 50% of the data came from certolizumab.
- **Duration of follow-up:** duration ranged from 4 weeks to 52 weeks
- **Results and certainty:**

Anti-TNF alpha agents vs. placebo on induction of remission and serious infection in patients with moderate-to-severe CD*

Outcome (number of participants, number of studies, follow-up)	Study event rates, n/N (%)		Relative effect (95% CI)	Risk difference with anti-TNF agents	Certainty of evidence
	Control	Anti-TNF agents			
Failure to achieve remission (2756, 10, 4-12 weeks)	935/1158 (80.7)	1142/1598 (71.5)	RR 0.87 (0.80 to 0.94)	105 fewer per 1000 (from 48 fewer to 161 fewer)	Moderate[1]
Serious infections (2756, 10, 12-54 weeks)	22/1236 (1.8)	22/1408 (1.6)	RR 0.87 (0.47 to 1.60)	3 fewer per 1000 (from 14 fewer to 16 more)	Very low[2,3]

*Based on authors' identification of Ford 2011 (Am J Gastroenterol 2011;106:644–659) as the best source.
[1]Downgraded due to indirectness, as this summary estimate includes evidence for certolizumab pegol and the authors do not present sufficient information to permit examination of how certolizumab pegol influenced results
[2]Downgraded once due to concern over ascertainment bias
[3]Downgraded twice due to very serious imprecision

Anti-TNF alpha agents vs. placebo on maintenance of remission and serious infection in patients with moderate-to-severe CD*

Outcome (number of participants, number of studies, follow-up)	Study event rates, n/N (%)		Relative effect (95% CI)	Risk difference with anti-TNF agents	Certainty of evidence
	Control	Anti-TNF agents			
Failure to maintain remission (1390, 5, 26-60 weeks)	428/546 (78.4)	472/844 (55.9)	RR 0.71 (0.65 to 0.76)	227 fewer per 1000 (from 188 fewer to 274 fewer)	Moderate[1]

Serious infections (1907, 5, 26-60 weeks)	19/715 (2.7)	34/1192 (2.9)	RR 0.97 (0.54 to 1.76)	1 fewer per 1000 (from 12 fewer to 20 more)	Very low[2,3]

*Based on authors' identification of Ford 2011 (Am J Gastroenterol 2011;106:644–659) as the best source.
[1]Downgraded due to indirectness, as this summary estimate includes evidence for certolizumab pegol and the authors do not present sufficient information to permit examination of how certolizumab pegol influenced results
[2]Downgraded once due to concern over ascertainment bias
[3]Downgraded twice due to very serious imprecision

- **Other considerations:**
  - Data on lymphomas were also reported by the authors in their tabulated results for anti-TNF alpha agents for remission in CD. However, the authors obtained these data from the then-unpublished study by Lichtenstein et al (TREAT), and they note this study "evaluated risk across all immunomodulators (AZA, 6-MP, and MTX); however, in 95% of cases, this consisted of thiopurines". This is out of scope and therefore not reported here.
  - Because the data reported by Dassopoulous 2013 do not clearly limit to patients naïve to anti-TNF alpha agents (whereas the data in Singh 2018 do) and because the data reported by Dassopoulous 2013 include data for certolizumab (which may bias estimates, as noted in Stidham 2014 for example), we do not progress Dassopoulos 2013 to Evidence Synthesis.

DAVIES 2019
Davies SC, Nguyen TM, Parker CE, MacDonald JK, Jairath V, Khanna R. Anti-IL-12/23p40 antibodies for maintenance of remission in Crohn's disease. Cochrane Database Syst Rev. 2019 Dec 12;12:CD012804. PubMed

This Cochrane review was limited to only ustekinumab and the only relevant outcome reported was maintenance of remission. For this outcome, Davies 2019 included the same 2 trials of ustekinumab vs. placebo as Singh 2018 (ie, Sandborn 2012/CERTIFI and Feagan 2016/IM-UNITI) and showed consistent effects. Two differences in reporting were noted between Davies 2019 and Singh 2018. First, Davies 2019 reported the maintenance of remission outcome for the 2 trials separately only whereas Singh 2018 also reported a pooled result of the two trials. Second, Davies 2019 defined their outcome as failure to achieve maintenance of remission whereas Singh 2018 defined their outcome as achievement of maintenance of remission. However, the overall results of the two trials between the two SRs were generally consistent. Both reported a borderline significant benefit for Sandborn 2012/CERTIFI (Davies 2019 reported RR for failure to maintain clinical remission of 0.8, 95% CI 0.63 to 1.02; Singh 2018 reported OR for achieving maintenance of remission of 1.89, 95% CI 0.94 to 3.80) and both found a highly significant result for Feagan 2016/IM-UNITI. As shown in the Singh 2018 summary table, the pooled result of the two trials was highly significant (OR 2.02, 95% CI 1.35 to 3.30). Because of the narrow coverage of Davies 2019 (single relevant outcome from single agent), its lack of meta-analysis of the 2 eligible trials, and its consistent results for each trial with Singh 2018, we have prepared only a brief narrative summary of this Cochrane SR and do not progress it to Evidence Synthesis.

DRETZKE 2011
Dretzke J, Edlin R, Round J, Connock M, Hulme C, Czeczot J, Fry-Smith A, McCabe C, Meads C. A systematic review and economic evaluation of the use of tumour necrosis factor-alpha (TNF-α)

inhibitors, adalimumab and infliximab, for Crohn's disease. Health Technol Assess. 2011 Feb;15(6):1-244. doi: 10.3310/hta15060. PubMed

Relevant to FAQ3

Note: This systematic review was consulted only for QoL data from the maintenance trials of the anti-TNF alpha agents; we do this to provide insight into longer-term effects on QoL, as Abbass 2019 limited its consideration to induction trials (thus only providing information on early/short-term effects on QoL).

- **Study design:** systematic review of randomized trials
- **Population:** adult patients with moderate-to-severe
    - All patients received short-term induction therapy with anti-TNF alpha agents and then proceeded to maintenance with either placebo or an anti-TNF alpha agent.
    - This SR also considers induction trials, but we have limited our consideration here to maintenance trials; see "Other considerations" for more detail.
- **Intervention:** anti-TNF alpha agent
    - of 4 trials found, the anti-TNF alpha agents evaluated were infliximab and adalimumab
- **Comparison:** placebo

- **Number of studies:** 4
- **Number of participants:** 1,479
- **Duration of follow-up:** 48 to 56 weeks

- **Results and Certainty:**

Trial (Author Year)	**No participants, follow-up duration**	**Intervention**	**Key findings for IBDQ (range 32 to 224, higher scores better) and SF-36 (range 0 to 100 for overall score and subscales, higher scores better)***	**Certainty**
Rutgeerts 1999	73, 48 weeks	Infliximab	○ Median IBDQ score at randomization baseline and latest follow-up (48 weeks) for infliximab vs. placebo:† ○ randomization baseline: 165 vs. 169 ○ 48 weeks: 159 vs. 139	Very low (very serious risk of bias[1,2], imprecision[3])
Hanauer 2002 & 2004 (ACCENT I)	573, 54 weeks	Infliximab	<u>"Responders"</u> ○ Median IBDQ score at 54 weeks: ○ Infliximab 5mg/kg: 150; p = 0.015 vs. placebo ○ Infliximab 10mg/kg: 167; p < 0.0001 vs. placebo ○ Placebo: 136 ○ SF-36 score at 54 weeks PHYSICAL: ○ Infliximab: 39.2 +/- 11.9 ○ Placebo: 36.5 +/- 11.0 ○ SF-36 score at 54 weeks MENTAL: ○ Infliximab: 43.9 +/- 12.2 ○ Placebo: 42.1 +/- 12.0 ○ SF-36 score at 54 weeks mean improvement from baseline PHYSICAL: ○ Infliximab: 6.1 +/- 10.8; p = 0.014 vs. placebo ○ Placebo: 2.5 +/- 9.0 ○ SF-36 score at 54 weeks mean improvement from baseline MENTAL: ○ Infliximab: 5.1 +/- 12.8; p = 0.072 vs. placebo ○ Placebo: 2.0 +/- 10.9 <u>All patients</u> ○ % patients with IBDQ score > 170 at 54 weeks: ○ Infliximab 5mg/kg: 37.5; p = "not significant" vs. placebo ○ Infliximab 10mg/kg: 46.1; p < 0.05 vs. placebo ○ Placebo: 35.1	For outcomes in "responders": Very low (extremely serious risk of bias[1,2,4], imprecison[3]) For outcomes in all patients: Very low (very serious risk of bias[1,2], imprecision[3])

Sandborn 2007 (CLASSIC II)	55, 56 weeks	Adalimumab	○ Mean IBDQ score at randomization baseline and latest follow-up (56 weeks) for adalimumab 40 mg every other week, adalimumab 40 mg weekly, and placebo:‡ ○ randomization baseline: 187 vs. 191 vs. 188.5 ○ 56 weeks: 178.4 vs. 185.6 vs. 162.4	Low (very serious risk of bias[1,2], imprecision[3])
Colombel 2007 (CHARM)	778, 56 weeks	Adalimumab	○ Group IBDQ median score at 4 weeks ("responders"): ○ adalimumab 40 mg every other week: 174 ○ adalimumab 40 mg weekly: 165 ○ Placebo: 166.6 (data for quality of life outcomes after 4 weeks not available)	Very low (extremely serious risk of bias[1,2,4], imprecison[3])

* Comparative statistics (e.g., p values) are reported whenever they are available

† Obtained from figure (week 12 in the figure is the time at which patients were re-randomized into the maintenance trial)

‡ Week 4 in CLASSIC II is the week when patients were re-randomized (from CLASSIC I, the induction trial) into the maintenance trial (CLASSIC II)

1 Unclear amount of missing data and use of last observation carried forward for continuous outcomes

2 Considerable treatment switching in trials, and unclear how this was handled in analysis

3 Based on sample size and/or inadequate data to assess precision (e.g., no CIs).

4 This trial did not re-randomize induction responders to either maintenance therapy or placebo, but rather, reported outcomes for the subgroup of patients who were considered responders.

- **Other considerations:**
  - This SR also considers induction trials, but we have limited our consideration here to maintenance trials, as Abbass 2019 provides information on QoL at the short-term (Abbass 2019 limits its scope to induction trials).
  - Because Dretzke 2011 may not include more recent trials, we also conducted citation tracing from the more current SR Singh 2018 and searched PubMed/MEDLINE® for maintenance trials that might have been published after the closure of the search window of Sing 2018. This yielded Watanabe 2012, which we have summarized below.
  - Although all the trials are rated as providing Very low certainty, Hanauer 2002/2004 (ACCENT I) and Colombel 2007 (CHARM) suffer from extremely serious risk of bias (3 downgrades for risk of bias) whereas Rutgeerts 1999 and Sandborn 2007 (CLASSIC II) suffer from very serious risk of bias (2 downgrades for risk of bias). This is mainly a result of the data from Hanauer 2002/2004 (ACCENT I) and Colombel 2007 (CHARM) being subgroup analyses limited to "responders" (thus not a randomized comparison), whereas Rutgeerts 1999 and Sandborn 2007 (CLASSIC II) are maintenance trials that randomized patients who showed a response to treatment in an earlier induction trial (Targan 1997 and CLASSIC I, respectively). Hanauer 2002/2004 (ACCENT I) does report the outcome of "% patients with IBDQ score > 170 at 54 weeks" among all randomized patients, so this outcome is addressed separately from the other outcomes in this trial, but it still only has Very low certainty.

HAZLEWOOD 2015

Hazlewood GS, Rezaie A, Borman M, Panaccione R, Ghosh S, Seow CH, Kuenzig E, Tomlinson G, Siegel CA, Melmed GY, Kaplan GG. Comparative effectiveness of immunosuppressants and biologics for inducing and maintaining remission in Crohn's disease: a network meta-analysis. Gastroenterology. 2015 Feb;148(2):344-54.e5. PubMed

Relevant to FAQ2

- **Study design:** systematic review of randomized trials
- **Population:** adults with active Crohn's disease
    - although the inclusion criteria did not specify limiting to patients with moderate to severe Crohn's disease, the Discussion section pointed out that randomized controlled trials typically recruit Crohn's disease patients with moderate to severe disease activity and that the results are therefore most generalizable to such patients
    - included trials with or without prior exposure to anti-TNF therapy
- **Intervention:** infliximab, adalimumab, vedolizumab
    - additional agents included but not relevant to scoping: methotrexate, azathioprine/6-mercaptopurine, certolizumab, or combined therapies
- **Comparison:** placebo or an active agent
    - No head-to-head trials comparing biologic agents

- **Study inclusion criteria:**
    - search window close June 2014
    - > 24 weeks duration of treatment for trials assessing maintenance of remission
    - maintenance of remission trials not limited to only trials that randomized patients after successful induction but also included treat-through trials
        - Supplementary Table 4 columns indicate which trials were "Only Maintenance" and which were "Only treat-through"
            - "Only treat-through" - only EXTEND 2012 which evaluated adalimumab
            - "Only Maintenance" - all other maintenance trials, see table below

- **Number of studies:** reported per outcome/comparison (see table below)
- **Number of participants:** reported per outcome/comparison (see table below)
- **Duration of follow-up:**
    - for induction of remission
        - included trials assessing outcome between 4 and 17 weeks
        - outcome data was extracted at the time of the primary outcome specified in the trial, with the exception that data at or closest to 12 weeks was used when the time point of the primary outcome was not specified or induction was not the primary goal of the study
    - for maintenance of remission
        - outcome data was extracted at the end of the trial

- **Results and Certainty:**

Effects of adalimumab, infliximab and vedolizumab vs. placebo on remission outcomes

Outcome	No. of patients (studies)	Odds ratio (95% CI)	Control group event rate (%)	Certainty (reason for downgrade)*
induction of remission				
adalimumab Hanauer 2006/CLASSIC I Sandborn 2007/GAIN Watanabe 2012	714 (3)	2.89 (1.79 to 4.67)	9.1% (24/263)	Moderate (indirectness)[1]
infliximab Targan 1997	108 (1)	11.57 (1.49 to 90.10)	4.0% (1/25)	Low (inconsistency, imprecision)[2]
vedolizumab Feagan 2008 Sandborn 2013/GEMINI 2a Sands 2014/GEMINI 3	969 (3)	1.93 (1.33 to 2.81)	11.4% (47/413)	Moderate (indirectness)[1]
maintenance of remission				
adalimumab Colombel 2007/CHARM Sandborn 2007/CLASSIC II Rutgeerts 2012/EXTEND 2012 Watanabe 2012	726 (4)	4.88 (3.22 to 7.40)	13.1% (36/275)	Moderate (risk of bias)[3]
infliximab Hanauer 2002/ACCENT 1 Rutgeerts 1999	408 (2)	2.36 (1.22 to 4.55)	20.5% (30/146)	Moderate (risk of bias)[4]
vedolizumab Sandborn 2013/GEMINI 2b	461 (1)	2.20 (1.40 to 3.44)	21.6% (33/153)	High

* Some trials were judged by Hazlewood 2015 as 'unclear' on some risk of bias domains; Hazlewood 2015 does not provide any further detail about their 'unclear' assessments; for many of these 'unclear' assessments for trials that contributed substantially to the meta-analysis, we checked the original trial reports and did not find any concerns for risk of bias. A few with risk of bias (as noted in Singh 2018 and/or Singh 2014 are noted)

[1] Downgraded for indirectness because data reported for induction of remission combined patients with and without prior anti-TNF agent use whereas the primary question of interest for our Evidence Review is the effects in patients without prior anti-TNF agent use. Findings for these two outcomes were not included in Evidence Synthesis because of this indirectness.

[2] Imprecision downgrade because small number of events in control group, small sample size, and very wide CI. Inconsistency downgrade because the single trial with a very large effect size would be considered an outlier compared to all other trials in this systematic review, likely an artifact of a very low control group event rate not consistent with other trials. Although SR authors assessed trial as having unclear risk of bias for allocation concealment and blinding, the full text of the trial publication was checked and it was confirmed that concealed allocation and blinding were used.

[3] Colombel 2007/CHARM contributed 65% weight to meta-analysis and was rated in Singh 2014 and Singh 2018 as unclear risk of bias related to equal use of co-interventions in treatment and placebo groups.
[4] Hanauer 2002/ACCENT 1 contributed 70% weight to meta-analysis and was rated in Singh 2014 and Singh 2018 as unclear risk of bias related to equal use of co-interventions in treatment and placebo groups.

- **Other considerations:**
    - The induction of remission outcome was not progressed to evidence synthesis because we had numerous other sources that limited results to patients naïve to anti-TNF inhibitors.

LIN 2015
Lin L, Liu X, Wang D, Zheng C. Efficacy and safety of antiintegrin antibody for inflammatory bowel disease: a systematic review and meta-analysis. Medicine (Baltimore). 2015 Mar;94(10):e556. PubMed

This review was limited to only vedoluzimab and the only relevant outcome reported was induction of remission. It was judged to not add useful information to the other SRs we have summarized for 2 key reasons: 1) it did not include Sands 2014/GEMINI 3 which was published after the close of its search window, and 2) its meta-analysis on induction of remission pooled vedolizumab and natalizumab trials. Lin 2015 did not include a MA limited to vedolizumab trials.

MACDONALD 2016
MacDonald JK, Nguyen TM, Khanna R, Timmer A. Anti-IL-12/23p40 antibodies for induction of remission in Crohn's disease. Cochrane Database Syst Rev. 2016 Nov 25;11:CD007572. PubMed

This Cochrane review was limited to only ustekinumab and the only relevant outcome reported was induction of remission. Results were generally consistent with those reported in Singh 2018. Four differences in methods and reporting were noted between Macdonald 2016 and Singh 2018.

1. First, Macdonald 2016 defined their outcome as failure to induce clinical remission whereas Singh 2018 defined their outcome as induction of clinical remission.
2. Second, Macdonald 2016 reported results only pooled across trials of anti-TNF naive and anti-TNF experienced patients whereas Singh 2018 reported results only separately for each subgroup.
3. Third, Macdonald 2016 included in its MA (Analysis 2.1) results from 3 different intervention groups from Sandborn 2012 (ie, 1.0 mg/kg IV, 3.0 mg/kg IV, and 6.0 mg/kg IV – each reported separately as a subgroup) whereas Singh 2018 reported only results for 1 of the 3 subgroups. Singh 2018 pre-specified that when data for multiple doses of the same medication were available, they considered only data for the approved dose and administration.
4. Fourth, MacDonald 2016 included Sandborn 2008 (n = 53) which was not included in Singh 2018. It is not clear why Singh 2018 did not include Sandborn 2008. According to Singh 2014 Table 1, this trial includes 104 patients total, 52 of whom were biologic naive, and the Singh 2014 analysis (Fig 1 – restricts to biologic naive patients) includes 52 patients. Therefore, the results were apparently available separately for naive and experienced patients (which was a requirement for inclusion in Singh 2018 for trials including both types of patients). However, Sandborn 2008 only contributed 3.9% weight to the Cochrane meta-analysis.

Despite these relatively minor differences, the pooled results showed a significant benefit of ustekinumab on induction of remission in Singh 2018 (separately in subgroups of trials in patients

with prior exposure to anti-TNF agents and patients without prior exposure) and in Macdonald 2019 (in overall analysis, as it did not subgroup on this factor). Because of the narrow coverage of Macdonald 2016 (single relevant outcome from single agent) and its generally consistent results with Singh 2018, we have prepared only a brief narrative summary of this Cochrane SR and do not progress it to Evidence Synthesis.

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:** any age with moderate-to-severe active CD and ulcerative colitis (UC)
- **Intervention:** anti-TNF agents **(**adalimumab, infliximab), azathioprine, and vedolizumab
    - data for vedolizumab (integrin) was sparse and reported only for surgery and not pooled by the authors
- **Comparison:** placebo
- **Study inclusion criteria:**
    - must have been published by May 2016 (search window closure)
    - use of medications currently approved for use in CD
- **Number of studies:** 5 CD trials and 2 UC trials
    - 4 of the 5 CD trials reported on drugs of interest
        - Rutgeerts 2004 with infliximab (hospitalization and surgery outcomes)
        - Lichtenstein 2005 with infliximab (hospitalization and surgery outcomes)
        - Feagan 2008 with adalimumab (hospitalization and surgery outcomes)
        - Feagan 2008 with vedolizumab (surgery outcome)
- **Number of participants:** reported per outcome/comparison (see table below)
- **Duration of follow-up:**
    - 54 weeks for Rutgeerts 2004 (ACCENT I), intervention infliximab
    - 54 weeks for Lichtenstein 2005 (ACCENT II), intervention infliximab
    - for Feagan 2008 (CHARM), 56 weeks for intervention adalimumab**,** 104 weeks for intervention vedolizumab
- **Results and Certainty:**

Outcome	Intervention	No. of patients (studies)	Odds ratio (95% CI)	Certainty (reason for downgrade)
Hospitalization	Infliximab and adalimumab	1633 (3)	0.46 (0.36, 0.60)	Moderate (risk of bias)[1]
Surgery	Infliximab and adalimumab	1633 (3)	0.23 (0.13, 0.42)	Moderate (risk of bias)[1]
Surgery	Vedolizumab	185 (1)	0.43 (0.13, 1.39)*	Moderate (imprecision)[2]

[1]Unclear risk of bias due to crossovers and potential contamination, not fully assessed in critical appraisal by Mao 2017

[2]Small number of events and sample size, wide 95% confidence interval.

*Mao 2017 did not report the odds-ratio estimates and we used the reported event numbers for intervention and control to calculate the odds ratio.

Control event rates: hospitalization outcome

Study	Intervention	Control event rate % (number of events/number of patients)
Rutgeerts 2004	Infliximab	37.8% (71/188)
Lichtenstein 2005	Infliximab	31.5% (45/143)
Feagan 2008	Adalimumab	15.3% (40/261)

Control event rates: surgery outcome

Study	Intervention	Control event rate % (number of events/number of patients)
Rutgeerts 2004	Infliximab	7.4% (14/188)
Lichtenstein 2005	Infliximab	12.6% (18/143)
Feagan 2008	Adalimumab	3.8% (10/261)
Feagan 2008	Vedolizumab	10.3% (6/58)

MOĆKO 2016

Moćko P, Kawalec P, Smela-Lipińska B, Pilc A. Effectiveness and safety of vedolizumab for treatment of Crohn's disease: a systematic review and meta-analysis. Arch Med Sci. 2016 Oct 1;12(5):1088-1096. PubMed

The results of Moćko 2016 are most comparable with those of Singh 2018, which included and pooled the same two trials for the induction of remission outcome (ie, Sandborn 2013/GEMINI 2, Sands 2014/GEMINI 3). Both SRs reported the results subgrouped by prior anti-TNF agent use. Moćko 2016 and Singh 2018 reported identical results for both trials included in the "prior treatment" subgroup. For the "naive" subgroup, Moćko 2016 and Singh 2018 reported identical results for Sands 2014/GEMINI 3; however, for Sandborn 2013/GEMINI 2, Moćko 2016 reported proportion of patients with induction remission about twice that reported by Singh 2018, for the treatment and placebo arms. We checked the full-text of the Sandborn 2013/GEMINI 2 trial publication and determined that Singh 2018 used the correct numbers for induction of remission for this trial and that Moćko 2016 used incorrect numbers in their anti-TNF treatment-naive subgroup (Fig 3C). Because of the apparent errors in Moćko 2016 in the anti-TNF treatment-naive subgroup analysis, which is our subgroup analysis of primary interest, and because the prior anti-TNF treatment subgroup and the "general population" combined analysis in Moćko 2016 each have identical results for both trials as Singh 2018, Moćko 2016 was determined to add no new useful information and it was not progressed to Evidence Synthesis.

Finally, Moćko 2016 also reported serious infection outcome for which there was insufficient evidence (with only 5 events total, 3 in vedolizumab group and 2 in placebo group [Fig 5c]).

SANDBORN 2013

Sandborn WJ, Feagan BG, Rutgeerts P, Hanauer S, Colombel JF, Sands BE, Lukas M, Fedorak RN, Lee S, Bressler B, Fox I, Rosario M, Sankoh S, Xu J, Stephens K, Milch C, Parikh A; GEMINI 2 Study Group.

Vedolizumab as induction and maintenance therapy for Crohn's disease. N Engl J Med. 2013 Aug 22;369(8):711-21. PubMed

Relevant to FAQ3

Note: This randomized controlled trial was consulted only for quality of life data because other outcomes were adequately included in systematic reviews

- **Study design:** randomized controlled trials (one for induction, one for maintenance)
- **Population:** adults 18-80 years old with active CD
- **Intervention:** vedolizumab (maintenance trial included 2 treatment arms: every 4 weeks, every 8 weeks)
- **Comparison:** placebo
- **Number of studies:** 1 (for maintenance therapy)
- **Number of participants:** 307 for comparison of interest (vedolizumab every 8 weeks vs. placebo)
    - n=461 achieved response and were randomized into the maintenance phase (weeks 6 to 52)
        - n=153 (placebo)
        - n=154 (assigned and received vedolizumab every 8 weeks)
        - n=154 (assigned and received vedolizumab every 4 weeks)
- **Duration of follow-up:**
    - maintenance: 6 weeks (re-randomization) to 52 weeks
- **Certainty: Very low**
    - Risk of bias: very serious concern due to incomplete outcome data
    - Imprecision: very serious concern due to limited reporting
    - Indirectness: > 50% of original trial cohort were nonresponsive or intolerant to anti-TNF agents
- **Results:** IBDQ is the only QoL outcome reported
    - IBDQ ranges from 32 to 224, with higher scores indicated better quality of life
    - adjusted mean change scores from week 6 in IBDQ total scores (using last observation carried forward for missing data)
        - at week 30
            - 2.6 with vedolizumab
            - -2.5 with placebo
        - at week 52
            - 5.0 with vedolizumab
            - -9.0 with placebo
    - Statistical comparisons not reported

SANDS 2018

Sands BE, Han C, Gasink C, Jacobstein D, Szapary P, Gao LL, Lang Y, Targan S, Sandborn WJ, Feagan BG. The Effects of Ustekinumab on Health-related Quality of Life in Patients With Moderate to Severe Crohn's Disease. J Crohns Colitis. 2018 Jul 30;12(8):883-895. PubMed

Relevant to FAQ3

- **Study design:** 3 randomized controlled trials

  - UNITI-1 trial (induction)
  - UNITI-2 trial (induction)
  - IM-UNITI trial (maintenance)
- **Population:** adult patients with moderately to severely active CD
  - UNITI-1 (patients with an inadequate response or intolerance to tumour necrosis factor antagonists)
  - UNITI-2 (patients with an inadequate response or intolerance to conventional therapy)
  - IM-UNITI trial limited to ustekinumab-treated responders
- **Intervention:** ustekinumab
  - UNITI-1: ustekinumab 130 mg IV, or ustekinumab "6 mg/kg" (260 mg if weight ≤ 55 kg, 390 mg if weight 55-85 kg, 520 mg if weight > 85 kg) IV
  - UNITI-2: ustekinumab 130 mg, IV or ustekinumab "6 mg/kg" IV
  - IM-UNITI: ustekinumab 90 mg subcutaneous every 12 weeks, or ustekinumab 90 mg subcutaneous every 8 weeks
- **Comparison:**
  - UNITI-1: a single intravenous [IV] infusion of placebo
  - UNITI-2: a single intravenous [IV] infusion of placebo
  - IM-UNITI: subcutaneous placebo

- **Number of studies:** 3 RCTs
- **Number of participants:**
  - n=741 (UNITI-1)
  - n=627 (UNITI-2)
  - n=388 (IM-UNITI)
- **Duration of follow-up:** to 52 weeks
  - induction therapy from baseline to 8 weeks (UNITI-1 and UNITI-2)
  - maintenance therapy from 8 weeks to 52 weeks (IM-UNITI) (44 weeks more)
- **Certainty: High**

- **Results:**

Quality of life outcomes (based on IBDQ scores) in induction trials*

Outcome and Comparison	Placebo	Ustekinumab	Difference from placebo
Mean baseline IBDQ score, UNITI-1, 130 mg	120.0	119.5	-0.5
Mean baseline IBDQ score, UNITI-1, 6 mg/kg	120.0	118.2	-1.8
Mean baseline IBDQ score, UNITI-2, 130 mg	122.7	118.2	-4.5
Mean baseline IBDQ score, UNITI-2, 6 mg/kg	**122.7**	**122.8**	**0.1**
Mean IBDQ score at 8 weeks, UNITI-1, 130 mg	131.9	137.5	5.6
Mean IBDQ score at 8 weeks, UNITI-1, 6 mg/kg	131.9	140.3	8.4
Mean IBDQ score at 8 weeks, UNITI-2, 130 mg	137.3	147.3	10.0
Mean IBDQ score at 8 weeks, UNITI-2, 6 mg/kg	**137.3**	**158.0**	**20.7**
Mean change from 0 to 8 weeks, UNITI-1, 130 mg	11.9	18.1	6.2 (p = 0.013)
Mean change from 0 to 8 weeks, UNITI-1, 6 mg/kg	11.9	22.1	10.2 (p < 0.001)
Mean change from 0 to 8 weeks, UNITI-2, 130 mg	14.7	29.1	14.4 (p < 0.001)
Mean change from 0 to 8 weeks, UNITI-2, 6 mg/kg	**14.7**	**35.3**	**20.6 (p < 0.001)**
At least 16-point increase in IBDQ from 0 to 8 weeks, UNITI-1, 130 mg	36.5%	46.9%	10.4% (p = 0.019)
At least 16-point increase in IBDQ from 0 to 8 weeks, UNITI-1, 6 mg/kg	36.5%	54.8%	18.3% (p < 0.001)
At least 16-point increase in IBDQ from 0 to 8 weeks, UNITI-2, 130 mg	41.1%	58.7%	17.6% (p < 0.001)
At least 16-point increase in IBDQ from 0 to 8 weeks, UNITI-2, 6 mg/kg	**41.1%**	**68.1%**	**27.0% (p < 0.001)**

* IBDQ score ranges from 32 to 224, with higher scores representing better quality of life. Clinically meaningful improvements defined as an increase of ≥16 points in IBDQ score. Most relevant population (TNF inhibitor-naïve patients) and most relevant dose (6 mg/kg) bolded.

Quality of life outcomes (based on IBDQ scores) in maintenance trial*

Outcome and Comparison	Placebo	Ustekinumab	Difference from placebo
Mean baseline IBDQ score, ustekinumab every 12 weeks	163.6	165.8	2.2
Mean baseline IBDQ score, ustekinumab every 8 weeks	**163.6**	**170.5**	**6.9**
Mean IBDQ score at 44 weeks, ustekinumab every 12 weeks	142.1	156.9	14.8
Mean IBDQ score at 44 weeks, ustekinumab every 8 weeks	**142.1**	**160.5**	**18.4**
Mean change from 0 to 44 weeks, ustekinumab every 12 weeks	-21.5	-8.9	12.6 ($p < 0.001$)
Mean change from 0 to 44 weeks, ustekinumab every 8 weeks	**-21.5**	**-9.9**	**11.5 ($p = 0.003$)**
At least 16-point increase in IBDQ from baseline of induction trial to 44 weeks of maintenance trial, ustekinumab every 12 weeks	50.4%	61.3%	10.9% (not significant)
At least 16-point increase in IBDQ from baseline of induction trial to 44 weeks of maintenance trial, ustekinumab every 8 weeks	**50.4%**	**67.9%**	**17.5% ($p = 0.014$)**

* IBDQ score ranges from 32 to 224, with higher scores representing better quality of life. Clinically meaningful improvements defined as an increase of ≥16 points in IBDQ score. Most relevant dose (every 8 weeks) bolded.

SINGH 2018

Singh S, Fumery M, Sandborn WJ, Murad MH. Systematic review and network meta-analysis: first- and second-line biologic therapies for moderate-severe Crohn's disease. Aliment Pharmacol Ther. 2018 Aug;48(4):394-409. PubMed

Relevant to FAQ2

- **Study design:** systematic review of randomized trials
- **Population:** adults with moderate to severe active Crohn's disease
  - either treatment-naive (first-line) or previously exposed to anti-TNF agents (second-line)
  - effect in subgroups of trials of first-line and second-line treatment reported but no combined overall effect reported
- **Intervention:** biologic therapy with anti-TNF agents (infliximab, adalimumab, certolizumab pegol), vedolizumab, or ustekinumab
  - estimates for all agents except certolizumab (excluded per Evidence Report scoping) were extracted for this summary
- **Comparison:** placebo

- although another biologic agent was eligible as a comparison group, we extracted only estimates comparing a biological agent vs. placebo
- no head-to-head comparison trials were identified

- **Study inclusion criteria:**
  - maintenance of remission defined as prevention of relapse in patients with clinical response to induction therapy (ie, treat-through trials not included)
  - > 22 weeks duration of treatment for trials assessing maintenance of remission
  - trials in which results were not stratified by prior anti-TNF exposure status (for induction therapy) were not included
  - when data for multiple doses of the same medication were available, review authors considered only data for approved dose and administration

- **Number of studies:** reported per outcome/comparison (see table below)
- **Number of participants:** reported per outcome/comparison (see table below)
- **Duration of follow-up:**
  - for induction of remission
    - included trials assessing outcome up to 14 weeks
    - when outcomes were reported at multiple time points, review authors used outcomes at week 8 or 6
  - for maintenance of remission, outcomes were assessed at last point of follow-up, usually week 52

- **Results and Certainty:**

Outcome/Agent/Trial	**No. of patients (studies)**	**Odds ratio (95% CI)**	**Control group event rate (%)**	**Certainty (reason for downgrade)**
Induction of remission				
first-line biologic therapy				
infliximab Lemann 2006 Targan 1997	166 (2)	6.35 (3.04 to 13.28)	28% (23/82)	High
adalimumab Hanauer 2006/CLASSIC I Watanabe 2012	174 (2)	3.80 (1.76 to 8.18)	13.1% (11/84)	High
vedolizumab Sandborn 2013/GEMINI II Sands 2014/GEMINI III*	294 (2)	2.68 (1.35 to 5.31)	10.2% (13/128)	High
ustekinumab Feagan 2016/UNITI–2	400 (1)	2.75 (1.76 to 4.32)	19.5% (39/200)	High
second-line biologic therapy				
adalimumab Sandborn 2007/GAIN Watanabe 2012	357 (2)	3.56 (1.82 to 6.94)	7.3% (13/179)	High

vedolizumab Sandborn 2013/GEMINI II Sands 2014/GEMINI III	490 (2)	1.52 (0.86 to 2.70)	9.7% (22/227)	High
ustekinumab Sandborn 2012/CERTIFI 2012 Feagan 2016/UNITI-1	759 (2)	2.66 (1.71 to 4.14)	8.4 % (32/379)	High
Maintenance of remission (among clinical responders)				
infliximab Hanauer 2002/ACCENT-I Rutgeerts 1999	296 (2)	2.87 (1.72 to 4.80)	20.5% (30/146)	Moderate (risk of bias) [1]
adalimumab Colombel 2007/CHARM Sandborn 2007/CLASSIC 2 Watanabe 2012	422 (3)	4.43 (2.69 to 7.29)	14.3% (30/210)	Moderate (risk of bias)[2]
vedolizumab Sandborn 2013/GEMINI II	307 (1)	2.32 (1.4 to 3.84)	21.6% (33/153)	High
ustekinumab Sandborn 2012/CERTIFI Feagan 2016/IM-UNITI	404 (2)	2.02 (1.35 to 3.30)	32.8% (67/204)	High

* This trial mistakenly listed in Singh 2018 Figures 2 and 3 as "GEMINI II 2014"; Characteristics of Included Studies (Table 1) clearly indicates that GEMINI 2 is Sandborn 2013 and GEMINI III is Sands 2014.
1 Hanauer 2002/ACCENT-I contributed 81% weight to meta-analysis and was rated in Singh 2014 and Singh 2018 as unclear risk of bias related to equal use of co-interventions in treatment and placebo groups.
2 Colombel 2007/CHARM contributed 81% weight to meta-analysis and was rated in Singh 2014 and Singh 2018 as unclear risk of bias related to equal use of co-interventions in treatment and placebo groups.

SINGH 2014
Singh S, Garg SK, Pardi DS, Wang Z, Murad MH, Loftus EV Jr. Comparative efficacy of biologic therapy in biologic-naïve patients with Crohn disease: a systematic review and network meta-analysis. Mayo Clin Proc. 2014 Dec;89(12):1621-35. PubMed

Relevant to FAQ2

- **Study design:** systematic review of randomized trials
- **Population:** adults with moderate to severe active Crohn's disease
  - limited to trials of patients without prior exposure to anti-TNF therapy
- **Intervention:** infliximab, adalimumab, vedolizumab, ustekinumab
  - additional agents included but not relevant to scoping: certolizumab and natalizumab
- **Comparison:** placebo
  - although another biologic agent was eligible as a comparison group, all included trials used placebo control

- **Study inclusion criteria:**
  - search window close September 2013

  - maintenance of remission defined as prevention of relapse in patients with clinical remission to induction therapy (ie, treat-through trials not included)
  - > 22 weeks duration of treatment for trials assessing maintenance of remission
  - trials in which results were not stratified by prior anti-TNF exposure status (for induction therapy) were not included
- **Number of studies:** reported per outcome/comparison (see table below)
- **Number of participants:** reported per outcome/comparison (see table below)
- **Duration of follow-up:**
  - for induction of remission
    - included trials assessing outcome up to 14 weeks
    - when outcomes were reported at multiple time points, review authors used outcomes at 2 to 4 weeks after the completion of induction regimen
  - for maintenance of remission
    - included trials assessing outcome up to 60 weeks
    - when outcomes were reported at multiple time points, review authors used outcomes at week 52

- **Results and Certainty:**

Outcome	No. of patients (studies)	Risk ratio (95% CI)	Intervention group event rate (%)	Control group event rate (%)	Certainty (reason for downgrade)
induction of remission					
infliximab Targan 1997 Lémann 2006	219 (2)	3.11 (0.72 to 13.45)	49.3% (68/138)	27.2% (22/81)	Moderate (imprecision)
adalimumab Hanauer 2006/CLASSIC I Watanabe 2012	263 (2)	2.30 (1.27 to 4.16)	30.7% (55/179)	13.1% (11/84)	High
vedolizumab Feagan 2008 Sandborn 2013/GEMINI II	378 (2)	1.76 (1.11 to 2.78)	26.4 % (64/242)	14.0% (19/136)	Moderate (risk of bias)[1]
ustekinumab Sandborn 2008	52 (1)	0.79 (0.44 to 1.39)	42.3% (11/26)	53.8% (14/26)	Very low (very serious imprecision, indirectness)[2]
maintenance of remission (among clinical responders)					
infliximab Hanauer 2002/ACCENT 1 Rutgeerts 1999	408 (2)	2.15 (1.52 to 3.05)	43.5% (114/262)	20.5% (30/146)	Moderate (risk of bias)[3]
adalimumab Colombel 2007/CHARM Sandborn 2007/CLASSIC II Watanabe 2012	597 (3)	2.65 (1.63 to 4.32)	42.6% (165/387)	14.3% (30/210)	Moderate (risk of bias)[4]
vedolizumab Sandborn 2013/GEMINI II	461 (1)	1.75 (1.25 to 2.44)	37.7% (116/308)	21.6% (33/153)	High

ustekinumab Sandborn 2012/CERTIFI 2012	145 (1)	1.52 (0.96 to 2.42)	41.7% (30/72)	27.4% (20/73)	Moderate (imprecision)

1 Feagan 2008 contributed majority of weight to meta-analysis and was rated in Singh 2014 as unclear risk of bias related to equal use of co-interventions in treatment and placebo groups.
2 Sandborn 2008 had such a high control group event rate it does not appear to reflect the population of interest.
3 Hanauer 2002/ACCENT 1 contributed majority of weight to meta-analysis and was rated in Singh 2014 and Singh 2018 as unclear risk of bias related to equal use of co-interventions in treatment and placebo groups.
4 Colombel 2007/CHARM contributed > 50% weight to meta-analysis and was rated in Singh 2014 and Singh 2018 as unclear risk of bias related to equal use of co-interventions in treatment and placebo groups.

STIDHAM 2014
Stidham RW, Lee TC, Higgins PD, Deshpande AR, Sussman DA, Singal AG, Elmunzer BJ, Saini SD, Vijan S, Waljee AK. Systematic review with network meta-analysis: the efficacy of anti-TNF agents for the treatment of Crohn's disease. Aliment Pharmacol Ther. 2014 Jun;39(12):1349-62. PubMed

Relevant to FAQ2

- **Study design:** systematic review of randomized trials
- **Population:** adults with Crohn's disease
  - although the inclusion criteria did not specify limiting to patients with moderate to severely active Crohn's disease, the trials included were consistent with those of other SRs that did limit to such patients
  - included trials with or without prior exposure to anti-TNF therapy
- **Intervention:** anti-TNF agents
  - adalimumab, infliximab, and certolizumab
- **Comparison:** placebo

- **Study inclusion criteria:**
  - search window close August 2013

- **Number of studies:** reported per outcome/comparison (see table below)
- **Number of participants:** reported per outcome/comparison (see table below)
- **Duration of follow-up:**
  - for induction of remission
    - included trials assessing outcome within 12 weeks
      - not clear which time point would be used if outcome assessed at > 1 time point within 12 weeks
  - for maintenance of remission
    - included trials assessing outcome at 24 to 30 weeks
      - not clear which time point would be used if outcome assessed at > 1 time point between 24 and 30 weeks
      - in justifying their time range for maintenance outcome, review authors noted that "While some studies included 52 week data, more complete

data were available for 24–30 week time frames, permitting a more homogenous endpoint comparison between studies…"

- **Results and Certainty:**

Outcome	No. of patients (studies)	Risk ratio/RR (95% CI)	Intervention group event rate (%)	Control group event rate (%)	Certainty (reason for downgrade)
induction of remission					
infliximab Targan 1997	52 (1)	3.7 (0.87 to 15.80)	29.6% (8/27)	8.0% (2/25)	Low (inconsistency, imprecision)[1]
adalimumab Hanauer 2006/CLASSIC I Sandborn 2007/GAIN	475 (2)	2.94 (1.86 to 4.66)	25.9% (61/235)	8.75% (21/240)	Moderate (indirectness)[2]
certolizumab* Schreiber 2005 Sandborn 2007/CLASSIC II Sandborn 2011	1244 (3)	1.22 (1.0 to 1.50)	25.2% (158/627)	20.6% (127/617)	High
*pooled effect**	1771 (6)	1.66 (1.17 to 2.36)	25.5% (227/889)	17.0% (150/882)	
maintenance of remission					
infliximab Hanauer 2002/ACCENT 1	223 (1)	1.86 (1.21 to 2.86)	38.9% (44/113)	20.9% (23/110)	Moderate (risk of bias)[3]
adalimumab Colombel 2007/CHARM Sandborn 2007/CLASSIC II	379 (2)	2.06 (1.50 to 2.82)	44.0% (84/191)	20.2% (38/188)	Moderate (risk of bias)[4]
certolizumab* Schreiber 2007/PRECISE Sandborn 2007	1088 (2)	1.62 (1.30 to 2.02)	27.4% (150/547)	17.0% (92/541)	High
*pooled effect**	1690 (5)	1.78 (1.51 to 2.09)	32.7% (278/851)	18.2% (153/839)	

*Certolizumab results reported here with the interpretation that certolizumab may have lower efficacy than the other agents scoped of interest, and this is why we do not advanced pooled TNF drug class effect estimates forward that are based in part on certolizumab.

1 Imprecision downgrade because small number of events in control group, small sample size, and very wide CI that overlaps with no effect. Inconsistency downgrade because only single trial with a very large effect size that may be considered an outlier.

2 Downgraded for indirectness because data reported for induction of remission combined patients with and without prior anti-TNF agent use whereas the primary question of interest for our Evidence Review is the effects in patients without prior anti-TNF agent use.

3 Hanauer 2002/ACCENT-I was rated in Singh 2014 and Singh 2018 as unclear risk of bias related to equal use of co-interventions in treatment and placebo groups.

4 Colombel 2007/CHARM contributed majority of weight to meta-analysis and was rated in Singh 2014 and Singh 2018 as unclear risk of bias related to equal use of co-interventions in treatment and placebo groups.

Ultimately Stidham 2014 did not introduce new findings compared to later systematic reviews so was not advanced to synthesis efforts.

WATANABE 2012
Watanabe M, Hibi T, Lomax KG, Paulson SK, Chao J, Alam MS, Camez A; Study Investigators. Adalimumab for the induction and maintenance of clinical remission in Japanese patients with Crohn's disease. J Crohns Colitis. 2012 Mar;6(2):160-73. doi: 10.1016/j.crohns.2011.07.013. Epub 2011 Aug 26. PubMed

Relevant to FAQ3

Note: This trial was consulted only for quality of life data for the anti-TNF agents, and we limit our focus to the maintenance trial (see "Other considerations" below for more detail).

- **Study design:** randomized trial
- **Population:** Japanese patients ≥15 and ≤75 years of age with moderate-to-severe CD who showed a response to the induction phase of the trial

- **Intervention:** adalimumab 40 mg every other week
- **Comparison:** placebo

- **Study inclusion criteria:** showed response to induction therapy during induction trial
    - induction trial inclusion criteria allowed for prior exposure to anti-TNF therapy, but patients could not have had prior non-response to primary anti-TNF therapy

- **Number of studies:** 1
    - this publication also reports on the induction trial, but we limit our focus here to the maintenance trial (see "Other considerations" below for more detail)
- **Number of participants:** 50
    - only patients randomized to the maintenance trial are considered here
    - only 43 of the 50 are included in the dataset used to analyze efficacy outcomes (the "modified" full analysis set)
        - the full analysis set was comprised of all patients who entered the randomized, double-blind portion and received at least 1 dose of the study drug, and the modified full analysis set was comprised of those in the full analysis set who had received adalimumab during the induction trial
- **Duration of follow-up:** 52 weeks

- **Results:**
    - IBDQ (32 to 224, higher scores are better)
        - mean score at baseline of randomization into maintenance trial: 175 vs. 178 in adalimumab vs. placebo groups, respectively (obtained from figure)
        - mean score at 52 weeks after randomization: 170.1 vs. 156.5 in adalimumab vs. placebo groups, respectively (170.1 reported directly by the authors, 156.5 obtained from figure)
        - difference in change from baseline between two groups was not formally assessed
        - difference between two groups at week 52 was not significantly different
    - SF-36, physical component (0 to 100, higher scores are better)

        - graphical data not reported; authors only report results briefly in text of publication
        - from baseline of maintenance trial to week 52 after randomization into the maintenance trial, authors note patients treated with adalimumab "were able to maintain" the improvement in SF-36 they experienced from induction therapy through week 52 of the maintenance trial (authors words), whereas patients assigned to placebo had a 2.2-point reduction in their SF-36 score; however, it is questionable whether this is a meaningful difference in change from baseline between groups given the range of the SF-36 scale
        - difference between two groups at week 52 was not significantly different

- **Certainty: Very low**
    - **Risk of bias:** Very serious concern
        - substantial cross-over and/or discontinuation
            - by week 52, of 50 people randomized to maintenance trial
                - 34 (20 from placebo group and 14 in adalimumab group) moved to open-label treatment with adalimumab, and it is not clear how these people factored into the analyses
                - 17 discontinued prior to the 52-week follow-up point (13 who moved to open-label adalimumab, 3 who stayed in placebo group, and 1 who stayed in adalimumab group)
        - authors use last observation carried forward for missing continuous data
    - **Imprecision:** Serious concern
        - small sample size and inadequate information provided to assess precision
    - **Indirectness:** No serious concern
    - **Inconsistency:** No serious concern
    - **Other considerations:** We limited our consideration of Watanabe 2012 to the quality of life data from the maintenance trial only, as we have multiple SRs that include Watanabe 2012 for the outcomes of induction and maintenance of remission. For quality of life, the Abbass 2019 SR provides information on short-term quality of life (i.e., from induction therapy) and the Dretzke 2011 SR provides information on longer-term quality of life (i.e., from maintenance trials), but could not have included Watanabe 2012 given its search window and date of publication. With Very low certainty Watanabe 2012 was not carried forward to Evidence Synthesis.

Characteristics and Results of Studies Reporting Infections and Malignancies

Chandar 2015 and Dassopoulos 2013 reported above also included infections and/or malignancies.

ASKLING 2011
Askling J, Fahrbach K, Nordstrom B, Ross S, Schmid CH, Symmons D. Cancer risk with tumor necrosis factor alpha (TNF) inhibitors: meta-analysis of randomized controlled trials of adalimumab, etanercept, and infliximab using patient level data. Pharmacoepidemiol Drug Saf. 2011 Feb;20(2):119-30. PubMed

Relevant to FAQ6

- **Study design:** individual patient data (IPD) meta-analysis of randomized trials
- **Population:** adults who received at least one dose of adalimumab or infliximab
    - this study also includes data for etanercept, but we focus this summary on infliximab and adalimumab per Scoping
- **Intervention:** adalimumab or infliximab
- **Comparison:** placebo or standard-care

- **Study inclusion criteria:**
    - >4 weeks duration
    - could not be exclusively comprised of patients with prior exposure to a TNF inhibitor
    - corporate sponsorship with individual patient data available
        - study was done at the request of the European Medicines Agency to the Market Authorization Holders (MAHs), with the MAHs funding the project, identifying eligible trials, and providing IPD, but the project was planned and conducted by an independent group
- **Number of studies:** 46
    - 23 each for adalimumab and infliximab
- **Number of participants:** 13,668
- **Duration of follow-up:** 7,620 person-years
- **Certainty and Results:**

Non-melanoma skin cancer with anti-TNF alpha therapy*

Outcome	Users of anti-TNF agents			Non-users of anti-TNF agents			Hazard ratio (95% credible interval)†	Certainty
	Person-years of follow-up	No. of events	Incidence rate per 1,000 person-years	Person-years of follow-up	No. of events	Incidence rate per 1,000 person-years		
Adalimumab	2863	23	8.0	1468	5	3.4	2.59 (1.01, 7.67)	Low[1,2]
Infliximab	1954	14	7.2	650	4	6.2	1.19 (0.39, 4.61)	Very low[2,3]

Age was included as a covariate in individual drug models

*Defined as all cancer events (definite or probable cancers) diagnosed during the study period, using the date of diagnosis as the event date, irrespective of judgments on pre-trial prevalence. The authors also reported analyses that excluded events that were in retrospect judged to be "definitely" or "probably" prevalent at the trial start. We have not reported those here give n it is not clear how meaningful these additional analyses are in the context of the outcomes shown in the table and the Low to Very low certainty of the data regardless of the outcome used.

†The authors report the drug-specific HRs and the 95% CrIs reflect the range of HRs found under three different priors: (1) a mean HR of approximately 2 (95% CrI 0.04 to 110), (2) a mean HR of approximately 1 (95% CrI 0.02 to 55), and (3) a mean HR of approximately 2 (95% CrI 0.50 to 8.2). There are some minor discrepancies in the footnotes for the tabul ated data and the methods reported in the methods appendix; we present the methods reported in the appendix. Additionally, the authors present only one HR and 95% CrI for the outcome shown in the above table, so it is not clear if all 3 priors were applied to this outcome (and they all produced the same result) or if the different priors were not applied to this outcome.

[1]Downgraded once for imprecision (lower bound of the 95% CrI includes absence of important harm)

[2]The reporting did not present sufficient information for an examination of risk of bias or consistency, so we downgraded once (we felt downgrading once in each category may be overly punitive).

[3]Downgraded twice due to very serious imprecision (point estimate and upper bound of the 95% CrI suggest increased risk, but the lower bound of the 95% CrI suggests no harm and possible – though implausible – reduction in risk)

- **Other considerations:**
  - Although Askling 2011 also reports on "all cancers", we focused on non-melanoma skin cancer because:
    - RCTs generally have a very limited ability to detect infrequent or latent disease like cancer (unlike observational cohort studies), being driven by their often-smaller sample size (thus being underpowered) and shorter duration of follow-up.
    - The authors defined the outcome of "all cancers" very broadly; this increases the risk of diluting or obfuscating harms due to specific cancers, which is an important consideration given the prior probability (i.e., existing concerns) over the possibility that anti-TNF alpha agents might increase the risk of hematologic or dermatologic malignancies specifically.
    - Non-melanoma skin cancer had a statistically significant signal of increased risk despite the numerous biases against finding a risk in RCTs, which may suggest an even stronger signal of a genuine risk despite the Low to Very low certainty of the evidence.

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 IBD (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

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

FORD 2013

Ford AC, Peyrin-Biroulet L. Opportunistic infections with anti-tumor necrosis factor-α therapy in inflammatory bowel disease: meta-analysis of randomized controlled trials. Am J Gastroenterol. 2013 Aug;108(8):1268-76. PubMed

Relevant to FAQ6

- **Study design:** systematic review and meta-analysis of RCTs
- **Population:** adult patients with active or quiescent IBD (CD and UC)
    - >90% of participants >16 years of age
- **Intervention:** adalimumab, certolizumab, golimumab, or infliximab
    - certolizumab is outside scoping, but summary results including certolizumab are considered here given the authors' subgroup analysis by type of anti-TNF alpha agent did not suggest heterogeneity of treatment effect for certolizumab
- **Comparison:** placebo
- **Study inclusion criteria:**
    - literature search to 2012
    - ≥14 days of therapy with ≥1 administration of biologic agent
    - reported on opportunistic infections
    - first period of crossover RCTs were also eligible for inclusion
- **Number of studies:** 22 RCTs
    - 21 articles reported on 22 RCTs (15 CD trials, 7 UC trials)
- **Number of participants:** 7,054

  - 4,566 in CD trials
  - 2,488 in UC trials
- **Duration of follow-up:** 2 to 56 weeks
- **Results and certainty:**

Opportunistic and serious opportunistic infections with anti-TNF alpha agents in IBD

Outcome (number of participants, number of studies)	Control group risk, n/N (%)	Intervention group risk, n/N (%)	Relative risk (95% CI)	Certainty
Opportunistic infection (7,054, 22)	9/2919 (0.31%)	39/4135 (0.94%)	2.05 (1.10 to 3.85)	High certainty that anti-TNF agents increase risk; Low certainty in reported magnitude of increase (very serious risk of bias)[1]
More serious opportunistic infection* (7,054, 22)	7/2919 (0.24%)	27/4135 (0.65%)	1.95 (0.97 to 3.90)	Moderate certainty that anti-TNF agents increase risk; Very low certainty in reported magnitude of increase (very serious risk of bias)[1,2]

*Excludes oral or esophageal candidiasis and herpes zoster infection

[1] 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.

[2] We downgrade further for imprecision with confidence intervals including no effect.

Ford 2013 ultimately not progressed to Evidence Synthesis because findings were consistent with Bonovas 2016.

KIRCHGESNER 2018

Kirchgesner J, Lemaitre M, Carrat F, Zureik M, Carbonnel F, Dray-Spira R. Risk of Serious and Opportunistic Infections Associated With Treatment of Inflammatory Bowel Diseases. Gastroenterology. 2018 Aug;155(2):337-346.e10. PubMed

Relevant to FAQ6

- **Study design:** nationwide population-based observational study
- **Population:** all patients 18 years or older identified with IBD 2009-2014 in France with inflammatory bowel disease
- **Intervention:** patients treated with anti-TNF monotherapy agents (infliximab and adalimumab) or combination therapy (anti-TNF plus thiopurine)
- **Comparison:** patients not treated with anti-TNF monotherapy agents

- **Number of participants:** 190,694
  - 26,255 treated with anti-TNF agents
  - 128,285 not treated with anti-TNF agents or thiopurines
  - 47,572 treated with thiopurine monotherapy
  - 12,023 treated with combination therapy
- **Duration of follow-up:** 57,835 person-years of follow-up in the exposed anti-TNF group
  - 719,407 person-years of follow-up in the unexposed (group no anti-TNF, no thiopurines)

- **Certainty: Moderate**
  - Observational evidence starts as low certainty using GRADE methods but if the effect measure is expressed as a RR or HR, the certainty may be upgraded one level if the estimate is >2 or <0.5 (based on direct evidence, with no plausible confounders). This is adjusted analysis that considered time-fixed and time-varying confounders and while adjustment still cannot control for all unknown prognostic factors, we feel that the estimate of effect is robust and as such upgraded one level. We found no issues with precision, consistency or directness.

- **Results:**

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
†† Two groups of covariates were considered in the adjusted modelling: i) time-fixed covariates measured at cohort entry and included sex, age, disease duration, exposure to methotrexate and amino salicylates in the preceding 6 months, IBD-related endoscopy and imaging in the preceding year, history of IBD-related hospitalization or surgery, and comorbidities and ii) time-varying covariates, including IBD activity as measured by exposure to corticosteroids and occurrence of IBD-related hospitalization or surgery. Hazard ratios of site-specific serious infections and opportunistic infections are available in Supplementary Table 6; notably, all HRs were >2.0 in patients exposed to anti-TNF monotherapy vs unexposed to thiopurines or anti-TNFs for serious infections except gastrointestinal infections HR 1.89 (1.57 to 2.26); ear, nose, and/or throat infections HR 1.76 (1.15 to 2.70); and musculoskeletal infections HR 1.81 (1.02 to 3.22). Similarly, all opportunistic infections by pathogen HRs were >2.0 except fungal infections HR 1.90 (0.75 to 4.80)

As noted in the table below, among patients exposed to thiopurines, additional exposure to anti-TNF therapy was associated with serious infections (HR 2.11) and opportunistic infections (hazard ratio 2.11), and associations were similar in CD and in UC

Multivariable adjusted HRs (95% CI) of serious and opportunistic infections according to treatment exposure by IBD subtype

Type of infection and IBD subtype	Exposed to Combination Therapy vs Anti-TNF Monotherapy	Exposed to Combination Therapy vs Thiopurine Monotherapy	Exposed to Anti-TNF Monotherapy vs Thiopurine Monotherapy
Serious infection overall	1.23 (1.05 to 1.45)	2.11 (1.80 to 2.48)	1.71 (1.56 to 1.88)
• CD	1.17 (0.96 to 1.43)	2.00 (1.64 to 2.44)	1.70 (1.52 to 1.91)
• UC	1.32 (1.00 to 1.74)	2.48 (1.91 to 3.22)	1.88 (1.58 to 2.25)
Opportunistic infection overall	1.96 (1.32 to 2.91)	2.11 (1.45 to 3.08)	1.08 (0.83 to 1.40)
• CD	1.88 (1.13 to 3.13)	1.91 (1.17 to 3.12)	1.02 (0.74 to 1.39)
• UC	1.91 (1.01 to 3.61)	2.73 (1.54 to 4.85)	1.43 (0.89 to 2.29)

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.

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

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 to 2.56)	1.45 (0.79 to 2.67)	1.02 (0.55 to 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 basal 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 patients	No. of events	No. of patients	No. of 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.

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).

SIEGEL 2009

Siegel CA, Marden SM, Persing SM, Larson RJ, Sands BE. Risk of lymphoma associated with combination anti-tumor necrosis factor and immunomodulator therapy for the treatment of Crohn's disease: a meta-analysis. Clin Gastroenterol Hepatol. 2009 Aug;7(8):874-81. PubMed

Relevant to FAQ6

- **Study design:** systematic review and meta-analysis of randomized controlled trials, cohort studies (prospective or retrospective), or case series
- **Population:** adult patients with CD
- **Intervention:** infliximab, adalimumab, and certolizumab pegol
  - could be for induction or maintenance therapy
  - an average of 66% of participants were taking immunomodulators as well
- **Comparison:** general CD population or those with CD taking immunomodulator monotherapy
  - standardized incidence ratios (SIRs) were calculated by comparing the pooled rate of non-Hodgkin's lymphoma (NHL) among people using anti-TNF alpha agents with (1) the expected rate of NHL derived from the Surveillance Epidemiology & End Results (SEER) database and (2) the NHL rate from a meta-analysis of people with CD who were treated with the immunomodulators azathioprine or 6-mercaptopurine
  - Siegel 2009 note the largest study of lymphoma risk in patients with CD did not show an increased baseline risk when compared with the general population; they thus felt SEER was a reasonable source for estimating the baseline rate of NHL in people with CD
- **Study inclusion criteria:**
  - literature search to 2007
  - reported adverse conditions
  - median follow-up of at least 48 weeks
- **Number of studies:** 26
  - 9 RCTs
  - 3 cohort studies
  - 14 case series
- **Number of participants:** 8,905
  - 6,503 patients for infliximab (22 studies)
  - 1,497 patients for adalimumab (3 studies)
  - 905 patients for certolizumab pegol (1 study)
- **Duration of follow-up:** mean duration of follow-up was 74 weeks
  - 21,178 patient-years observation for infliximab, adalimumab, and certolizumab groups
- **Certainty and results:**

Rate of NHL for SEER, Immunomodulator, and Anti-TNF Treated Patients

	NHL rate per 10,000 patient-years	SIR	95% CI	Certainty
SEER all age groups	1.9	-	-	-
IM alone	3.6	-	-	-
Anti-TNF vs SEER	6.1	3.23	1.5 to 6.9	Very low (risk of bias, inconsistency, imprecision)[1-3]
Anti-TNF vs. SEER (sensitivity analysis excluding studies with > 15% dropout)	9.4	4.9*	1.8 to 12.3	
Anti-TNF vs IM alone	6.1	1.7	0.5 to 7.1	Very low (risk of bias, inconsistency, very serious imprecision)[1,2,4]

IM, immunomodulator; NHL, non-Hodgkin's lymphoma; SEER, Surveillance, Epidemiology, and End Results program; SIR, standardized incidence ratio

*The authors report an SIR of 9.4, but it appears this may be a transposition error. Given the NHL rate with anti-TNF alpha agents per 10,000 patient-years is estimated at 9.4 and the SEER rate per 10,000 patient-years is estimated at 1.9, it is

implausible that the SIR would be 9.4. In contrast, an SIR of 4.9 would be compatible with these estimates (e.g., 1.9 * 4.9 = 9.31, with the marginal discrepancy possibly being attributable to the effects of rounding).

[1]Certainty started at low due to the principally observational nature of the data
[2]Heterogeneity in rates across studies
[3]Serious imprecision due to small number of events (only 13 events total with anti-TNF therapy)
[4]Very serious imprecision (small number of events and wide CI)

Risk estimates from a systematic review of diverse study types and durations of observation are not clearly informative. To estimate the risk of NHL with anti-TNF therapy we identified the largest cohort study with the most events (Lichtenstein) and this study had 6 events over 13,126 patient-years, or an estimated 4.6 per 10,000 patient-years.

Evidence report for biologics in Crohn's disease

Reference list

Prepared by EBSCO Information Services

February 13, 2020

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

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