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Davies SC, Hussein IM, Nguyen TM, Parker CE, Khanna R, Jairath V

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TABLE OF CONTENTS

HEADER 1
ABSTRACT 1
PLAIN LANGUAGE SUMMARY 2
SUMMARY OF FINDINGS 4
BACKGROUND 6
OBJECTIVES 7
METHODS 7
RESULTS 8
Figure 1. 10
Figure 2. 12
DISCUSSION 14
AUTHORS' CONCLUSIONS 15
REFERENCES 16
CHARACTERISTICS OF STUDIES 20
DATA AND ANALYSES 25
Analysis 1.1. Comparison 1: Tofacitinib versus placebo, Outcome 1: Failure to achieve clinical remission at 52 weeks (5 mg/10 mg) 26
Analysis 1.2. Comparison 1: Tofacitinib versus placebo, Outcome 2: Failure to achieve clinical response at 52 weeks (5 mg/10 mg) 27
Analysis 1.3. Comparison 1: Tofacitinib versus placebo, Outcome 3: Failure to achieve endoscopic remission at 52 weeks (5 mg/10 mg) 27
Analysis 1.4. Comparison 1: Tofacitinib versus placebo, Outcome 4: Adverse Events (5 mg/10 mg) 27
Analysis 1.5. Comparison 1: Tofacitinib versus placebo, Outcome 5: Serious Adverse Events (5 mg/10 mg) 27
Analysis 1.6. Comparison 1: Tofacitinib versus placebo, Outcome 6: Withdrawals due to adverse events (5 mg/10 mg) 28
Analysis 1.7. Comparison 1: Tofacitinib versus placebo, Outcome 7: Failure to maintain mucosal healing at 52 weeks (5 mg/10 mg) 28
Analysis 1.8. Comparison 1: Tofacitinib versus placebo, Outcome 8: Any Infection (5 mg/ 10 mg) 28
Analysis 1.9. Comparison 1: Tofacitinib versus placebo, Outcome 9: Serious infection (5 mg/ 10 mg) 28
Analysis 1.10. Comparison 1: Tofacitinib versus placebo, Outcome 10: Herpes zoster (5 mg/ 10 mg) 29
Analysis 1.11. Comparison 1: Tofacitinib versus placebo, Outcome 11: Failure to maintain remission (IBDQ score) 29
Analysis 1.12. Comparison 1: Tofacitinib versus placebo, Outcome 12: Failure to maintain response (IBDQ score) 29
APPENDICES 29
FEEDBACK 32
WHAT'S NEW 33
HISTORY 33
CONTRIBUTIONS OF AUTHORS 33
DECLARATIONS OF INTEREST 33
SOURCES OF SUPPORT 33
DIFFERENCES BETWEEN PROTOCOL AND REVIEW 34
INDEX TERMS 34

[Intervention Review]

Oral Janus kinase inhibitors for maintenance of remission in ulcerative colitis

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ABSTRACT

Background

Tofacitinib is an oral Janus kinase (JAK) inhibitor which blocks cytokine signaling involved in the pathogenesis of autoimmune diseases including ulcerative colitis (UC). The etiology of UC is poorly understood, however research suggests the development and progression of the disease is due to a dysregulated immune response leading to inflammation of the colonic mucosa in genetically predisposed individuals. Additional medications are currently required since some patients do not respond to the available medications and some medications are associated with serious adverse events (SAEs). JAK inhibitors have been widely studied in diseases including rheumatoid arthritis and Crohn's disease and may represent a promising and novel therapeutic option for the treatment of UC.

Objectives

The primary objective was to assess the efficacy and safety of oral JAK inhibitors for the maintenance of remission in participants with quiescent UC.

Search methods

We searched the following databases from inception to 20 September 2019: MEDLINE, Embase, CENTRAL, and the Cochrane IBD Group Specialized Register, WHO trials registry and clinicaltrials.gov. References and conference abstracts were searched to identify additional studies.

Selection criteria

Randomized control trial (RCTs) in which an oral JAK inhibitor was compared with placebo or active comparator in the treatment of quiescent UC were eligible for inclusion.

Data collection and analysis

Two review authors independently screened studies for inclusion and extraction. Bias was assessed using the Cochrane 'Risk of bias' tool. The primary outcome was the proportion of participants who failed to maintain remission as defined by any included studies. Secondary outcomes included failure to maintain clinical response, failure to maintain endoscopic remission, failure to maintain endoscopic response, disease-specific quality of life, adverse events (AEs), withdrawal due to AEs and SAEs. We calculated the risk ratio (RR) and 95% confidence intervals (95% CI) for each dichotomous outcome. Data were analyzed on an intention-to-treat basis. The overall certainty of the evidence supporting the outcomes was evaluated using the GRADE criteria.

Main results

One RCT (593 participants) including patients with moderately to severely active UC met the inclusion criteria. Patients who achieved a clinical response after eight weeks of induction treatment with tofacitinib (10 mg twice daily) or placebo were randomly assigned in a 1:1:1 ratio to receive maintenance therapy with tofacitinib at 5 mg twice daily, 10 mg twice daily or placebo for 52 weeks. The primary endpoint was remission at 52 weeks and the secondary endpoints included mucosal healing at 52 weeks, sustained remission at 24 and 52 weeks and glucocorticosteroid-free remission. This study was rated as low risk of bias. The study did not report on the proportion of participants who maintained remission at 52 weeks as clinical remission was not required for study entry (just clinical response). Thus we report on the proportion of participants who achieved clinical remission, clinical response, and endoscopic remission at 52 weeks; the proportion of participants who maintained remission at 52 weeks, and on AEs, SAEs and withdrawal due to AEs. However, the included study did not report on endoscopic response or disease-specific quality of life.

Sixty-three per cent (247/395) of tofacitinib participants failed to achieve clinical remission at 52 weeks compared to 89% (176/198) of placebo participants (RR 0.70, 95% CI 0.64 to 0.77; high-certainty evidence). The number needed to treat for an additional beneficial outcome is 4. Forty-three per cent (171/395) of tofacitinib participants failed to maintain clinical response at 52 weeks compared to 80% (158/198) of placebo participants (RR 0.54, 95% CI 0.48 to 0.62; high-certainty evidence). Eighty-four per cent (333/395) of tofacitinib participants failed to achieve endoscopic remission at 52 weeks compared to 96% (190/198) of placebo participants (RR 0.88, 95% CI 0.83 to 0.92; high-certainty evidence).

AEs were reported in 76% (299/394) of tofacitinib participants compared with 75% (149/198) of placebo participants (RR 1.01, 95% CI 0.92 to 1.11; high-certainty evidence). Commonly reported AEs included worsening UC, nasopharyngitis, arthralgia (joint pain)and headache. SAEs were reported in 5% (21/394) of tofacitinib participants compared with 7% (13/198) of placebo participants (RR 0.81, 95% CI 0.42 to 1.59; low-certainty evidence). SAEs included non-melanoma skin cancers, cardiovascular events, cancer other than non-melanoma skin cancer, Bowen's disease, skin papilloma and uterine leiomyoma (a tumour in the uterus). There was a higher proportion of participants who withdrew due to an AE in the placebo group compared to the tofacitinib group. Nine per cent (37/394) of participants taking tofacitinib withdrew due to an AE compared to 19% (37/198) of participants taking placebo (RR 0.50, 95% CI 0.33 to 0.77; moderate-certainty evidence). The most common reason for withdrawal due to an AE was worsening UC. The included study did not report on endoscopic response or on mean disease-specific quality of life scores.

Authors' conclusions

High-certainty evidence suggests that tofacitinib is superior to placebo for induction of clinical and endoscopic remission at 52 weeks in participants with moderate-to-severe UC who had a clinical response after eight weeks of induction treatment with tofacitinib (10 mg twice daily) or placebo. The optimal dose of tofacitinib for maintenance therapy is unknown. High-certainty evidence suggests that there is no increased risk of AEs with tofacitinib compared to placebo. However, we are uncertain about the effect of tofacitinib on SAEs due to the low number of events. Further studies are required to look at the long-term effectiveness and safety of using tofacitinib and other oral JAK inhibitors as maintenance therapy in participants with moderate-to-severe UC in remission.

PLAIN LANGUAGE SUMMARY

Oral Janus kinase inhibitors (tofacitinib) for maintenance of remission in ulcerative colitis

What is ulcerative colitis?

Ulcerative colitis is a chronic (long-term) inflammatory bowel disease that affects the large bowel. The most common symptoms of ulcerative colitis include bloody diarrhea, abdominal pain and a sudden almost uncontrollable urge to pass stool. Some people experience symptoms outside of the bowels including sore joints, mouth sores and inflammation in their eyes. When someone is experiencing symptoms of ulcerative colitis, they are said to have 'active' disease. When symptoms of ulcerative colitis improve with treatment, the disease is said to be responding to therapy. When symptoms of ulcerative colitis stop, the disease is said to be in 'remission'. People with ulcerative colitis in remission are often given therapy with drugs to try and prolong (maintain) their remission or response to therapy.

What are Janus kinase inhibitors?

Janus kinase inhibitors (including tofacitinib) are a class of medications which reduce inflammation in the body. Tofacitinib is currently being used in autoimmune diseases such as rheumatoid arthritis and ulcerative colitis. These drugs come in pill form and are taken by mouth (oral).

What did the researchers investigate?

The researchers investigated whether tofacitinib helps maintain remission in people with inactive ulcerative colitis and whether this medication causes any harm (side effects). The researchers searched the medical literature up to 20 September 2019.

Key results

We identified one study (593 participants) that compared tofacitinib versus a placebo (a fake medicine). The participants had moderate-to-severe ulcerative colitis that responded to tofacitinib or placebo induction therapy (10 mg twice daily for eight weeks). The study was of high methodological quality. High-certainty evidence suggests that tofacitinib (5 mg or 10 mg twice daily) is more effective than placebo at achieving clinical remission (stopping of symptoms) and endoscopic remission (i.e. healing of inflamed bowel mucosa) of ulcerative colitis at 52 weeks. The rates of side effects (tofacitinib: 76%; placebo: 75%) and serious side effects (tofacitinib: 5%; placebo: 7%) were similar in participants receiving tofacitinib and placebo. High-certainty evidence suggests there is no increased risk of side effects with tofacitinib compared to placebo. Commonly reported side effects included worsening ulcerative colitis, nasopharyngitis (i.e. common cold), arthralgia (i.e. joint pain) and headache. The certainty of the evidence for serious side effects was low due to a low number of events. Serious side effects included non-melanoma skin cancers, cardiovascular events (e.g. heart attack), cancer other than non-melanoma skin cancer, Bowen's disease (i.e. a type of skin cancer), skin papilloma (i.e. a tumour of the skin) and uterine leiomyoma (i.e. a tumour in the uterus). In addition, there was a higher rate of withdrawal from the study due to side effects in the placebo group compared to the treatment group. Nine per cent of participants taking tofacitinib withdrew due to a side effect compared to 19% of participants taking placebo (moderate-certainty evidence). The most common reason for study withdrawal due to a side effect was worsening ulcerative colitis.

Conclusions

High-certainty evidence suggests that tofacitinib is superior to placebo for achieving clinical and endoscopic remission at 52 weeks in participants with moderate-to-severe ulcerative colitis that responded to tofacitinib induction therapy. The optimal dose of tofacitinib for maintenance therapy is unknown. High-certainty evidence suggests that there is no increased risk of side effects with tofacitinib compared to placebo. However, we are uncertain about the effect of tofacitinib on serious side effects due to the low number of events. Further studies are required to look at the long-term benefits and harms of using tofacitinib and other oral Janus kinase inhibitors as maintenance therapy in participants with moderate-to-severe ulcerative colitis in remission.

SUMMARY OF FINDINGS

Summary of findings 1. Tofacitinib compared to placebo for maintenance of remission in ulcerative colitis

Tofacitinib compared to placebo for maintenance of remission in ulcerative colitis

Patient or population: participants with quiescent ulcerative colitis
Setting: outpatient
Intervention: tofacitinib (5 mg/10 mg)
Comparison: placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo	Risk with Tofacitinib				
Failure to achieve clinical remission (5 mg/10 mg) Follow-up: 52 weeks	Study population 889 per 1,000	622 per 1,000 (569 to 684)	RR 0.70 (0.64 to 0.77)	593 (1 study)	⊕⊕⊕⊕ HIGH	Clinical remission was defined as a total Mayo score of ≤2, with no sub score ≥1 and a rectal bleeding sub score of 0
Failure to maintain clinical response (5 mg/10 mg) Follow-up: 52 weeks	Study population 798 per 1,000	431 per 1,000 (375 to 495)	RR 0.54 (0.47 to 0.62)	593 (1 study)	⊕⊕⊕⊕ HIGH	Clinical response was defined as a decrease from induction-trial baseline in the total Mayo score of at least 3 points and at least 30%, with an accompanying decrease in the rectal bleeding sub score or 0 or 1
Failure to achieve endoscopic remission (5 mg/10 mg) Follow-up: 52 weeks	Study population 960 per 1,000	844 per 1,000 (796 to 883)	RR 0.88 (0.83 to 0.92)	593 (1 study)	⊕⊕⊕⊕ HIGH	Endoscopic remission was defined as a Mayo endoscopic sub score of 0
Adverse events (5 mg/10 mg) Follow-up: 52 weeks	Study population 753 per 1,000	760 per 1,000 (692 to 835)	RR 1.01 (0.92 to 1.11)	592 (1 study)	⊕⊕⊕⊕ HIGH	Adverse events include worsening of ulcerative colitis, nasopharyngitis, arthralgia and headache
Serious adverse events (5 mg/10 mg) Follow-up: 52 weeks	Study population 66 per 1,000	53 per 1,000 (28 to 104)	RR 0.81 (0.42 to 1.59)	592 (1 study)	⊕⊕⊖⊖ LOW[1]	Serious adverse events include cancer, intestinal perforation and cardiovascular events

Withdrawals due to adverse events (5 mg/10 mg) Follow-up: 52 weeks	Study population		RR 0.50 (0.33 to 0.77)	592 (1 study)	⊕⊕⊕⊖ MODERATE[2]	Adverse events leading to withdrawal include worsening of ulcerative colitis
	187 per 1,000	93 per 1,000 (62 to 144)				

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio.

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

[1] Downgraded two levels due to very serious imprecision (34 events)
[2] Downgraded one level due to serious imprecision (74 events)

BACKGROUND

Description of the condition

Ulcerative colitis (UC) is a chronic inflammatory bowel disease (IBD) of unknown origin that is characterized by continuous, superficial inflammation of the colon (Conrad 2014). Clinical manifestations of UC vary greatly, however, common symptoms are bloody diarrhea, fecal urgency and abdominal pain. Approximately 6% to 47% of patients experience extraintestinal manifestations such as arthritis, uveitis (a type of eye inflammation), oral ulcers, and primary sclerosing cholangitis (Rothfuss 2006). One of the hallmark features of UC is the relapsing and remitting disease course. Alternating flare-ups and periods of remission may be triggered by infection, treatment changes, environmental stressors, or may occur spontaneously (Lichtenstein 2006).

In North America, the prevalence of UC ranges from 120 to 250 cases per 100,000 persons and the incidence ranges from 8 to 20 cases per 100,000 person years (Loftus 2004). While the prevalence and incidence rates of UC are highest in North America and Europe, the condition is becoming more common in developing countries as Western diet and hygiene practices are adopted (Lichtenstein 2015). Patients can be diagnosed with UC at any age, however the disease has an age distribution characterized by two peaks of incidence at 15 to 30 years and at 50 to 70 years (Ordás 2012). Men and women are at equal risk for developing UC (Ponder 2013).

Although the etiology of UC is poorly understood, research suggests that disease development and progression is caused by a dysregulated immune response, which involves the overproduction and trafficking of chemokines, T cells and cytokines (Conrad 2014). Ultimately, this immune imbalance leads to inflammation of the colonic mucosa in genetically predisposed individuals.

The goal of therapy is to induce and maintain clinical remission, prevent complications, and improve the patient's quality of life (Feuerstein 2014). Conventional treatments for UC include 5-aminosalicylates, corticosteroids, azathioprine or 6-mercaptopurine and biological therapies (i.e. infliximab, golimumab, vedolizumab, ustekinumab). While corticosteroids are highly effective for induction treatment of IBD, they have proven to be less efficacious for maintenance therapy (Lichtenstein 2006). Current standard maintenance treatment for UC utilizes 5-aminosalicylates and thiopurines (Lichtenstein 2006). However, many patients will develop intolerance or have a lack of response to these therapies and may require colectomy. Therefore, treatment should be individualized based on previous symptoms and tolerance to medications. This concept along with the frequency of patients failing current maintenance regimens necessitates the development of new maintenance therapies for UC.

Description of the intervention

The Janus kinase (JAK) inhibitors are an oral small molecule therapy that inhibits the activity of at least one of the Janus kinase family of enzymes. This family of enzymes is responsible for the activation of signal transducers and activators of transcription (STATs). JAK-STAT pathways regulate signaling for multiple immune mediators implicated in the pathogenesis of IBD including UC at the level of transcription (Boland 2014). There are four cytoplasmic tyrosine kinases that comprise the Janus kinase (JAK) family, including JAK1, JAK2, JAK3 and TYK2 (Sandborn 2012). In rheumatoid arthritis, the oral JAK inhibitor tofacitinib has been found to be effective and well-tolerated in patients (Fleischmann 2012a; Fleischmann 2012b; Tanaka 2011). In 2012, tofacitinib was approved for the treatment of rheumatoid arthritis by the U.S. Food and Drug Adminstration (Traynor 2012). Tofacitinib is used to treat adults with moderately to severely active UC when anti-tumor necrosis factor-alpha medications fail to work or are not tolerated.

Tofabitinib is taken in a pill form twice daily with or without food. The recommended dosage of tofacitinib in patients with UC is 10 mg twice daily for induction of remission and 5 mg twice daily for maintenance of remission (Pfizer 2019a). The 5 mg tofacitinib pills are white, round, immediate-release film coated tablets and the 10 mg tofacitinib pills are blue, round and immediate-release film-coated (Pfizer 2019a). Common side effects of tofacitinib in UC patients include: nasal congestion, sore throat, nasopharyngitis, increased cholesterol levels, headache, upper respiratory tract infections, increased enzyme levels, rash, diarrhea and shingles (herpes zoster). Additional serious adverse events (SAEs) include serious infections, cancer and immune system problems, perforation in the stomach/intestines and allergic reactions. Tofacitinib affects the immune system and can lower the ability of the immune system to fight infections, therefore serious infections can result from taking tofacitinib including tuberculosis and other infections caused by bacteria, fungi or viruses. Lymphoma and other cancers such as skin cancers may occur in patients taking tofacitinib with higher doses (10 mg twice daily) resulting in a higher risk of skin cancers. Some patients taking tofacitinib can get tears in their stomach or intestines, which most commonly occurs with nonsteroidal anti-inflammatories, corticosteroids, or methotrexate. Lastly, allergic reactions may occur such as hives or the swelling of the lips, tongue, or throat (Pfizer 2019b).

How the intervention might work

Cytokines play a key role in the cell signaling associated with immune dysregulation and inflammatory response. Chemokine receptors, which are dependent on all four JAK kinases, play an integral role in cytokine signaling. Inhibition of JAKs decrease multiple cytokines implicated in the pathogenesis of UC including type 1 interferon, interferon-GAMMA, and various interleukins (Sandborn 2017). Drugs that inhibit the JAKs, and as a result, block cytokine signaling, are termed JAK inhibitors (Coskun 2013). The JAK-STAT pathway has an important role in the inflammatory pathway for IBD and may represent a promising treatment for individuals with UC (Danese 2016).

Tofacitinib is an oral, small-molecule JAK inhibitor that inhibits all JAKs, but preferentially inhibits JAK1 and JAK3 (Meyer 2010). It has a short pharmacokinetic half life of three hours and is rapidly absorbed and eliminated, with a peak concentration at 0.5 hours (Dowty 2014). Steady state concentrations are reached in 25 to 48 hours after twice daily administration. The bioavailability of tofacitinib is 74% and clearance is through approximately 70% hepatic metabolism and 30% renal excretion. The metabolism of tofacitinib is primarily due to the CYP3A4 enzyme with a minor contribution from the CYP2C19 enzyme (Pfizer 2019a).

Why it is important to do this review

Corticosteroids, aminosalicylates, immunosuppressives and biologics are the main classes of drugs currently used for the treatment of UC. Additional medications are needed since not all patients respond to these agents, and some of these medications are associated with SAEs (Sandborn 2012). JAK inhibitors have been widely studied in diseases including rheumatoid arthritis and Crohn's disease and may represent a promising and novel therapeutic option for the treatment of UC.

OBJECTIVES

The primary objective was to assess the efficacy and safety of oral Janus kinase (JAK) inhibitors for the maintenance of remission in participants with quiescent ulcerative colitis (UC).

METHODS

Criteria for considering studies for this review

Types of studies

Randomized controlled trials (RCTs) were considered based on the inclusion criteria.

Types of participants

Participants of all ages with quiescent UC, as defined by a combination of clinical, endoscopic, radiographic or histological criteria, were considered for inclusion.

Types of interventions

Studies where an oral JAK inhibitor was compared with placebo or an active comparator were considered for inclusion.

Types of outcome measures

Primary outcomes

The primary outcome was the proportion of participants who failed to maintain clinical remission (as defined by the included studies).

Secondary outcomes

The secondary outcomes included the proportion of participants who failed to maintain clinical response (as defined by the included studies); the proportion of participants who failed to maintain endoscopic remission (as defined by the included studies); the proportion of participants who failed to maintain endoscopic response (as defined by the included studies); disease-specific quality of life, adverse events (AEs), serious adverse events (SAEs), and withdrawal due to AEs.

Search methods for identification of studies

Electronic searches

We searched the following databases for relevant studies on 20 September 2019:

1. MEDLINE (Ovid, 1946 to present);
2. Embase (Ovid, 1984 to present);
3. CENTRAL;
4. Clinicaltrials.gov;
5. WHO trials registry; and
6. the Cochrane IBD Group Specialized Register.

The search strategies are listed in Appendix 1.

Searching other resources

We searched the reference lists of potentially relevant trials and papers to identify additional studies. Conference proceedings from Digestive Disease Week, United European Gastroenterology Week and the European Crohn's and Colitis Organisation Congress were handsearched to identify studies reported in abstract form only. We also searched for ongoing studies using the clinicaltrials.gov database.

Data collection and analysis

Selection of studies

Two review authors (SD and TMN) independently screened titles and abstracts identified by the literature search to determine eligibility based on the inclusion criteria described above. Disagreements among review authors were resolved through discussion until consensus was reached. If consensus was not reached, a third review author (RK) was consulted to resolve the disagreement.

Data extraction and management

Two review authors (SD and TMN) independently extracted data. Disagreements among authors regarding risk of bias were resolved through discussion until consensus was reached. If consensus was not reached, a third author (RK) was consulted The following data were retrieved from included studies:

1. general information (title, journal, year, publication type);
2. study information (design, methods of randomization, concealment of allocation and blinding, power calculation, a prior and post hoc analyses);
3. intervention and control (type and dose of medication and placebo or active comparator);
4. eligibility (total number of patients screened and randomized);
5. baseline characteristics for each arm (age, sex, race, disease severity, concurrent medications, prior medications);
6. follow-up (length of follow-up, assessment of treatment compliance, withdrawals, number of patients lost to follow-up; and
7. outcomes (primary and secondary outcomes).

Assessment of risk of bias in included studies

Two review authors (SD, TMN) independently evaluated the methodological quality of each included study using the Cochrane 'Risk of bias' tool (Higgins 2011a). Factors assessed included:

1. sequence generation (i.e. was the allocation sequence adequately generated?);
2. allocation sequence concealment (i.e. was allocation adequately concealed?);
3. blinding (i.e. was knowledge of the allocated intervention adequately prevented during the study?);
4. incomplete outcome data (i.e. were incomplete outcome data adequately addressed?);
5. selective outcome reporting (i.e. are reports of the study free of suggestion of selective outcome reporting?); and,

6. other potential sources of bias (i.e. was the study apparently free of other problems that could put it at high risk of bias?).

The studies were judged to be of high, low or unclear risk of bias based on these factors. Disagreements among authors regarding risk of bias were resolved through discussion until consensus was reached. If consensus was not reached, a third review author (RK) was consulted to resolve the disagreement.

The GRADE approach was used to evaluate the overall certainty of evidence supporting the primary and secondary outcomes (Guyatt 2008; Schünemann 2011). Evidence from RCTs are considered high-certainty evidence, however this evidence could be downgraded due to:

1. risk of bias;
2. indirect evidence;
3. inconsistency (unexplained heterogeneity);
4. imprecision; and,
5. publication bias.

The overall certainty of evidence for each outcome was classified as high certainty (i.e. further research is very unlikely to change our confidence in the estimate of effect); moderate certainty (i.e. further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate); low certainty (i.e. further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate); or very low certainty (i.e. we are very uncertain about the estimate).

The following outcomes were reported in the 'Summary of findings' table:

1. failure to achieve clinical remission at 52 weeks;
2. failure to maintain clinical response at 52 weeks;
3. failure to achieve endoscopic remission at 52 weeks;
4. AEs at 52 weeks;
5. SAEs at 52 weeks; and
6. withdrawals due to AEs at 52 weeks.

Measures of treatment effect

We used Review Manager (RevMan 5.3.5) to analyze data. All data were analyzed on an intention-to-treat basis. The risk ratio (RR) and corresponding 95% confidence interval (CI) were calculated for dichotomous outcomes. For continuous outcomes, we planned to calculate the mean difference (MD) and corresponding 95% CI. We followed Cochrane guidance to calculate the number needed to treat for the primary outcome (Higgins 2011b).

Unit of analysis issues

We planned to combine for fixed intervals of follow-up (e.g. clinical remission at 52 weeks) if studies reported multiple observations for the same outcome. If identified, we planned to include cross-over trials only if data were available from the first phase of the study (i.e. before cross-over). Separate comparisons were planned for the oral JAK inhibitor versus placebo and the oral JAK inhibitor versus active comparator. If studies allocated participants to more than one treatment arm, we planned to pool the arms for the primary analysis.

Dealing with missing data

If necessary, we would have contacted the original study authors in the case of unclear or missing data. Participants with missing outcomes would have been assumed to be treatment failures. Where appropriate, we planned to conduct sensitivity analyses to assess the impact of this assumption on the effect estimate.

Assessment of heterogeneity

Heterogeneity was assessed using the Chi^2 test (a P value of 0.10 was considered statistically significant) and the I^2 statistic. An I^2 value of 25% indicated low heterogeneity, 50% indicated moderate heterogeneity and 75% indicated high heterogeneity (Higgins 2003). We planned to use sensitivity analyses to explore potential explanations for heterogeneity.

Assessment of reporting biases

We planned to evaluate potential reporting bias by comparing outcomes listed in protocols with published manuscripts. If the protocols were not available, we intended to compare the outcomes listed in the methods section of the published manuscripts to those described in the results section. If a sufficient number of studies was included (i.e. $\geq$ 10) in the pooled analyses, we planned to investigate potential publication bias using funnel plots (Egger 1997).

Data synthesis

We planned to combine data from individual trials for meta-analysis when the interventions, patient groups and outcomes were sufficiently similar (as determined by consensus). We would have pooled RR and 95% CIs for dichotomous outcomes. For continuous outcomes, we planned to pool MD and corresponding 95% CIs. We planned to calculate the standardized mean difference (SMD) and 95% CI when different scales were used to measure the same underlying construct.

Subgroup analysis and investigation of heterogeneity

Planned subgroup analyses included:

1. studies investigating children and studies investigating adults;
2. different drug doses and routes of administration; and
3. studies investigating patients with high disease activity.

Sensitivity analysis

We planned to carry out the following sensitivity analyses to examine the impact of the following variables on the pooled effect:

1. random-effects versus fixed-effect modeling;
2. low risk of bias only versus unclear or high risk of bias; and
3. relevant loss to follow-up (> 10%): best-case versus worst-case scenario.

RESULTS

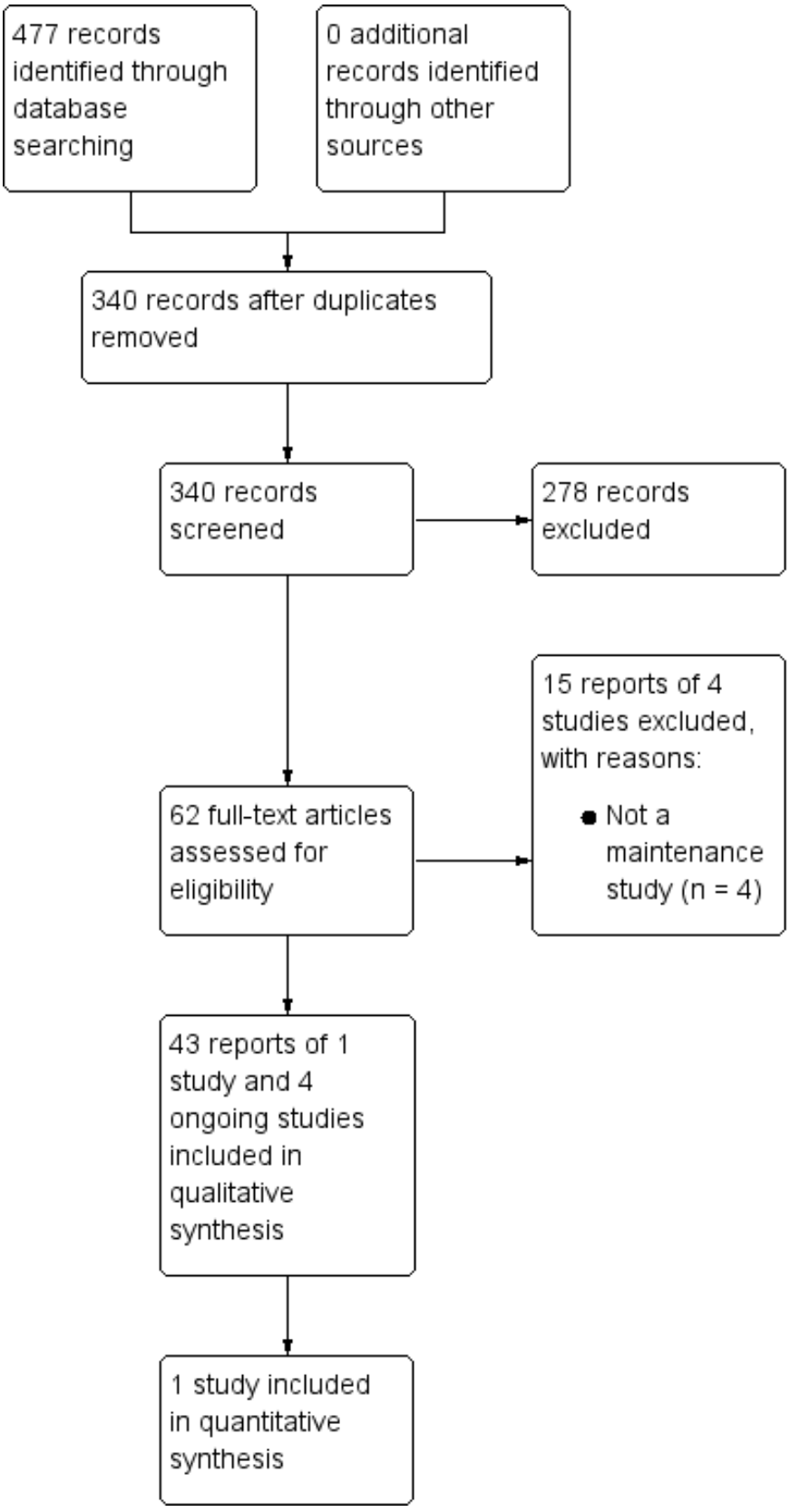
Description of studies

Results of the search

The literature search was conducted on 20 September 2019, and identified 477 records. After duplicates were removed, we screened 341 records for inclusion. Overall, 43 reports of one study (N = 593)

and four ongoing studies met the pre-defined inclusion criteria and were included in this review (Figure 1).

Figure 1. Study flow diagram.



Included studies

Sandborn 2017 included three phase 3, randomized, double-blind, placebo-controlled trials of tofacitinib in the treatment of adults with moderate-to-severe ulcerative colitis (UC) (N = 593 participants). Participants were required to have an overall Mayo score of 6 to 12, with a rectal bleeding sub-score of 1 to 3 and an endoscopic sub-score of 2 or 3. OCTAVE 1 and OCTAVE 2 randomly assigned patients with active UC to receive induction therapy with 10 mg twice daily of tofacitinib or placebo for eight weeks. Patients who responded to treatment then had the opportunity to take part in the OCTAVE SUSTAIN trial where they were randomly assigned to receive maintenance therapy of tofacitinib (5 mg or 10 mg twice daily) or placebo for 52 weeks. Patients were not required to have achieved clinical remission, endoscopic remission or mucosal healing at study entry. The primary outcome for the OCTAVE SUSTAIN trial was clinical remission at 52 weeks. The secondary outcomes included mucosal healing at 52 weeks, sustained remission (occurring at both 24 and 52 weeks), glucocorticosteroid-free (i.e. occurring without the administration of glucocorticosteroids for > 4 weeks before the assessment).

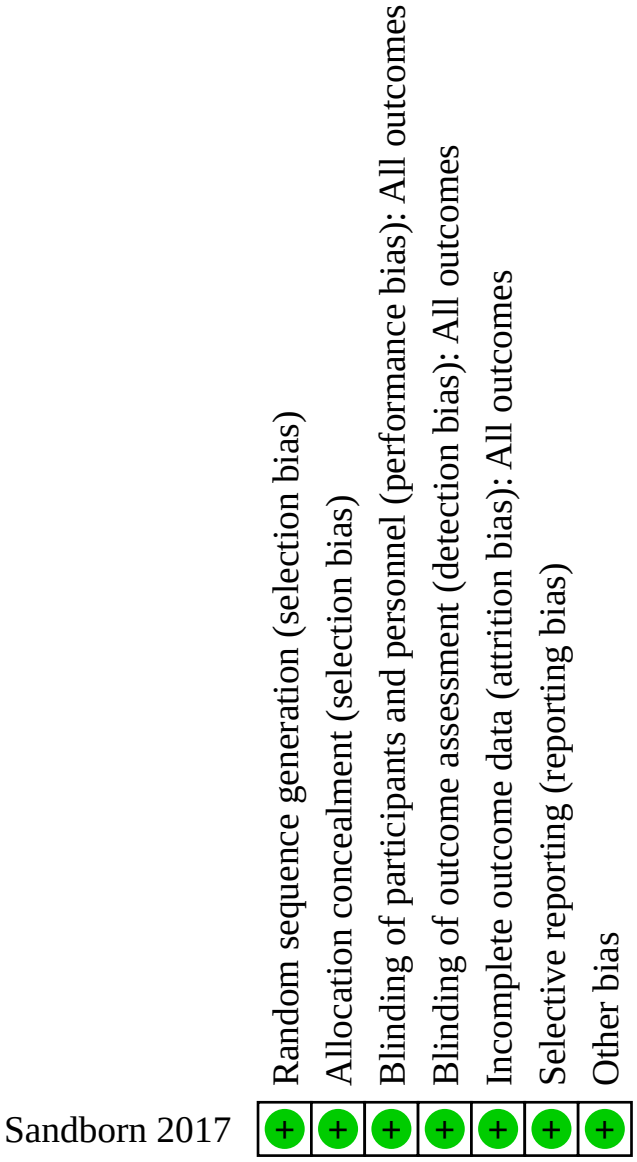
Excluded studies

We excluded 16 reports of four studies (See Characteristics of excluded studies). All four studies were double-blind, RCTs that only examined tofacitinib therapy for the induction of remission in active UC (Sandborn 2012; Sands 2016; Sandborn 2019; Sands 2018).

Risk of bias in included studies

The 'Risk of bias' analysis is summarized in Figure 2.

Figure 2. 'Risk of bias' summary: review authors' judgements about each 'Risk of bias' item for each included study.



Allocation

Sandborn 2017 utilized a central tele-randomization system with stratification according to assignment in OCTAVE 1 or OCTAVE 2 and remission status. The study was rated as low bias for random sequence generation and allocation concealment.

Blinding

Blinding in Sandborn 2017 was given a low risk of bias since the methods of blinding for the participants, personnel and outcome assessors were described and adequate.

Incomplete outcome data

Dropouts were balanced across groups and an intention-to-treat analysis was used, therefore we rated this item as low risk of bias.

Selective reporting

All outcomes were reported in Sandborn 2017 and we rated this item as low risk of bias.

Other potential sources of bias

Sandborn 2017 appears to be free of other sources of bias and was rated as a low risk of bias.

Effects of interventions

See: **Summary of findings 1** Tofacitinib compared to placebo for maintenance of remission in ulcerative colitis

Sandborn 2017 did not report on the proportion of participants who maintained remission at 52 weeks as clinical remission was not required for study entry (just clinical response). Thus we report on the proportion of participants who achieved clinical remission and endoscopic remission at 52 weeks; the proportion of participants who failed to maintain clinical response at 52 weeks, and on AEs, SAEs and withdrawal due to AEs.

Failure to achieve clinical remission

Sandborn 2017 defined clinical remission as a total Mayo score of ≤ 2, with no sub score ≥ 1 and a rectal bleeding sub score of 0. Tofacitinib was more effective than placebo for achieving clinical remission at 52 weeks. Sixty-three per cent (247/395) of tofacitinib participants (5 mg/10 mg twice daily) failed to achieve clinical remission at 52 weeks compared to 89% (176/198) of placebo participants (RR 0.70, 95% CI 0.64 to 0.77, high-certainty evidence; Analysis 1.1). The number needed to treat for an additional beneficial outcome is 4.

Failure to maintain clinical response

Sandborn 2017 defined clinical response as a decrease from induction-trial baseline in the total Mayo score of at least three points and at least 30%, with an accompanying decrease in the rectal bleeding sub score or 0 or 1. Tofacitinib was more effective than placebo for maintenance of clinical response at 52 weeks. Forty-three per cent (171/395) of participants receiving tofacitinib (5 mg/10 mg twice daily) failed to maintain clinical response at 52 weeks compared to 80% (158/198) of participants in the placebo group (RR 0.54, 95% CI 0.48 to 0.62; Analysis 1.2). A GRADE analysis showed that the overall certainty of evidence for this outcome was rated as high.

Failure to achieve endoscopic remission

Sandborn 2017 defined endoscopic remission as an endoscopic sub score of zero. Tofacitinib was more effective than placebo for endoscopic remission at 52 weeks. Eighty-four per cent (333/395) of tofacitinib participants failed to maintain endoscopic remission at 52 weeks compared to 96% (190/198) of placebo participants (RR 0.88, 95% CI 0.83 to 0.92, high-certainty evidence; Analysis 1.3).

Failure to achieve endoscopic response

Endoscopic response was not reported in the Sandborn 2017 study.

Disease-specific quality of life

Sandborn 2017 did not report on mean quality of life scores based on the Inflammatory Bowel Disease Questionnaire (IBDQ). This study did report on remission based on IBDQ scores (see post-hoc outcomes below).

Adverse events (AEs)

There does not appear to be a difference between the tofacitinib and placebo groups in AE rates. Seventy-six per cent (299/394) of tofacitinib participants reported an AE in comparison to 75% (149/198) of placebo participants (RR 1.01, 95% CI 0.92 to 1.11, high-certainty evidence; Analysis 1.4). The most commonly reported AEs included worsening of ulcerative colitis (UC), nasopharyngitis, arthralgia (joint pain) and headache.

Serious adverse events (SAEs)

Five per cent (21/394) of participants receiving tofacitinib had a SAE compared to 7% (13/198) of the placebo group (RR 0.81, 95% CI 0.42 to 1.59, low-certainty evidence; Analysis 1.5). There does not appear to be a difference in the SAE rates between the tofacitinib and placebo groups. However, a risk of harm cannot be excluded because the upper limit of the CI showed a 60% higher risk of SAEs. SAEs included non-melanoma skin cancers (squamous-cell carcinoma and basal-cell carcinoma), cardiovascular events (myocardial infarction and hemorrhagic stroke) ductal breast carcinoma, Bowen's disease, skin papilloma and uterine leiomyoma.

Withdrawal due to adverse events (AEs)

There was a higher proportion of placebo participants who withdrew due to an AE compared to the tofacitinib participants. Nine per cent (37/394) of participants on tofacitinib withdrew due to AEs in comparison to 19% (37/198) of participants in the placebo group (RR 0.50, 95% CI 0.33 to 0.77, moderate-certainty evidence; Analysis 1.6). AEs leading to withdrawal included worsening UC. The other AEs leading to withdrawal were not described.

Planned subgroup and sensitivity analyses

Sandborn 2017 enrolled adult participants with moderate-to-severe UC, so we were unable to conduct a subgroup analysis comparing children to adults or a subgroup analysis comparing participants with severe disease to mild disease. There was only one included study so we did not conduct sensitivity analyses based on random-effects versus fixed-effect modeling, low risk of bias versus high or unclear risk of bias, or relevant loss to follow-up best-case versus worst-case scenario.

Failure to achieve mucosal healing (post-hoc outcome)

Failure to achieve mucosal healing at 52 weeks was defined as a Mayo endoscopic sub score of ≤1. The study results suggest a higher rate of mucosal healing in the tofacitinib group compared to the placebo group. Failure to achieve mucosal healing at 52 weeks was seen in 58% (231/395) of tofacitinib participants compared to 87% (172/198) of placebo participants (RR 0.67, 95% CI 0.61 to 0.74; Analysis 1.7).

Any infection (post-hoc outcome)

The rate of infection was higher in the tofacitinib group compared to the placebo group. Thirty-eight per cent (149/394) of tofacitinib participants experienced an infection compared to 24% (48/198) of participants in the placebo group (RR 1.56, 95% CI 1.18 to 2.06; Analysis 1.8).

Serious infection (post-hoc outcome)

The rate of serious infections was similar between the tofacitinib and placebo groups. Approximately 1% (3/394) tofacitinib participants experienced a serious infection compared to 1% (2/198) of placebo participants (RR 0.75, 95% CI 0.13 to 4.47; Analysis 1.9). A case of diverticulitis and a case of subcutaneous abscess were reported in the placebo group. A case of peritonsillar abscess and a case of urinary tract infection were reported in the 5 mg twice daily group and lastly, a case of bacterial diarrhea was reported in the 10 mg twice daily group.

Herpes zoster (post-hoc outcome)

Herpes zoster (shingles) infection results from the reactivation of latent varicella–zoster virus within the sensory ganglia. The infection is characterized by bilateral radicular pain and a vesicular rash (Oxman 2005). A slightly higher rate of herpes zoster infection occurred in the tofacitinib group than the placebo group. Three per cent (13/394) of tofacitinib participants were affected by herpes zoster infection compared to 0.5% (1/198) of participants in the placebo group (RR 6.53, 95% CI 0.86 to 49.58; Analysis 1.10).

Disease-specific quality of life (post-hoc outcome)

Failure to maintain clinical remission and response based on IBDQ criteria were defined as the proportion of patients with an IBDQ score of indicative remission (i.e. a score of ≥170) and the proportion of patients with an IBDQ score indicative of a treatment response (i.e. a score ≥16 points higher than the baseline score in the induction trial). After 52 weeks, 57% (224/395) of participants in the treatment group failed to maintain remission based on their IBDQ scores, compared to 85% (169/198) of participants in the placebo group (RR 0.66, 95% CI 0.60 to 0.74; Analysis 1.11).

Tofacitinib also showed benefit over placebo for treatment response based on IBDQ. Fifty per cent (197/395) of tofacitinib participants failed to maintain treatment response based on the IBDQ at 52 weeks, compared to 81% (160/198) of participants in the placebo group (RR 0.62, 95% CI 0.55 to 0.70; Analysis 1.12).

DISCUSSION

Summary of main results

One randomized controlled trial (RCT) with 593 participants was identified through the literature search and met the inclusion criteria (Sandborn 2017). Our primary results suggest that tofacitinib is superior to placebo for induction of clinical (high-certainty evidence) and endoscopic remission (high-certainty evidence) at 52 weeks in participants with moderate-to-severe ulcerative colitis (UC) who had a clinical response to eight weeks of induction treatment with tofacitinib (10 mg twice daily) or placebo. Participants in the tofacitinib group were also more likely to maintain clinical response (high-certainty evidence) at 52 weeks. Further research is needed to determine the optimal dose of tofacitinib for maintenance therapy in people with quiescent moderate-to-severe UC. The rates of adverse events (AEs) (high-certainty evidence) were similar in tofacitinib and placebo treated participants. The rates of severe adverse events (SAEs) were similar in tofacitinib and placebo treated participants but the certainty of the evidence was low. Participants receiving tofacitinib were less likely than participants receiving placebo to withdraw due to an AE (moderate-certainty evidence). The most frequently reported AEs included nasopharyngitis, arthralgia and headache. SAEs included non melanoma skin cancers, cardiovascular events and other cancers. Overall, these results suggest a therapeutic benefit for the use of tofacitinib in the maintenance of remission in UC.

Sandborn 2017 also reported on additional outcomes that were not originally reported in the protocol but were included as post-hoc outcomes in our analysis. The first post-hoc outcome was the failure to achieve mucosal healing as defined by a Mayo endoscopic sub score of ≤1. The results suggested there was a higher rate of mucosal healing in the tofacitinib group compared to the placebo group. The second post-hoc outcome was the rate of infections including any infections, serious infections and herpes zoster. There was no difference in the rate of serious infections between the tofacitinib and placebo group. However, there was a higher rate of any infections and herpes zoster in the tofacitinib group compared to placebo.

The last post-hoc outcomes are the clinical remission and clinical response rates based on the Inflammatory Bowel Disease Questionnaire (IBDQ) score. IBDQ remission was defined by an IBDQ score of ≥170. IBDQ response was defined as an IBDQ score ≥16 points higher than the baseline score in the induction trial. Participants in the tofacitinib group were significantly more likely to maintain clinical remission and treatment response based on IBDQ scores compared to patients receiving placebo.

In addition to Sandborn 2017, there are four ongoing studies assessing the efficacy of oral Janus kinase (JAK) inhibitors for the maintenance of remission in UC (NCT02819635; NCT02914522; NCT03281304; NCT03627052). NCT02819635 is a randomized, double-blind, placebo-controlled trial evaluating the safety and efficacy of upadacitinib (ABT-494) for the induction and maintenance of remission in patients with moderately to severely active UC. NCT02914522 is a randomized, double-blind, placebo-controlled study assessing the efficacy and safety of filgotinib for the induction and maintenance of remission in people with moderately to severely active UC (SELECTION). The primary outcome is the proportion of participants achieving clinical remission at 10 and 58 weeks. NCT03281304 is a double-blind, randomized, parallel group study of tofacitinib (Cp-690,550) in people with UC in stable remission. The primary outcome is clinical remission at 24 weeks. Lastly, NCT03627052 is a phase two, double-blind, dose-ranging, placebo-controlled study with open-label extension evaluating the safety and efficacy of itacitinib in people with moderate-to-severe UC. The primary outcome is the proportion of participants with a clinical response at 12 weeks.

Overall completeness and applicability of evidence

The results of this review are applicable to people with moderate-to-severe UC who are in remission. However, the overall evidence cannot be considered complete as only one study (593 participants) was identified that assessed oral JAK maintenance therapy compared to a placebo in participants with quiescent moderate-to-severe UC. The study reported on most of our pre-specified primary and secondary outcomes including: clinical remission, clinical response, endoscopic remission, AEs, SAEs and withdrawal due to AEs. The included study did not report on endoscopic response or disease-specific quality of life, although it did report on clinical remission and response based on IBDQ scores. Further

studies are required to confirm the efficacy and safety of tofacitinib in people with quiescent moderate-to-severe UC.

Quality of the evidence

We used the Cochrane 'Risk of bias' tool to asses the risk of bias for the included RCT (Sandborn 2017). The risk of bias was rated as low risk for all domains. The overall certainty of evidence for the outcomes was assessed using the GRADE analysis (See Summary of findings 1). The certainty of the evidence for the outcomes failure to achieve clinical remission, failure to maintain clinical response, failure to achieve endoscopic remission, and AEs was high. The certainty of the evidence for SAEs was low due to very serious imprecision. The certainty of the evidence for withdrawals due to AEs was moderate due to serious imprecision.

Potential biases in the review process

The methods and reporting of this review were based on the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011a). The protocol for this review (Hussein 2016) was previously published and an extensive literature search was developed and conducted to identify all eligible studies. The screening, data extraction, risk of bias and GRADE analysis were independently assessed by two review authors. Despite these processes, there are still some potential limitations for this review. The main limitations of this review was the one included study and sparse data for some outcomes. Further research is necessary to confirm the efficacy and safety of tofacitinib for maintenance of remission in people with quiescent moderate-to-severe UC.

Agreements and disagreements with other studies or reviews

We could not find any other studies or reviews assessing the use of tofacitinib in the maintenance of moderate-to-severe UC. A study completed by Panes 2018 agreed that tofacitinib was effective for maintaining quality of life outcomes in the OCTAVE Sustain trial.

AUTHORS' CONCLUSIONS

Implications for practice

High-certainty evidence suggests that tofacitinib is superior to placebo for achieving clinical and endoscopic remission at 52 weeks in participants with moderate-to-severe ulcerative colitis (UC) who had a clinical response after eight weeks of induction treatment with tofacitinib (10 mg twice daily) or placebo. The optimal dose of tofacitinib for maintenance therapy is unknown. High-certainty evidence suggests that there is no increased risk of adverse events (AEs) with tofacitinib compared to placebo. However, we are uncertain about the effect of tofacitinib on severe adverse events (SAEs) due to the low number of events.

Implications for research

Further studies are required to look at the long-term effectiveness and safety of using tofacitinib and other oral Janus kinase (JAK) inhibitors as maintenance therapy in participants with moderate-to-severe UC in remission.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Sandborn 2017

Study characteristics	
Methods	Three phase 3, randomized, double-blind, placebo-controlled trials of tofacitinib therapy in adults with ulcerative colitis OCTAVE 1 and OCTAVE 2 examined patients with moderately to severely active ulcerative colitis and were randomly assigned to receive induction therapy with tofacitinib (10 mg twice daily) or placebo for 8 weeks In the OCTAVE SUSTAIN trial, patients were randomly assigned to receive maintenance therapy with tofacitinib 5 mg or 10 mg twice daily or placebo for 52 weeks
Participants	593 patients who had a clinical response to induction therapy were randomly assigned to receive maintenance therapy Patients were not required to have achieved clinical remission, endoscopic remission or mucosal healing at baseline **Inclusion criteria** Patients were 18 years of age or older and had a confirmed diagnosis of ulcerative colitis for at least 4 months Patients had moderately to severely active disease, which was defined as a Mayo score of 6 to 12, with a rectal bleeding sub score of 1 to 3 and an endoscopic sub score of 2 or 3

Sandborn 2017 *(Continued)*

	Exclusion criteria The presence of clinical findings suggestive of Crohn's disease, ulcerative colitis limited to the distal 15 cm of colon, clinical signs of fulminant colitis, toxic megacolon, or indeterminate, microscopic, ischemic,or infectious colitis
Interventions	Patients were randomized to one of three treatment arms: 5 mg tofacitinib twice daily (n = 198) 10 mg tofacitinib twice daily (n = 197) Placebo twice daily (n = 198)
Outcomes	**Primary outcome:** remission at 52 weeks **Secondary outcomes:** mucosal healing at 52 weeks, sustained remission (occurring at both 24 and 52 weeks), glucocorticosteroid-free (i.e. occurring without the administration of glucocorticosteroids for >4 weeks before the assessment)
Notes	This study also includes outcomes of the OCTAVE 1 and 2, however we are only focused on the OCTAVE SUSTAIN trial

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Utilized central tele-randomization system with stratification according to the assignment in OCTAVE 1 or OCTAVE 2 and remission status
Allocation concealment (selection bias)	Low risk	Central allocation
Blinding of participants and personnel (performance bias) All outcomes	Low risk	The sponsor's personnel directly involved in the study conduct are blinded. The drug and placebo are identical in appearance
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The central pathologist is blinded, as well as the members assessing the endpoints
Incomplete outcome data (attrition bias) All outcomes	Low risk	Dropouts were balanced across groups An intention-to-treat analysis was used
Selective reporting (reporting bias)	Low risk	All outcomes were reported
Other bias	Low risk	No other bias detected

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Sandborn 2012	Not a maintenance study

Study	Reason for exclusion
Sandborn 2019	Not a maintenance study
Sands 2016	Not a maintenance study
Sands 2018	Not a maintenance study

Characteristics of ongoing studies *[ordered by study ID]*

NCT02819635

Study name	A multicenter, randomized, double-blind, placebo-controlled study to evaluate the safety and efficacy of upadacitinib (ABT-494) for induction and maintenance therapy in subjects with moderately to severely active ulcerative colitis
Methods	Allocation: randomized Intervention model: parallel assignment Masking: quadruple (participant, care provider, investigator, outcomes assessor) Primary purpose: treatment Estimated enrollment: 844 participants
Participants	Adults (18-75 years) with ulcerative colitis Diagnosis of ulcerative colitis for 90 days or greater prior to baseline, confirmed by colonoscopy during the screening period, with exclusion of current infection, colonic dysplasia and/or malignancy Active ulcerative colitis with an adapted Mayo score of 5 to 9 points and endoscopic sub score of 2 to 3 (confirmed by central reader) Demonstrated an inadequate response to, loss of response to, or intolerance to corticosteroids, immunosuppressants, and/or biologic therapies
Interventions	1. Placebo 2. ABT-494 (Upadacitinib) Dose D
Outcomes	**Primary outcome** 1. Proportion of participants who achieve clinical remission per adapted Mayo score at week 8 2. Proportion of participants who achieve clinical remission per adapted Mayo score at week 44 **Secondary outcome** 1. Proportion of participants who discontinued corticosteroid use that achieved clinical remission per adapted Mayo score at week 44 2. Proportion of participants achieving clinical response per adapted Mayo score at week 8 3. Proportion of participants achieving clinical remission per full Mayo score at week 44 4. Proportion of participants achieving clinical remission per full Mayo score at week 8 5. Proportion of participants with endoscopic improvement at week 44 6).Proportion of participants with endoscopic improvement at week 8

NCT02819635 *(Continued)*

Starting date	28 September 2016
Contact information	AbbVie
Notes	

NCT02914522

Study name	Filgotinib in the induction and maintenance of remission in adults with moderately to severely active ulcerative colitis (SELECTION1)
Methods	Allocation: randomized Intervention model: parallel assignment Masking: double (participant, investigator) Primary purpose: treatment Enrollment:1351 participants
Participants	Adults (18-75 years) with documented moderate to active UC of at least 6 months and with a minimum disease extent of 15 cm from the anal verge Previously demonstrated an inadequate clinical response, loss of response to, or intolerance to at least 1 of the following agents: corticosteroids, immunomodulator's, tumor necrosis factor alpha (TNFa) antagonists, or vedolizumab
Interventions	1. Placebo 2. Drug: filgotinib (once daily) Dose A 3. Drug: filgotinib (once daily) Dose B
Outcomes	**Primary outcome (maintenance)** 1. Proportion of participants achieving remission based on components of MCS at week 58 **Secondary outcomes (Maintenance)** 1. Proportion of participants achieving MCS remission at week 58 2. Proportion of participants achieving remission based on components of MCS at weeks 10 and 58 3. Proportion of participants achieving 6-month corticosteroid-free remission based on components of MCS at week 58 4. Proportion of participants achieving endoscopic sub score of 0 at week 58 5. Proportion of participants achieving histologic remission at week 58 6. Proportion of participants achieving MCS remission (alternative definition) at week 58 7. Pharmacokinetic plasma concentrations of filgotinib and its metabolite GS-829845
Starting date	14 November 2016
Contact information	Gilead Sciences
Notes	

NCT03281304

Study name	A phase 3b/4, multi-center, double-blind, randomized, parallel group study of Tofacitinib (Cp-690,550) in subjects with ulcerative colitis in stable remission
Methods	Allocation: randomized Intervention model: parallel assignment Masking: quadruple (participant, care provider, investigator, outcomes assessor) Primary purpose: treatment Estimated enrollment: 130 participants
Participants	Adults (< 18 years) currently enrolled in Study A3921139 on CP-690,550 10 mg (twice daily) In stable remission on CP-690,550 10 mg (twice daily)
Interventions	1. CP-690,500 5 mg 2. CP-690,550 10 mg
Outcomes	**Primary outcome** 1) Remisson based on Mayo score at 6 months **Secondary outcomes** 1. Time to loss of remission based on modified Mayo score from first visit up to 18 months 2. Remission based on modified Mayo score at 18 months 3. Remission based on modified partial Mayo score at 18 months 4. Remission based on total Mayo score at 18 months 5. Remission based on partial Mayo score at 18 months 6. Change from baseline in modified Mayo score from baseline to 18 months 7. Change from baseline in modified partial Mayo score from baseline to 18 months 8. Change from baseline in total Mayo score from baseline to 18 months 9. Change from baseline in partial Mayo score from baseline to 18 months 10. Mucosal healing at 18 months 11. Clinical response based on Mayo score at 18 months 12. Change from baseline in fecal calprotectin from baseline to 18 months 13. Change from baseline in hs-CRP from baseline to 18 months
Starting date	16 November 2017
Contact information	Pfizer
Notes	

NCT03627052	
Study name	A phase 2, double-blind, dose-ranging, placebo-controlled study with open-label extension to evaluate the safety and efficacy of itacitinib in moderate to severe ulcerative colitis
Methods	Allocation: randomized Intervention model: parallel assignment Masking: double (participant, investigator) Estimated enrollment: 206 participants
Participants	Adult UC patients with a confirmed diagnosis of UC at least 12 weeks before screening and have a 3-component Mayo score of 4 to 9
Interventions	1. Itacitinib 2, Placebo
Outcomes	**Primary outcome** 1. Proportion of participants with a clinical response at week 12 **Secondary outcomes** 1. Proportion of participants with endoscopic response at week 12 2. Proportion of participants with mucosal healing at week 12 3. Proportion of participants in endoscopic remission at week 12 4. Proportion of participants in clinical remission at week 12 5. Change from baseline in 3-component Mayo score at week 12 6. Change from baseline in Physician's Global Assessment score at week 12 7. Change in quality of life score as measured by the Inflammatory Bowel Disease Questionnaire (IBDQ) at weeks 4 and 12 8. Cmax of itacitinib at weeks 2, 4, and 12] 9. Cmin of itacitinib at weeks 2,4, and 12 10. Stool concentration of itacitinib - 24-hour collection at week 4 11. Number of treatment-emergent adverse events up to approximately 60 weeks
Starting date	20 September 2018
Contact information	Incyte Corporation
Notes	

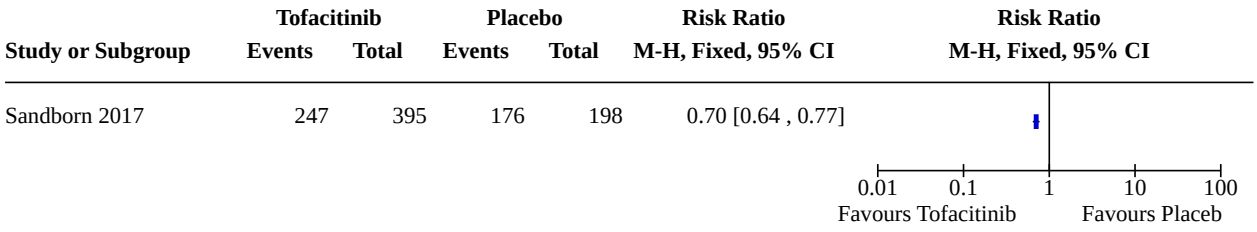
CRP: C-reactive protein; **MCS:** Mayo Clinic Score; **UC:** ulcerative colitis

DATA AND ANALYSES

Comparison 1. Tofacitinib versus placebo

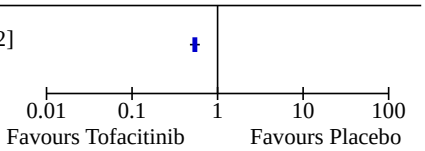
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Failure to achieve clinical remission at 52 weeks (5 mg/10 mg)	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
1.2 Failure to achieve clinical response at 52 weeks (5 mg/10 mg)	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
1.3 Failure to achieve endoscopic remission at 52 weeks (5 mg/10 mg)	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
1.4 Adverse Events (5 mg/10 mg)	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
1.5 Serious Adverse Events (5 mg/10 mg)	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
1.6 Withdrawals due to adverse events (5 mg/10 mg)	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
1.7 Failure to maintain mucosal healing at 52 weeks (5 mg/10 mg)	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
1.8 Any Infection (5 mg/ 10 mg)	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
1.9 Serious infection (5 mg/ 10 mg)	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
1.10 Herpes zoster (5 mg/ 10 mg)	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
1.11 Failure to maintain remission (IBDQ score)	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
1.12 Failure to maintain response (IBDQ score)	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected

Analysis 1.1. Comparison 1: Tofacitinib versus placebo, Outcome 1: Failure to achieve clinical remission at 52 weeks (5 mg/10 mg)



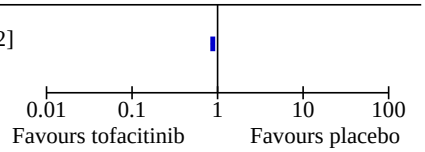
Analysis 1.2. Comparison 1: Tofacitinib versus placebo, Outcome 2: Failure to achieve clinical response at 52 weeks (5 mg/10 mg)

Study or Subgroup	Tofacitinib Events	Tofacitinib Total	Placebo Events	Placebo Total	Risk Ratio M-H, Fixed, 95% CI
Sandborn 2017	171	395	158	198	0.54 [0.48 , 0.62]



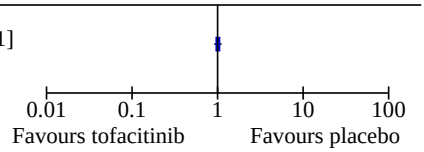
Analysis 1.3. Comparison 1: Tofacitinib versus placebo, Outcome 3: Failure to achieve endoscopic remission at 52 weeks (5 mg/10 mg)

Study or Subgroup	Tofacitinib Events	Tofacitinib Total	Placebo Events	Placebo Total	Risk Ratio M-H, Fixed, 95% CI
Sandborn 2017	333	395	190	198	0.88 [0.83 , 0.92]



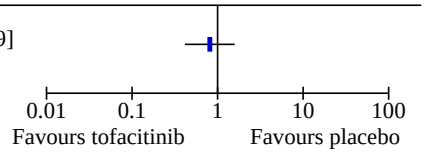
Analysis 1.4. Comparison 1: Tofacitinib versus placebo, Outcome 4: Adverse Events (5 mg/10 mg)

Study or Subgroup	Tofacitinib Events	Tofacitinib Total	Placebo Events	Placebo Total	Risk Ratio M-H, Fixed, 95% CI
Sandborn 2017	299	394	149	198	1.01 [0.91 , 1.11]



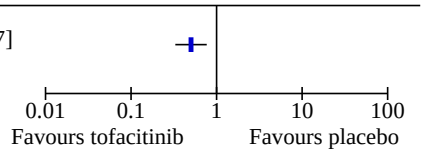
Analysis 1.5. Comparison 1: Tofacitinib versus placebo, Outcome 5: Serious Adverse Events (5 mg/10 mg)

Study or Subgroup	Tofacitinib Events	Tofacitinib Total	Placebo Events	Placebo Total	Risk Ratio M-H, Fixed, 95% CI
Sandborn 2017	21	394	13	198	0.81 [0.42 , 1.59]



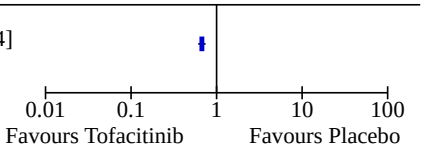
Analysis 1.6. Comparison 1: Tofacitinib versus placebo, Outcome 6: Withdrawals due to adverse events (5 mg/10 mg)

Study or Subgroup	Tofacitinib Events	Tofacitinib Total	Placebo Events	Placebo Total	Risk Ratio M-H, Fixed, 95% CI
Sandborn 2017	37	394	37	198	0.50 [0.33 , 0.77]



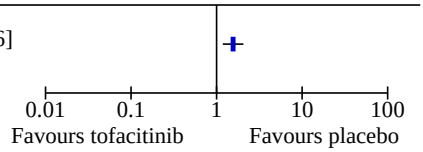
Analysis 1.7. Comparison 1: Tofacitinib versus placebo, Outcome 7: Failure to maintain mucosal healing at 52 weeks (5 mg/10 mg)

Study or Subgroup	Tofacitinib Events	Tofacitinib Total	Placebo Events	Placebo Total	Risk Ratio M-H, Fixed, 95% CI
Sandborn 2017	231	395	172	198	0.67 [0.61 , 0.74]



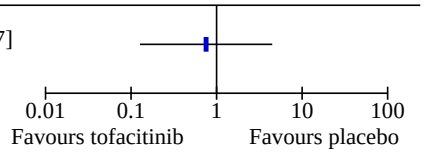
Analysis 1.8. Comparison 1: Tofacitinib versus placebo, Outcome 8: Any Infection (5 mg/ 10 mg)

Study or Subgroup	Tofacitinib Events	Tofacitinib Total	Placebo Events	Placebo Total	Risk Ratio M-H, Fixed, 95% CI
Sandborn 2017	149	394	48	198	1.56 [1.18 , 2.06]



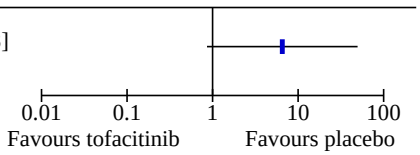
Analysis 1.9. Comparison 1: Tofacitinib versus placebo, Outcome 9: Serious infection (5 mg/ 10 mg)

Study or Subgroup	Tofacitinib Events	Tofacitinib Total	Placebo Events	Placebo Total	Risk Ratio M-H, Fixed, 95% CI
Sandborn 2017	3	394	2	198	0.75 [0.13 , 4.47]



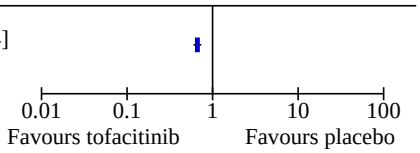
Analysis 1.10. Comparison 1: Tofacitinib versus placebo, Outcome 10: Herpes zoster (5 mg/ 10 mg)

Study or Subgroup	Tofacitinib Events	Tofacitinib Total	Placebo Events	Placebo Total	Risk Ratio M-H, Fixed, 95% CI
Sandborn 2017	13	394	1	198	6.53 [0.86 , 49.58]



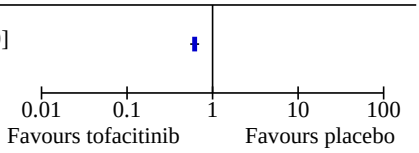
Analysis 1.11. Comparison 1: Tofacitinib versus placebo, Outcome 11: Failure to maintain remission (IBDQ score)

Study or Subgroup	Tofacitinib Events	Tofacitinib Total	Placebo Events	Placebo Total	Risk Ratio M-H, Fixed, 95% CI
Sandborn 2017	224	395	169	198	0.66 [0.60 , 0.74]



Analysis 1.12. Comparison 1: Tofacitinib versus placebo, Outcome 12: Failure to maintain response (IBDQ score)

Study or Subgroup	Tofacitinib Events	Tofacitinib Total	Placebo Events	Placebo Total	Risk Ratio M-H, Fixed, 95% CI
Sandborn 2017	197	395	160	198	0.62 [0.55 , 0.70]



APPENDICES

Appendix 1. Search strategies

EMBASE

1. random$.tw.
2. factorial$.tw.
3. (crossover$ or cross over$ or cross-over$).tw.
4. placebo$.tw.
5. single blind.mp.
6. double blind.mp.
7. triple blind.mp.
8. (singl$ adj blind$).tw.
9. (double$ adj blind$).tw.

10. (tripl$ adj blind$).tw.

11. assign$.tw.

12. allocat$.tw.

13. crossover procedure/

14. double blind procedure/

15. single blind procedure/

16. triple blind procedure/

17. randomized controlled trial/

18. or/1-17

19. exp ulcerative colitis/

20. colitis.mp.

21. inflammatory bowel disease.mp.

22. IBD.mp.

23. UC.mp.

24. Or/19-23

25. JAK.mp.

26. Janus.mp.

27. jakinibs.mp.

28. JAK*.mp.

29. TYK2.mp.

30. (Tofacitinib or Xeljanz or Jakvinus or CP-690550).mp.

31. (Ruxolitinib or Jakafi or Jakavi or INCB018424 or INC424).mp.

32. (Baricitinib or Olumiant or INCB28050 or LY3009104).mp.

33. (Upadacitinib or ABT494 or ABT-494).mp.

34. (Filgotinib or GLPG0634).mp.

35. (Peficitinib or ASP015K).mp.

36. Or/25-35

37. 18 and 24 and 36

MEDLINE

1. random$.tw.

2. factorial$.tw.

3. (crossover$ or cross over$ or cross-over$).tw.

4. placebo$.tw.

5. single blind.mp.

6. double blind.mp.

7. triple blind.mp.

8. (singl$ adj blind$).tw.

9. (double$ adj blind$).tw.

10. (tripl$ adj blind$).tw.

11. assign$.tw.

12. allocat$.tw.

13. randomized controlled trial/

14. or/1-13

15. exp ulcerative colitis/

16. colitis.mp.

17. inflammatory bowel disease.mp.

18. IBD.mp.

19. UC.mp.

20. Or/15-19

21. JAK.mp.

22. Janus.mp.

23. jakinibs.mp.

24. JAK*.mp.

25. TYK2.mp.

26. (Tofacitinib or Xeljanz or Jakvinus or CP-690550).mp.

27. (Ruxolitinib or Jakafi or Jakavi or INCB018424 or INC424).mp.

28. (Baricitinib or Olumiant or INCB28050 or LY3009104).mp.

29. (Upadacitinib or ABT494).mp.

30. (Filgotinib or GLPG0634).mp.

31. (Peficitinib or ASP015K).mp.

32. or/21-31

33. 14 and 20 and 32

Cochrane Library

#1 MeSH descriptor: [Colitis, Ulcerative] explode all trees

#2 colitis OR UC OR IBD OR inflammatory bowel disease

#3 # 1 or #2

#4 JAK OR Janus or jakinibs or JAK1 or JAK2 or JAK3 or TYK2 or Tofacitinib or Ruxolitinib or Filgotinib or Baricitinib or Peficitinib

#5 #3 AND #4

Cochrane IBD Specialized Register

(JAK OR Janus or jakinibs or JAK1 or JAK2 or JAK3 or TYK2 or Tofacitinib or Ruxolitinib or Filgotinib or Baricitinib or Upadacitinib or Peficitinib) in title/abstract

Clinicaltrials.gov

1. Oral Janus Kinase and Ulcerative colitis

2. Tofacitinib and Ulcerative colitis

3. Ruxolitinib and Ulcerative colitis

4. Baricitinib and Ulcerative colitis

5. Upadacitinib and Ulcerative colitis

6. Filgotinib and Ulcerative colitis

7. Peficitinib and Ulcerative colitis

WHO trials registry (ICTRP)

1. Oral Janus Kinase and Ulcerative colitis

2. Tofacitinib and Ulcerative colitis

3. Ruxolitinib and Ulcerative colitis

4. Baricitinib and Ulcerative colitis

5. Upadacitinib and Ulcerative colitis

6. Filgotinib and Ulcerative colitis

7. Peficitinib and Ulcerative colitis

F E E D B A C K

Comment on oral Janus kinase inhibitors for maintenance of remission in ulcerative colitis, August 2020

Summary

Name: Irene Modesto
Email Address: irene.modesto@pfizer.com
Affiliation: Pfizer Inc, New York
Role: Senior Director, Medical Strategy Head Gastroenterology and Global Medical

Comment on: Oral Janus kinase inhibitors for maintenance of remission in ulcerative colitis We have read the article ‘Oral Janus kinase inhibitors for maintenance of remission in ulcerative colitis’(1) with interest and we acknowledge the value of a review compiling evidence on the use of Janus kinase inhibitors for the treatment of ulcerative colitis (UC). As the accurate reporting of clinical trial endpoint definitions and data is crucial in the understanding of treatment effects, particularly in an era of evolving therapeutic paradigm, we would like you to consider our suggestion to clarify the data reported by Davies 2020(1) from OCTAVE Sustain, a phase 3, randomised, double-blind, placebo-controlled trial of tofacitinib for maintenance therapy in patients with UC.(2) Davies 2020 refer to the proportion of patients who failed to maintain clinical remission, endoscopic remission or mucosal healing at Week 52, thus potentially confusing the reader to believe that patients had achieved these endpoints at the beginning of the maintenance study and had experienced a loss of response.(1) At baseline of OCTAVE Sustain, eligible patients were required to have achieved a clinical response following 8-weeks’ induction treatment with either tofacitinib 10 mg twice daily or placebo, but were not required to have achieved clinical remission, endoscopic remission or mucosal healing, and therefore the right definition should be ‘patients that failed to achieve clinical remission, endoscopic remission or mucosal healing at Week 52 of OCTAVE Sustain’.(2) In conclusion, there is a need to bring to your attention the above information to avoid misunderstanding and misinterpretation of the efficacy endpoints used in the pivotal phase 3 study of tofacitinib and the analyses performed. We trust that you will inform the authors of this publication of our concerns. Sincerely yours, Irene Modesto, MD, PhD Senior Director, Medical Strategy Head Gastroenterology and Global Medical Lead for Xeljanz UC, Inflammation & Immunology Global Medical Affairs, Pfizer Inc, New York, NY, USA References 1. Davies SC, Hussein IM, Nguyen TM, Parker CE, Khanna R, Jairath V. Oral Janus kinase inhibitors for maintenance of remission in ulcerative colitis. Cochrane Database of Systematic Reviews. 2020(1). 2. Sandborn WJ, Su C, Sands BE, D'Haens GR, Vermeire S, Schreiber S, et al. Tofacitinib as induction and maintenance therapy for ulcerative colitis. N Engl J Med. 2017;376(18):1723-36. Declarations of interest Irene Modesto is an employee and shareholder of Pfizer Inc. Declaration of funding interest These studies were sponsored by Pfizer Inc. Medical writing support, under the guidance of the authors, was provided by Helen Findlow,

PhD, CMC Connect, McCann Health Medical Communications and was funded by Pfizer Inc, New York, NY, USA in accordance with Good Publication Practice (GPP3) guidelines (Ann Intern Med 2015;163:461–464).

Thank you.

Reply

Thank you for your comment. We agree with your suggestion to clarify the reporting of endpoint definitions for the OCTAVE Sustain trial. The endpoint definitions have been revised as appropriate. Thank you.

Contributors

Sarah C Davies, Isra M Hussein, Tran M Nguyen, Claire E Parker, Reena Khanna, Vipul Jairath

WHAT'S NEW

Date	Event	Description
12 August 2020	Amended	Review has been amended in response to reader feedback regarding endpoint definitions for the one included study

HISTORY

Protocol first published: Issue 10, 2016
Review first published: Issue 1, 2020

CONTRIBUTIONS OF AUTHORS

Sarah C Davies (SD) was involved in the search and selection of studies for inclusion in the review, collection of data for the review, assessment of the risk of bias in the included studies, analysis of data, assessment of the certainty in the body of evidence, interpretation of data and writing the review.

Isra M Hussein (IMH) was involved in the collection of data for the review.

Tran M Nguyen (TMN) was involved in the co-ordination of the review, search and selection of studies for inclusion in the review, collection of data for the review, assessment of the certainty in the body of evidence, interpretation of data and writing the review.

Reena Khanna (RK) was involved in the conception of the review, design of the review and interpretation of data.

Vipul Jairath (VJ) was involved in the conception of the review, design of the review and interpretation of data.

DECLARATIONS OF INTEREST

IMH, CEP, SD and TMN have no known conflicts of interest.

RK has received consulting fees from AbbVie, Janssen, Pfizer, Shire, Takeda, Genetec/Roche, Robarts Clinical Trials, Pendopharm, Innomar, Encycle, Merck.

VJ has received has received consulting fees from AbbVie, Eli Lilly, GlaxoSmithKline, Arena pharmaceuticals, Genetech, Pendopharm, Sandoz, Merck, Takeda, Janssen, Robarts Clinical Trials, Topivert, and Celltrion; and speaker's fees from Takeda, Janssen, Shire, Ferring, Abbvie, and Pfizer

SOURCES OF SUPPORT

Internal sources

- None, Other

External sources

- None, Other

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

1. Additional post-hoc analyses were reported in the final review that were not originally reported in the protocol. These outcomes include:
   a. failure to achieve mucosal healing at 52 weeks;
   b. infections (any infection, serious infection, herpes zoster); and
   c. clinical remission and response based on the Inflammatory Bowel Disease Questionnaire (IBDQ) score.
2. The decision as to what outcomes were reported in the 'Summary of findings' table was post hoc, as we did not pre-specify what outcomes would be included in the 'Summary of findings' table in the protocol.
3. We calculated the number needed to treat for the primary outcome.

INDEX TERMS

Medical Subject Headings (MeSH)

Colitis, Ulcerative [*drug therapy]; Janus Kinase Inhibitors [*therapeutic use]; Maintenance Chemotherapy; Piperidines [*therapeutic use]; Protein Kinase Inhibitors; Pyrimidines [*therapeutic use]; Pyrroles [*therapeutic use]; Quality of Life; Randomized Controlled Trials as Topic

MeSH check words

Humans