FINAL REPORT

Harm Profile of JAK Inhibitors in Ulcerative Colitis

June 2024

Drug Assessment Working Group

Therapeutics Initiative

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Glossary and abbreviations

ARTIS	Anti-Rheumatic Therapies in Sweden
BID	Twice a day
EMA	European Medicines Agency
FDA	US Food and Drug Administration
JAKi	Janus kinase inhibitors
LTE	Long-term extension
MTX	Methotrexate
NMA	Network meta-analysis
ORAL SURV	ORAL Surveillance safety trial
OCTAVE	Tofacitanib ulcerative colitis drug development program clinical trial series
RCT	Randomized controlled trial
SAE	Serious adverse event
SELECT	Upadacitinib ulcerative colitis drug development program clinical trial series
TNFi	Tumor necrosis factor inhibitor
TOFA	Tofacitinib
UC	Ulcerative colitis
UPAD	Upadacitinib

BACKGROUND

In 2012 oral tofacitinib (TOFA) 5 mg twice daily monotherapy became the first US Food and Drug Administration (FDA) approved JAK inhibitor (JAKi) for treatment of rheumatoid arthritis (RA), followed by approval of a 11 mg daily dose in 2017. In 2017, European Medicines Agency (EMA) first approved TOFA 5 mg twice daily in combination with methotrexate for RA. The timeline of FDA and EMA approval of JAKis for rheumatic conditions is provided in Appendix A (Winthrop 2022)(1).

Health Canada's 2022 approval for the indication ulcerative colitis (UC) for TOFA 5 mg or 10 mg twice daily, followed FDA and EMA approval in 2021. A second JAKi, upadacitinib (UPAD), was approved by Health Canada in 2023. The TOFA product monograph contains this indication description for UC.

- **Ulcerative Colitis**

APO-TOFACITINIB (tofacitinib) is indicated for the treatment of adult patients with moderately to severely active ulcerative colitis (UC) with an inadequate response, loss of response or intolerance to either conventional UC therapy or a TNFα inhibitor.

Limitations of Use: Use of APO-TOFACITINIB in combination with biological UC therapies or with potent immunosuppressants such as azathioprine and cyclosporine is not recommended.

The ORAL Surveillance (ORAL SURV) study was a post authorization open label non inferiority randomized trial that found increases in major adverse cardiovascular events (MACE) and cancers with TOFA as compared to a tumor necrosis factor (TNF) inhibitor in patients with active RA despite MTX treatment.(2) As findings emerged in 2019 regulators began treating the risk of serious adverse events (SAE) of TOFA and other JAKi as a class effect for all rheumatic conditions. Therefore they extended label warnings beyond RA (the indication in the ORAL SURV trial) to include UC.

Health Canada, for example, conducted a safety review[1] followed by a public advisory[2] in early 2022. The review based on ORAL SURV concluded that

- Health Canada's review of the clinical research study found a link between the use of [the JAK inhibitor tofacitinib] Xeljanz/Xeljanz XR and the risks of serious heart-related problems and cancer.
- Health Canada has worked with the manufacturer to update the [Canadian product monograph] CPM to highlight the risks of serious heart-related problems and cancer, including a warning statement about the use of Xeljanz/Xeljanz XR in older patients, patients who are current or past smokers, and patients with cardiovascular or cancer risk factors.

[1] https://dhpp.hpfb-dgpsa.ca/review-documents/resource/SSR00278

[2] https://recalls-rappels.canada.ca/en/alert-recall/health-canada-safety-review-finds-link-between-use-xeljanz-and-xeljanz-xr-tofacitinib

In relation to UC the public advisory stated:

- The higher dose of Xeljanz 10 mg twice daily is only authorized for patients with ulcerative colitis, a large intestine inflammation causing sores and bleeding, who have not responded well to other medications. For patients with ulcerative colitis, the prescribing information recommends that they use the lowest effective dose and for the shortest duration needed to help them improve their condition.

Following reviews of upacitinib and baricitinib a risk communication to health professions[3] was issued in the fall of 2022 that covered abrocitinib, fedratinib, ruxolitinib in addition to tofacitinib, upadacitinib and baricitinib.

- Based on these safety findings and similar mechanisms of action, Health Canada cannot rule out the risks of MACE, thrombosis (including fatal events) and malignancies, for other JAK inhibitors (CIBINQO, INREBIC, JAKAVI, OLUMIANT, and RINVOQ).

- As a precautionary measure, Health Canada is working with the manufacturers to update and align these risks in the CPMs for JAK inhibitors.

The EMA concluded that the warnings arising from the ORAL SURV trial applied to all approved uses of JAK inhibitors in chronic inflammatory disorders (RA, PsA, AS, juvenile idiopathic arthritis, ulcerative colitis, atopic dermatitis and alopecia areata). They made recommendations to try to minimize the risk of serious adverse events (SAE) by limiting use in 'those aged 65 years or above, those at increased risk of major cardiovascular problems (such as heart attack or stroke), those who smoke or have done so for a long time in the past and those at increased risk of cancer' 'if no suitable alternative treatments are available'. Also the EMA advised caution in those with 'risk factors for blood clots in the lungs and in deep veins (venous thromboembolism, VTE) other than those listed above'. Finally the EMA recommends that 'doses should be reduced in patient groups who are at risk of VTE, cancer or major cardiovascular problems, where possible.' [4]

This report reviews open-label randomized and non-randomized experimental studies as well as observational studies of harm associated with JAKi for ulcerative colitis in the post authorization time period.

Epidemiology: Ulcerative colitis (UC) is a relapsing remitting inflammatory bowel disease (IBD). The annual incidence of UC ranges from 8.8 to 23.1 per 100,000 person-years in North America, 0.6 to 24.3 per 100,000 person-years in Europe, and 7.3 to 17.4 in Oceania (Du 2020(3)). Diagnosis requires mucosal biopsy.

Often starting in the rectum, UC extends through the colon and if left untreated results in bowel damage which predisposes to colon cancer. Removing the colon is a final and curative surgical solution. Symptoms include abdominal pain, cramping, gurgling, urgency, diarrhea, blood or pus in stools and

[3] https://recalls-rappels.canada.ca/en/alert-recall/janus-kinase-inhibitors-and-risk-major-adverse-cardiovascular-events-thrombosis

[4] https://www.ema.europa.eu/en/news/ema-confirms-measures-minimise-risk-serious-side-effects-janus-kinase-inhibitors-chronic-inflammatory-disorders

weighloss. Ages of onset is bimodal that peaks in the 20-40 age groups with a smaller peak in the 60-70s age groups.

UC mechanism of action is not known. It is believed to be related to exposure to risk factors in genetically susceptible individuals. Risk factors include medications, living conditions and hygiene, prior appendectomy (protective), smoking and less diversity in the composition of the gut microbiome (Du 2020(3)). Exacerbations of inflammation are due to inappropriate immune responses to microbes that typically reside on mucosa without harming health.

Drug characteristics: As smaller molecules, JAKi are seen to have advantages over biologic alternatives in terms of less immunogenicity, shorter half-life and more rapid onset of action. JAKis modulate the immune system by interfering with the JAK-STAT signaling pathway in lymphocytes by inhibiting one or more of the Janus kinase family of enzymes (Crispino 2021(4)). There are 15 compounds approved as JAKis with more under investigation. JAKis have been approved for a number of rheumatic and multiple non-rheumatic conditions including Crohn's Disease, atopic dermatitis, hidradenitis, vitiligo, and systemic lupus erythematosus (SLE).

Targeting segments of the JAK- STAT pathway

The JAKi drug class emerged from research in the late 1980s to early 1990s that produced a better understanding of the JAK-STAT pathway. This lead to research linking JAK-STAT pathway dysfunction to autoimmune diseases generally. There is an ongoing effort to understand the role of JAK-STAT pathway dysfunction plays in particular autoimmune conditions. Drugs targeting different JAK-STAT segments are therefore being developed and tested in ongoing research programs(Garber 2011)(5).

JAKs are one part of the JAK-STAT pathway that works on the cell surface. STAT components deliver signals to the cell nucleus. The JAK-STAT pathways are also involved in tumour formation, cell division and cell death (Kotyla 2021)(6).

JAK-STAT is a signalling pathway that can act to reduce the cytokine storm that overreacts in autoimmune rheumatic conditions. It is a chemical pathway that carries signals via a chain of interactions between proteins from outside a cell to the cell nucleus. The Janus kinase JAK 'family' is made up of tyrosine protein kinases that are activated when cytokines bind to their receptors and transmit regulatory signals. (Hu 2021)(7).

STATs are signal transducers and activator of transcription. When a molecule (ligand) binds to a receptor on the cell surface, JAKs add phosphates. STAT proteins bind to the phosphates to form dimer (bonded pair) that enters the cell nucleus, binds to the DNA and causes transcription of the target genes.

The four main JAK pathways are JAK1, JAK2, JAK3 and TYK2. The main protein messengers are expressed in most tissues in the body and have distinct functions. An exception is JAK3 which has more limited action on bone marrow, lymphatic endothelial and smooth muscle. Janus kinases have two phosphate transferring domains – one that exhibits the kinase activity, the other that negatively regulates the activity of the other (Lee 2023)(8).

Standard of therapy: The European Crohn's and Colitis Organization (ECCO) updated their guidelines on medical treatment of UC in 2021 (Raine 2020)(9) using their standardized evidence review and guideline development approach. This is their recommendation on use of TOFA for UC.

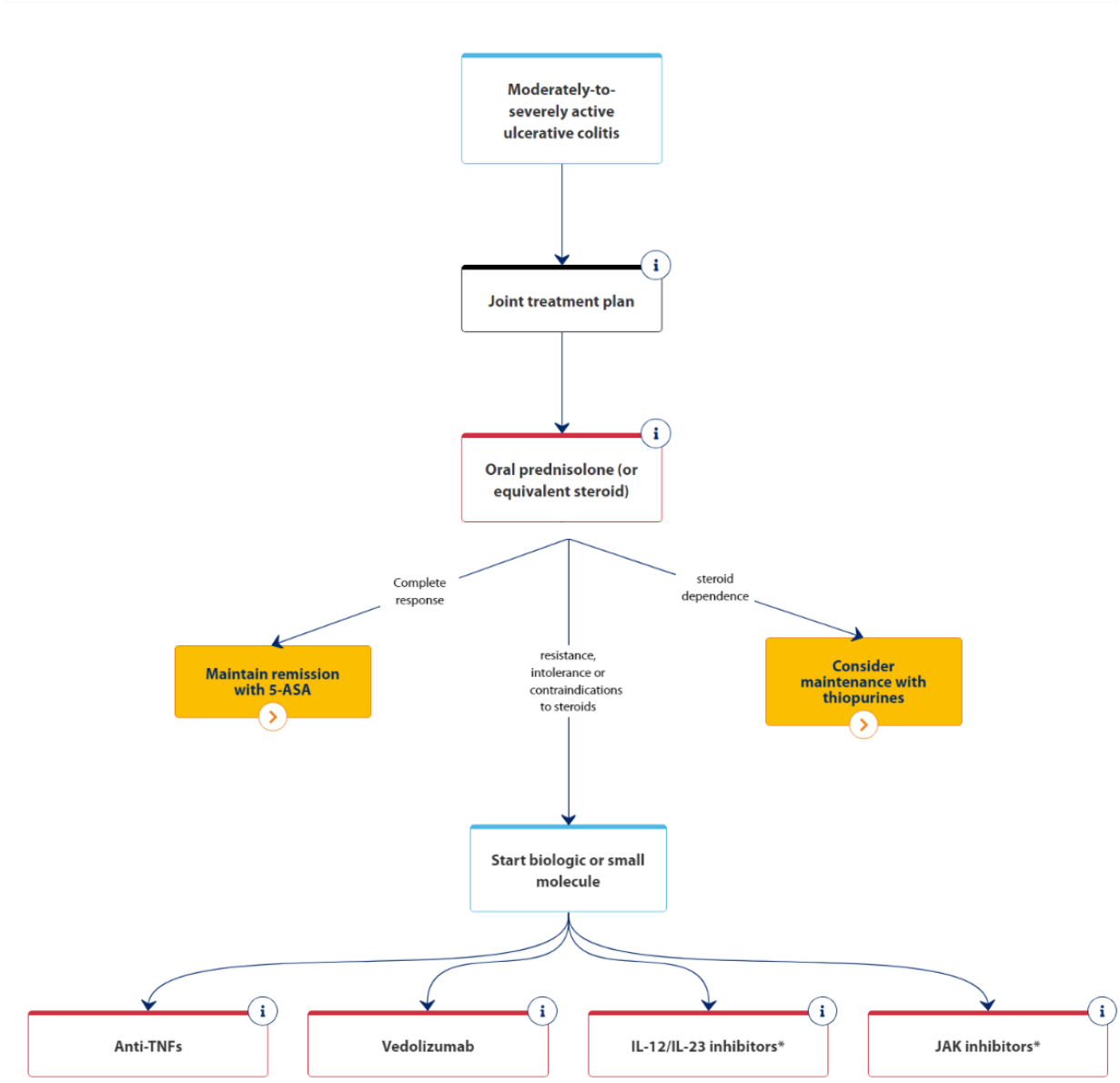
> We recommend treatment with tofacitinib to induce remission in patients with moderate-to-severe UC who have inadequate response or intolerance to conventional therapy [strong recommendation, moderate quality of evidence]

A treatment algorithm for induction therapy for moderate to severe UC[5] was developed (Figure 2). If after treatment with prednisolone or equivalent steroid, there is resistance, intolerance or contraindications to steroids, the recommendation is to start treatment with one of the following biologic or small molecule pharmaceutical product: Anti-TNFs, vedolizumab, IL-12/IL-23 inhibitors or JAK inhibitors.

ECCO endorsed the EMEA recommendation that the lowest efficacious dose of TOFA be used and to avoid TOFA 10 mg twice daily as maintenance treatment in patients with known VTE risk factors (Raine 2020)(9). UPAD was not included in most current guidelines as regulatory approval for UC was relatively recent in 2022/23.

[5] https://www.e-guide.ecco-ibd.eu/interventions-therapeutic/tofacitinib

Figure 2: ECCO[6] algorithm for induction therapy in moderate-to-severe UC



[6] https://www.e-guide.ecco-ibd.eu/algorithm/induction-therapy-moderate-severe-ulcerative-colitis

BC Pharmacare coverage status and criteria: TOFA is available in BC to treat UC through the pharmacare special authorization limited coverage program[7] when criteria are met (update Feb 2024). To initiate or switch treatment a pre-treatment assessment score of ≥ 4 with a rectal bleeding subscore of ≥ 2 is required based on scored scales of stool frequency, rectal bleeding, and physician's global assessment. Details of glucocorticoid trial are also required. The same application process is required for adalimumab, infliximab, ozanimod and vedolizumab as well as TOFA.

PharmaCare covers a maximum 30 days' supply per fill. Coverage is limited to 10 mg twice daily for 8 weeks (loading doses) then 5 mg twice daily dosing thereafter. TOFA authorization cannot be used in combination with biologic drugs for ulcerative colitis.

UPAD is not currently covered under the BC special authorization program for ulcerative colitis.

Clinical evidence review

METHODS

The Therapeutics Initiative (TI) Drug Assessment Working Group (DAWG) used its Evaluation Framework and Rules of Evidence to address the following policy relevant question:

What is the harm profile of JAK inhibitors tofacitinib and upadacitinib for ulcerative colitis?

Rheumatoid arthritis was the first approved rheumatoic condition indication for TOFA. Therefore TOFA RA harm evidence is the longest and most extensive. The seminal longitudinal open-label harm surveillance study is ORAL Surveillance (ORAL SURV). This trial led to changes in the boxed label warnings for JAKis and is considered a class effect until further research demonstrates less harm with different JAKis used for specific indications. ORAL SURV findings are reviewed in section 2.

This review is focused on the evidence of harms following regulatory approval. Evidence on benefit from the drug sponsors drug development program phase 3 trials was reviewed by CADTH and is summarized in section 4. An pooled analysis by the European Crohn's and Colitis Organization (ECCO) of the TOFA efficacy evidence for UC is presented (Appendix B).

Study designs to inform drug harm evaluation

Evidence on JAKi harms was identified from studies in the post approval time period that used a variety of research designs. Evaluation of harm in RCTs used for regulatory approval is commonly limited by selection bias (strict inclusion and exclusion criteria, run-in and extension phases), short durations, incomplete follow-up and incomplete or selective reporting. As a result, these RCTs may not find less common SAEs that can be fatal, life-threatening or have life changing consequences.

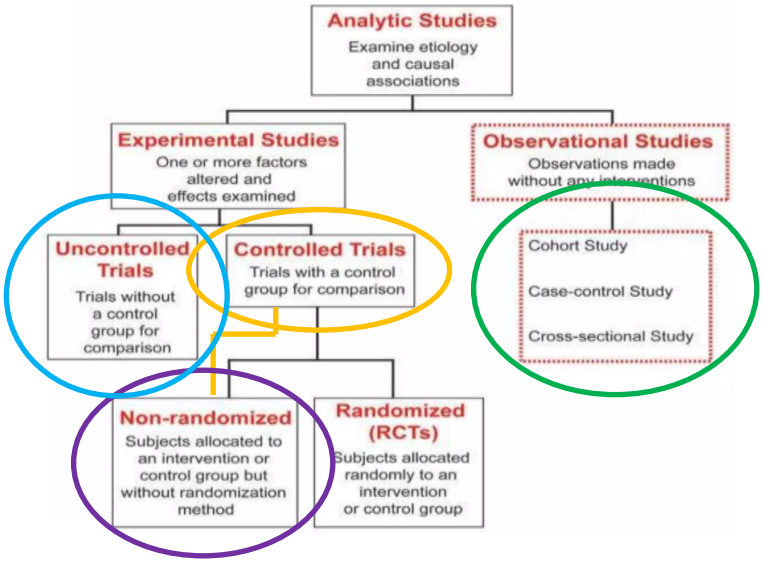
Routine clinical practice, most often studied through observational studies, includes diverse clinical settings and disparate patient populations where longer exposure can lead to negative health impacts and accumulation of data on SAEs not found through the shorter smaller RCTs used for regulatory approval.

[7] https://www2.gov.bc.ca/assets/gov/health/forms/5388fil.pdf

Figure 3 shows a breakdown of analytic study designs (Song and Chung)(10). Observational cohort, case-control and cross-sectional in this diagram are defined by an absence of active control over the intervention. These designs include cross sectional epidemiological studies of disease prevalence and incidence rates as well as longitudinal cohort studies, including some long term extension studies of randomized populations, that look for associations between disease states and drug exposure. More recently, sophisticated observational study methodologies can create comparative cohorts that mimic some of the benefits of RCTs

Analytic studies also include non-RCT studies with an intervention. These include uncontrolled studies (without a comparison group) and controlled studies in which the intervention was not randomly allocated

Fig 3 Non-RCT designs including observational studies, uncontrolled trials and non-randomized controlled trials



Search methods

Our Information Specialist searched the following databases without publication status or language restrictions:

- Ovid MEDLINE ALL (from 1946 to 12 Mar 2024);
- Ovid Embase (from 1974 to 13 Mar 2024);
- Ovid EBM Reviews – Cochrane Central Register of Controlled Trials (2023, Issue 4)

We also searched clinicaltrials.gov, WHO International Clinical Trials Registry, Drugs@FDA, European Medicines Agency public assessment reports and the manufacturer's website for all relevant RCT reports. Reports prepared by independent groups such as the FDA, Health Canada, EMA, Prescrire, NICE, AHRQ and Drug Therapy Bulletin (DTB), if available, were retrieved and summarized.

Selection criteria

The table below summaries the population, intervention, comparators and outcomes (PICO) used to create the search strategy.

Population	**Adults including older adults > 18 years of age** **Ulcerative Colitis (condition of interest)** **Plus, rheumatoid arthritis because** **1) limited harm evidence from PsA and AS studies** **2) JAKi harms being treated as a class effect by regulators** **3) the bulk of the harm evidence is from rheumatoid arthritis populations**
Intervention	**Tofacitinib, upadacitinib**
Comparator	**Placebo, active or none ie observational data**
Outcomes	**All harm outcomes weighted according to the hierarchy of outcomes** **All cause mortality** **Fatal SAE** **Non-Fatal SAE** **Special Interest SAE: infection, malignancies, thrombosis, cardiovascular events** **Total AE** **Withdrawal due to AE** **Persistence adherence with treatment** **NOTE: Results of this harm analysis is considered alongside efficacy evidence in a separate report to consider relative harm vs benefit**

Exclusion criteria: Studies of JAKi use as a rescue therapy for acute severe UC

Analytic approach

All complete, primary and secondary studies were sought, regardless of funder. Studies were identified and sorted by indication, outcome and study design.

Reasons for exclusion were documented. The most common reasons were: older secondary reviews that omitted newer studies, short duration (< 6 mo), discontinuation cohorts, small sample size (<250), uncertainty in selection of study participants, treatment combinations, or uninterpretable findings.

The reported adverse event findings were summarized by study characteristics and design. The findings were then interpreted in terms of reliability, validity and consistency. Finally, the key gaps in JAKi harm evidence and any other ongoing considerations were noted.

Evaluating Heterogenous Harm Studies for Signals using Triangulation

This review obtained data from a variety of study designs and then 'triangulated' them to determine consistency and strength of findings (Hammerton 2022; Winterstein 2021)(11, 12). The strengths and weaknesses of real-world data sources as summarized by Crisafulli 2023(13) are presented in Table 1 below.

For the majority of the studies in this review, patient data was not directly collected for reporting harm.

The studies used in this review include:

- 'integrated' drug sponsors clinical trial data from the drug development program
- health care administrative and claims data
- disease registries
- pharmacosurveillance databases

'**Integrated analyses**' is the term used to refer to pooling of manufacturer sponsored studies conducted as part of the regulatory process. The patient sample reflects ideal experimental conditions and not routine clinical practice. In the extension phases, the benefits of randomization are lost. For TOFA, the manufacturer generated many post-hoc subgroup analyses of the regulatory RCTs.

Claims datasets used in 'real world' analyses of TOFA and other JAKis varied greatly. National datasets in countries like Sweden and Denmark, include the majority of their populations allowing epidemiologic studies of incidence and prevalence of conditions and outcomes. Data elements and fields in administrative datasets may not conform to the harm outcome measures used in clinical research. Raw claims data is out of the control of researchers which eliminates some forms of bias.

Disease registries compile data on rheumatic conditions that was more clinically relevant and extensive than claims datasets. However, the population likely represent patients with severe disease that attend specialists.

Pharmaco-surveillance datasets are inclusive of most drugs and may have more detailed information on adverse events voluntarily reported. Data is collected over multiple years which provides significant potential to identify harm signals.

Appendix C provides an overview of the strengths and weaknesses of real-world study designs.

FINDINGS

1. ORAL Surveillance (ORAL SURV)

The Oral Rheumatoid Arthritis Trial (ORAL) Surveillance (SURV) was a post market randomized (phase 3b-4), open-label, noninferiority, safety end-point trial required by the US FDA as a condition of market entry in 2012(2). Patients with RA aged > 50 years with at least one cardiovascular risk factor were included. From a total of 6599 screened, 4362 were randomized to open label TOFA 5 mg twice daily (1455), TOFA 10 mg twice daily (1456) or subcutaneous TNFi (2451). In 2019 an excess of fatal adverse events in the 10 mg twice daily group resulted in those patients being switched to the lower dose (5 mg twice daily). The main findings are listed below:

ORAL SURVEILLANCE FINDINGS

The primary outcome, incidence of MACE (including death from CV causes, nonfatal myocardial infarction, or nonfatal stroke) for tofacitinib (combined doses) vs. TNF inhibitor, was 3.4% vs. 2.5%. Noninferiority was not shown (hazard ratio [HR] 1.33, 95% confidence interval [CI] 0.91-1.94) as upper boundary of the 95% CI was > 1.8. Noninferiority was shown for 10 mg tofacitinib compared to 5 mg tofacitinib (HR 1.15, 95% CI 0.77-1.71) as upper boundary of the 95% CI < 2.0.

The primary outcome, incidence of cancers for tofacitinib (combined doses) vs. TNF inhibitor, was 4.2% vs. 2.9%. Noninferiority was not shown (HR 1.48, 95% CI 1.04-2.09) as upper boundary of the 95% CI was > 1.8. Noninferiority was shown for 10 mg compared to 5 mg tofacitinib (HR 1.00, 95% CI 0.7-1.43) as upper boundary of the 95% CI was < 2.0.

Secondary outcomes for tofacitinib vs. TNF inhibitor:

- Serious adverse event: tofacitinib 5 mg (24.1%), tofacitinib 10 mg (26.8%), TNF inhibitor (21.1%)
- Serious infection: tofacitinib 5 mg (9.7%), tofacitinib 10 mg (11.6%), TNF inhibitor (8.2%)

From https://www.acc.org/latest-in-cardiology/clinical-trials/2022/02/01/15/21/oral-surveillance

Four new black label warnings were issued for tofacitinib from 2019 to 2021 as results of ORAL SURV emerged. Of note, the integrated analysis of the drug development program results of TOFA and UPAD for PsA or RA patient populations, did not identify the clinically significant harms in the study population sampled.

As noted above, in keeping with the FDA and EMA, we expanded our harm assessment of TOFA for other indications to include studies of RA patients in keeping with the FDA and EMA, and given the importance of the ORAL SURV trial findings to the JAKi drug class evaluations.

ORAL SURV was an open label study. The lack of blinding greatly increases potential bias assessing efficacy outcomes. However, ORAL SURV was assessing harm and blinding was applied to the adjudication of harm outcomes, which was done by external independent committees struck for that purpose. Cardiovascular events, malignancy events, opportunistic infections, hepatic events, and gastrointestinal perforation events

had specialized adjudicators. Unlike drug sponsored RCTs where researchers have an interest in disqualifying serious adverse events as unrelated to the use of the drug, in ORAL SURV every adverse event was evaluated using additional clinical information and adjudicated blindly. Moreover, adjudicators were not tasked with making a judgement about whether a particular type of adverse event could be plausibly or conclusively linked to the study drug.

Of particular interest to ORAL SURV were seriousness adverse events (SAEs). SAEs are defined by life-threatening consequences and include cases requiring hospitalization or that prolong hospitalization, causing significant disability, birth defect or death. Impact can vary greatly within SAE categories. SAEs must be reporte to regulators during the course of an RCT, however they are seldom, if ever, the focus of a trial like ORAL SURV.

ORAL SURV compared a JAK inhibitor to a TNF inhibitor, not to placebo. Therefore, it is not known whether TOFA increase or lowers the risks of MACE, malignancy, and VTE versus placebo. This may never be known because a study as large and long as ORAL SURV would be needed to answer this question.

In addition, JAKi need studies comparing them within their class, and with other 'disease modifying antirheumatic drugs' (DMARDS) and other inflammatory arthritic, and non-arthritic indications.

New insights and opinions are likely to continue to be generated given that the clinical community first had access to the full ORAL SURV findings in 2022. This was at the end of the first decade of use as TOFA was approved for use for RA in 2012.

2 Tofacitinib and upadacitinib for UC: CADTH review

For the purposes of our review, the CADTH reimbursement review(14) of TOFA for treatment of moderate to severe UC in adults provides an adequate review of the regulatory RCTs (15) that led to approval when criteria of inadequate or loss of response or intolerances are met.

Following are CADTH summaries of included studies and the efficacy and harm findings.

Included studies

The systematic review included three phase III randomized placebo control trials of patients with moderately to severely active ulcerative colitis. OCTAVE Induction 1 (N = 614) and OCTAVE Induction 2 (N = 547) randomized patients in a 4:1 ratio for treatment with tofacitinib 10 mg twice daily delivered orally in tablet form or treatment with placebo for eight weeks. In OCTAVE Sustain (N = 593) randomized patients in a 1:1:1 ratio for treatment with tofacitinib 5 mg twice daily delivered orally in tablet form; tofacitinib 10 mg twice daily delivered orally in tablet form; or treatment with placebo for 52 weeks(14).

Efficacy findings

The CADTH reimbursement committee recommended that provinces cover TOFA for UC with conditions on the basis of the evidence provided by the sponsors phase 3 trials.

In OCTAVE Induction 1 and OCTAVE Induction 2, the proportion of patients with remission at week 8 was greater in the tofacitinib 10 mg arm (18.5% and 16.6%, respectively) compared with placebo (8.2% and 3.6%). The difference in proportion from placebo was statistically significant at 10.3% (95% CI, 4.3% to 16.3%; P = 0.0070) and 13.0% (95% CI, 8.1% to 17.9%; P = 0.0005). In OCTAVE Sustain, the proportion of patients with remission at Week 52 was greater in both the tofacitinib 5 mg and the tofacitinib 10 mg arms (34.3% and 40.6%, respectively) compared with placebo (11.1%). The difference in proportion from placebo was statistically significant at 23.2% (95% CI, 15.3% to 31.2%; P < 0.0001) and 29.5% (95% CI, 21.4% to 37.6%; P < 0.0001) (14).

Harm findings

AEs were similar overall between tofacitinib and placebo. **Serious adverse events (SAEs) occurred in 3.4% and 4.2% of patients in the tofacitinib 10 mg arm in OCTAVE Induction 1 and OCTAVE Induction 2, respectively, and in 4.1% and 8.0% of patients in the placebo arm. In OCTAVE Sustain, SAEs occurred in 5.1%, 5.6%, and 6.6% of patients in the tofacitinib 5 mg, tofacitinib 10 mg, and placebo arms, respectively. The most common SAE involved gastrointestinal disorders, specifically worsening of UC.** In the OCTAVE Induction 1 and OCTAVE Induction 2 infections and infestations occurred in more patients in the tofacitinib 10 mg arms (23.3% and 18.2%, respectively), compared with the placebo arms (15.6% and 15.2%, respectively). In OCTAVE Sustain, infections and infestations occurred in 35.9%, 39.8%, and 24.2% of patients in the tofacitinib 5 mg, tofacitinib 10 mg, and placebo arms, respectively. Notable harms of interest such as infections with Herpes zoster, nasopharyngitis, and upper respiratory tract infections occurred in more patients in the tofacitinib arms in the 52-week OCTAVE Sustain trial. An increased incidence of infection with H. zoster was observed in the 10 mg tofacitinib arm in OCTAVE Sustain (5.1%) compared with 1.0% for the recommended

maintenance dose of 5 mg tofacitinib and 0.5% for placebo. Infection with H. zoster in the OCTAVE Induction 1 and OCTAVE Induction 2 tofacitinib 10 mg arms occurred in 0.6% and 0% of patients, respectively; compared with 0.8% and 1.0% in the placebo arms. Infection with nasopharyngitis in the OCTAVE Induction 1 and OCTAVE Induction 2 tofacitinib 10 mg arms occurred in 7.1% and 4.9% of patients, respectively; compared with 7.4% and 3.6% in the placebo arms. In OCTAVE Sustain, nasopharyngitis occurred in 9.6%, 13.8%, and 5.6% of patients in the tofacitinib 5 mg, tofacitinib 10 mg, and placebo arms, respectively. Upper respiratory tract infection in the OCTAVE Induction 1 and OCTAVE Induction 2 tofacitinib 10 mg arms occurred in 3.2% and 2.3% of patients, respectively; compared with 0.8% and 4.5% in the placebo arms. In OCTAVE Sustain, upper respiratory tract infection occurred in 6.6%, 6.1%, and 3.5% of patients in the tofacitinib 5 mg, tofacitinib 10 mg, and placebo arms(14).

CADTH report on included study limitations

Limitations with the reviewed studies included: the statistical analyses of secondary outcome measures across all trials were not adjusted for multiplicity; no active comparator was used across trials (placebo-controlled); withdrawals in the 52-week study were extensive and differential by treatment arm. In the Induction trials, 3% to 13% of patients withdrew from the studies. In OCTAVE Sustain, 43.9%, 35.7% and 73.2% of patients in the tofacitinib 5 mg, tofacitinib 10 mg, and placebo arms discontinued the study. The greatest proportions of patients that discontinued were within the placebo arms in in OCTAVE Induction 2 and OCTAVE Sustain. Across all trials, study discontinuation was most often attributed to insufficient clinical response.

Interpretation

The timing of the CADTH review in 2019 was not informed by the early ORAL SURV findings that led to additional black box warnings. Both were published in 2019. The CADTH analysis therefore illustrates the inadequacy of depending on sponsors phase 3 studies for conditions and their treatment in which serious adverse events may accrue over longer periods of time. OCTAVE 1 and 2 trials were 8 weeks. Only responders entered the maintenance OCTAVE 3 trial that followed patients up to 52 weeks. In addition to the limitations of this set of studies, we would add the inadequacy of the trials as designed to provide findings on serious adverse events that develop over longer periods of time.

3 Tofacitinib and upadacitinib for UC: non-RCT harm studies

The rationale for treatment of ulcerative colitis (UC) by JAKi, like the treatment of rheumatic conditions, is to dampen the release of pro-inflammatory cytokine associated with auto-immune disorders. There are multiple sequences of chemical interactions that are part of the JAK-STAT pathway. There are 4 JAK subgroups with overlapping receptors responsibilities (Crispino 2021)(Sedano 2022)(4, 16).

TOFA is categorized as a pan-JAK inhibitor. By interfering with JAK 1 and JAK 3 enzymes TOFA interfers without selectivity with the JAK-STAT signalling pathway.

UPAD is a second generation JAK inhibitors selective for JAK1 over other subtypes.

The hypothesized benefit of increased specificity is not to improve efficacy but to reduce the potentially higher risk of 'off-target' adverse events revealed by ORAL SURV for the pan-JAKi TOFA.

It is hypothesized that the higher risk of 'off-target' serious adverse events found with TOFA vs TNFi may be decreased by selectively targeting specific JAK subtypes as UPAD does with JAK1.

Research on TOFA and UPAD harms beyond the phase 3 RCTs summarized in section 2 is listed below, summarized and interpreted. The main findings of studies reported by the authors are provided in Appendix D.

Summary

Randomized - extension

Panaccione 2024(17) - Responders after 16 weeks extended TOFA induction then rerandomized to maintenance phase of up to 52 weeks

Vermeire 2023 (18) - Responders within 8 weeks UPAD induction then rerandomized to maintenance phase of up to 52 weeks

Randomized - open-label

Sandborn 2022(19) - Extension trial with up to 7.0 yrs followup of patients initially enrolled in UPAD induction phase RCTs

Observational - non-comparative

Kim 2024(20) - population based cohort study using Korean National database of herpes zoster reactivation with JAKi continuation vs discontinuation

Lindsay 2023(21) - chart review from 8 UK clinics of indicators of inadequate response to advanced therapies for UC including TOFA use

Ma 2023(22) – retrospective cohort of TOFA for moderately to severely active UC using data from standardized case reporting form of consecutive Canadian outpatients from 8 centres

Deepak 2021(23) – retrospective cohort study with Tofacitinib Real-world Outcomes in Patients with ulceratIve colitis and Crohn's disease US consortium study as data source

Rubin 2021(24) – analysis of case reports on TOFA use for UC from drug sponsors pharmacosurveillance dataset in early post market period

Mahadevan 2019(25) – retrospective cohort analysis of pregnancy outcomes using data from sponsors drug development research dataset

Case reports

Lyman 2023(26) - varicella zoster vasculopathy

Verma 2023(27) - military tuberculosis

Weber 2023(28) - acute appendicitis

Charpy 2022(29) - disseminated tuberculosis

Sanchez 2022(30) - disseminated cryptococcosis

Wetwittayakhlang 2021(31) - Kaposi sarcoma

Tominaga 2020a(32) - lung abscess

Tominaga 2020b(33) - multiple esophageal ulcers

Verstockt 2020(34) - invasive nocardiosis, disseminated varicella zoster reactivation, and pneumocystis jiroveci pneumonia

Observational - comparative

Russell 2024(35) - post colectomy chart review data on subjects with and without TOFA exposure in US medical centre

Adimadhyam 2023(36) - retrospective cohort study using US health care insurers data on TOFA and vedolizumab

Buisson 2023(37) - retrospective cohort study using French hospital clinical records on TOFA and vedolizumab

Straatmijer 2023(38) Dutch National registry study of TOFA and vedolizumab

Cheng 2022(39) - retrospective cohort study using US commercial health care insurers data on TOFA, ustekinumab and anti-TNF (adalimumab, infliximab, golimumab, or certolizumab pegol)

Kochar 2022(40) - retrospective cohort study of new TOFA or TNFi users using US claims database

Seo 2022(41) - retrospective cohort study using Korean national health care data TOFA and anti-TNF

Pooled data/subgroup analyses

There was one UPAD pooled analysis based on 3 trials from the sponsors drug development program for UC (Danese 2022(42)). Danese 2022 reported no deaths were reported in either induction or maintenance periods. In induction studies, SAE in UC1 were eight [3%] vs nine (6%) and in UC2 11 [3%] vs eight [5%] for UPAD 45 mg vs placebo. In the maintenance trial SAE were ten [7%] vs nine [6%] vs 19 [13%] for 15 mg, 30 mg, and placebo groups. Serious infections, were five [3%] vs four [3%] vs six [4%] in the upadacitinib 15 mg, 30 mg, and placebo groups respectively.

TOFA drug development program for UC indication: post hoc analyses of serious adverse events by subgroups in sponsors drug development program pooled RCT data:

- by endoscopic subscore (MES) (Lee 2023(43));
- by age (Lichtenstein 2023(44));
- by corticosteroid use at baseline (Vavricka 2022(45))
- by body mass index (BMI) (Farraye 2021(46))
- of clostridium difficile infections (Loftus 2023(47));
- of MACE adverse events (Schreiber 2023(48))
- of serious and non serious herpes zoster (Winthrop 2023a(49));
- of malignancy adverse events (Lichtenstein 2021(50))
- of infectious adverse event (Winthrop 2021(51))
- of venous thromboembolic (Sandborn 2019(52))
- of serious and non serious herpes zoster AE **(**Winthrop 2023a(49));
- with up to 7.8 years of follow-up (Sandborn 2023(53));

TOFA drug development program trial data for

- SAE in combined UC, RA and PsA indications (Winthrop 2023b(54))
- SAE in combined UC, RA, PsO, and PsA indications (Burmester 2021(55))

Summary

Three drug sponsor studies were identified: Panaccione 2024(17), Vermeire 2023 (18) and Sandborn 2022(19).

Randomized - extension

Two extension trials (Panaccione 2024(17), Vermeire 2023 (18)) provide data on the long term harm profile of UPAD use in UC. As part of the drug sponsors regulatory suite of studies these two studies recruited from efficacy induction RCTs then randomized to high (10mg daily) or low (5 mg daily) maintenance doses and provided follow up for 52 weeks.

Vermeire 2023(18) represents the followup of subjects who responded within an 8 week induction RCT. Those who did not respond within the 8 week induction trial – in placebo or active drug arms – were given the opportunity for a further 8 weeks active treatment. Panaccione 2024(17) extension study reports on the group with a 16 week induction period.

Vermeire 2023 (18) reported higher exposure-adjusted event rates (EAER) for serious infections in the placebo (5.9) vs UPAD 15 mg once daily (5.0) vs UPAD 30 mg once daily (3.2). Three of four malignancies were in UPAD treatment groups.

Panaccione 2024(17) reports serious treatment emergent adverse events. Event rates were higher in the UPAD 30mg daily group 4/40 (10%) vs UPAD 15mg daily group 1/35 (2.9%). Exposure adjusted event rates (E/100PY) (95% CI) were 7 (20.9) (5.4–36.4) in the UPAD 30mg daily group versus 1 (4.1) (0.0-12.2) in the UPAD 15mg daily group.

Randomized – open-label

Sandborn 2022(19) represents the final report of the TOFA in UC open-label extension trial which enrolled subjects previously enrolled in one of two 8 week phase 3 induction trials or a 52 week maintence trial. There was no randomization to dosage for those who completed induction or extension

trials. Those not in remission were assigned to the 10 mg twice daily group, while those in remission were assigned 5 mg twice daily. Dose adjustment was permitted after 8 weeks. Follow-up was 4.2 years in the low dose 5 mg BID group (1529 days, range 36-2422) and 1.9 years (668 days, range 1-2561) in the 10 mg BID group though some subjects were followed 'up to' 7 years.

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Observational - non-comparative

There were 6 observational – non-comparative research studies (n >1) identifed in our search: Kim 2024(20); Lindsay 2023(21); Ma 2023(22); Deepak 2021(23); Rubin 2021(24) and Mahadevan 2019(25). They provide data on rates of serious adverse events in settings outside of the idealized RCT ones. Specific serious AE were also reported include fatal, infectious, malignancy, venous thromboembolism and a congenital malformation (pulmonary valve stenosis).

Reported rates of SAE from these real-world retrospective cohorts were:

Kim 2024(20): 11.1% (51/460)

Lindsay 2023(21): 8% (35/408)

Ma 2023(22): 30.2% (36 serious events of 334 total events)

9.6 (6.8-13.0) incidence rate (event/100PY exposure (95% CI)

Deepak 2021(23): 5.8% (15/260) - 10.0 per 100 PYF [95%CI, 8.9– 11.2]

Reported rates of specific SAE were:

Rubin 2021(24): Among the 4226 TOFA adverse case reports for UC use submitted over first 27-month post market reporting period, 27.0% (1141/4226) included an SAE (no population denominator) and 18 (0.4%) were fatal.

Lindsay 2023(21): 8% (35/408) serious infections

Ma 2023(22):

- serious infections 6.7% (8/334 events); 9.6 (6.8-13.0) (event/100PY exposure (95% CI)
- venous thromboembolism 3.4% (4/334 events); 1.1 (0.3-2.7)
- malignancies 2.5% (3/334 events); 0.8 (0.2-2.3)

Mahadevan 2019(25) - 1 congenital malformation (pulmonary valve stenosis) was reported in the newborn of a 32-year-old RA patient who received tofacitinib 5 mg BID

Observational - non-comparative case reports

Case reports were published in the early post market period on varicella zoster vasculopathy(26), military tuberculosis(27), acute appendicitis(28), disseminated tuberculosis(29), disseminated cryptococcosis(30), Kaposi sarcoma (31), lung abscess(32), multiple esophageal ulcers(33) and invasive nocardiosis, disseminated varicella zoster reactivation, and pneumocystis jiroveci pneumonia(34).

Observational – comparative

Seven observational studies compared TOFA with a biologic or anti-TNF agent use (Adimadhyam 2023(36)) Buisson 2023(37), Straatmijer 2023(38), Cheng 2022(39), Kochar 2022(40), Seo 2022(41) and in one study to no TOFA exposure Russell 2024(35). No comparative UPAD studies were identified. None of the studies in this set were prospective.

Russell 2024(35) made the strongest claim of greater SAE of TOFA as compared to a biologic in their investigation of postoperative venous thromboembolism for patients with severe UC requiring colectomy. The authors report that their finding of no statistically significant difference between exposed 9/42 (22.0%) versus unexposed TOFA 7/84 (8.3%) was likely due to the study being underpowered. This underscores the importance of appropriately powering studies.

Statistical analysis of the differences between drug use groups was conducted in 3 studies. Adimadhyam 2023(36) found no difference between new users of TOFA or vedolizumab on all-cause hospitalization, adjusted hazard ratio, 1.23; 95% CI, 0.83-1.84; total abdominal colectomy, 1.79; 95% CI, 0.93-3.44; and hospitalization for any infection, 1.94; 95% CI, 0.83-4.52). Cheng 2022(39) reported rates of infection-related hospitalizations (HR, 0.59; 95% CI, 0.27–1.05). Kochar 2022(40) reported no elevated risk of VTE (HR: 1.72, 95% CI: 0.74–3.01) or MACE (HR: 2.50, 95% CI: 0.37–6.18) when TOFA vs anti-TNF users cohorts have been weighted using propensity scores. Seo 2022(41) reported overall incidences (100 person-years; 95% confidence interval) of SAEs of 4.06 (1.63–8.36) and 6.30 (4.59–8.43) in the tofacitinib and anti-TNFi groups, respectively

Pooled / subgroup analyses

16 post hoc and subgroup analyses based on the drug sponsors research development research program studies pooled and combined in a number of different ways.

Four analyses explored outcomes including SAE by baseline patient characteristics: endoscopic subscore (42), age (44), corticosteroid use (44), body mass index (46).

Seven analyses investigated adverse events: clostridium difficile infections (47), MACE (48), herpes zoster (49), malignancies (50), infectious adverse events (51) and venous thromboembolic events (49).

One study represent interim follow-up of outcomes of interest from completed and in progess studies pooled (53).

Two studies pooled data on infection rates from studies of a number of TOFA indications from sponsors drug development research programmes. Winthrop 2023b(54) reported serious influenza AE in drug development program trials for UC, RA and PsA by pooling data from 31 trials. Of the 1157 patients in the UC overall TOFA cohort, 115 patients (9.9%) reported combined influenza AEs, of which one (0.9%) was serious, and one (0.9%) had an SAE within 28 days of the onset of an influenza event (ureter obstruction caused by a blood clot).

Burmester 2021 reported on serious infection adverse events from trials investigating rheumatic conditions RA, PsO and PsA in addition to UC: 49 serious infection events occurred in 46 patients in the

overall cohort (474 randomized in UC1, 522 in UC2 plus 451 in the induction / maintenance group which included re-randomized completers of UC1 and UC2(55).

Interpretation

The available post authorization research on the harm profile of TOFA and UPAD for UC is not of sufficient strength to challenge boxed warning sections of TOFA and UPAD. These caution prescribers about increase in SAEs including death, blood clots, malignancy and cardiovascular adverse events with JAKi use. These warnings were based on ORAL SURV findings demomstrating that the harm profile of TOFA cannot be considered to be equivalent or superior to biologic agents used in the treatement of moderate to severe UC unresponsive to prior treatment in a real-world population with common risk factors. The non-inferiority test was not met. Warnings have been extended to the JAKi class and apply to it's use for all indications until a preponderance of evidence disproves the reasonable assumptions based on ORAL SURV evidence.

The 1 year UPAD extension RCTs and TOFA long-term open-label trial were weaker designs in terms of duration, real world representativeness and independent, expert adjudication of all-cause adverse events of special interest and emerging signals as compared to ORAL SURV.

The extension studies had adjudication features to identify ' with reasonable possibility of **being related** to UPAD'. ORAL SURV followed an 'all-cause' SAE approach which is more defended against subjective bias. ORAL SURV has demonstrated study designs without independent adjudication and sufficient follow-up will fail to detect serious adverse events that accrue over longer periods of time. The extension trials were 1 year -- far less than ORAL SURV. The median follow-up of less than 2 years in the 10mg twice daily dosage group of the TOFA open-label study indicates duration is likely also an issue. Sponsors are in a conflict of interest position in relation to drug harms and therefore independence is emerging as essential to adequate harm profile assessment.

The randomized open-label extension study had no fixed treatment groups for comparison: 1) dose groups were classified based on initial treatment assignment (in prior phase 3 RCTs); 2) there were baseline differences between dose groups; 3) 81.5% of patients were assigned to and received tofacitinib 10 mg BID at baseline; 4) patients were permitted to switch dose during the study (Sandborn 2022) (19).

The observational – non comparative set of 7 studies provides insights into rates of harm outcomes of special interest in various settings. The data sources were variable including Canadian, US, UK, French, Korean and Dutch databased resources as well as one which used the medical records of a US surgical unit. There are also two studies using adverse event reports which are not tied to specific study or geographical population denominators. It is not expected that the rates of SAE would be consistent across diverse settings and patient populations.

The observational – non comparative set of studies were triangulated with ORAL SURV findings. These studies show a significant burden of SAE that was revealed by ORAL SURV but not found in regulatory RCTs with less rigorous protocols. They have internal validity and therefore support the serious harm profile revealed by ORAL SURV.

The 8 case reports of SAE with use of a JAKi for UC is consistent with the serious harm profile revealed by ORAL SURV. Case reports provide signals and convey the clinical reality of identifying and managing serious adverse events.

Among the 7 observational/comparative studies, only one found an increase in SAE of TOFA compared to a biologic among postoperative venous thromboembolism for patients with severe UC requiring

colectomy Russell 2024(35). The authors report that their finding of no statistically significant difference between exposed 9/42 (22.0%) versus unexposed TOFA 7/84 (8.3%) was likely due to the study being underpowered.

The Straatmijer 2023(38) Dutch national disease registry study provides weak comparative evidence that there is a difference between vedolizumab or TOFA. However, there are many factors that may differ between drug use groups that could not be controlled including prescriber practices.

UC became an approved indication in 2019 and so the cumulative experience is less than for the rhuematice conditions. Nevertheless, while this set of studies is not suitable to make claims of differences between the harm profiles of JAKi vs biologics and anti-TNF drugs, they provide important descriptions of the serious harms consistent with those found with rheumatic disease treatment.

In summary, this set of post market extension, open label and observational studies (non-comparative and comparative) does not provide scientifically valid comparison data to support or refute the findings of ORAL SURV on SAEs. Nonetheless, these studies corroborates the type of harm associated with JAKi use and estimates of their frequency in various disease cohorts. Whether the harm profile of TOFA is more or less in UC than RA is unknown.

DISCUSSION

This TI review of JAKi harm for UC follows a TI review of JAKi harm in adult rheumatic conditions. JAKi are a relatively new class of drugs. In 2012, the FDA approved tofacitinib, the first JAKi, for treatment of rheumatoid arthritis. Approval required the manufacturer to conduct the ORAL SURV study that began to impact product information in 2019 and was completed and reported in 2022.

The longer follow-up and more thorough adjudication of harm events in ORAL SURV explains the greater ability to detect serious adverse events as compared to non-randomized analyses and pooled analysis reliant on the sponsor's drug development program of RCTs and extension phase studies. This is true for the indication UC as for the inflammatory arthritises.

As the earliest approved JAKi for inflammatory conditions, TOFA has the longest cumulative research evidence on harms as well as clinical exposure. Approval for TOFA use in UC came in 2018 so the post market approval period is shorter and combined with publication lag, the number and duration of UC research to evaluate the harm profile is still uncertain.

There is less cumulative research and experience with UPAD which gained approval for UC in 2022. The hypothesis that UPAD is safer than TOFA because it affects one JAKi subtype and TOFA is seen as a pan JAKi has not been studied. Therefore, regulators apply the ORAL SURV findings to warnings for both TOFA and UPAD use for UC.

Ulcerative colitis and the inflammatory bowel diseases including Crohn's disease, are a relatively new target for JAKi drug investigations. Each SAE category (infection, cancer, cardiovascular) has complex causal mechanisms that are incompletely understood and difficult to research because they are relatively infrequent.

CONCLUSIONS

There is sufficient scientifically valid scientific evidence that TOFA and UPAD, and until proven otherwise all JAKis, increase the incidence of serious adverse events (infections, malignancies, and cardiovascular conditions) compared with tumor necrosis factor-alpha inhibitors in all inflammatory conditions – including ulcerative colitis. Further clinical benefit and harm data are needed to establish their optimal use.

The drug regulatory process, especially when considering the first drug in a new therapeutic class, to treat a new type of clinical condition such as inflammatory bowel disease, requires a different, but equally rigorous, methodological framework both to establish and review serious harm, as opposed to efficacy, evidence.

APPENDICES

A. Timeline of approved indictions for Janus kinase inhibitors for rheumatic diseases (Winthrop 2022)(1)

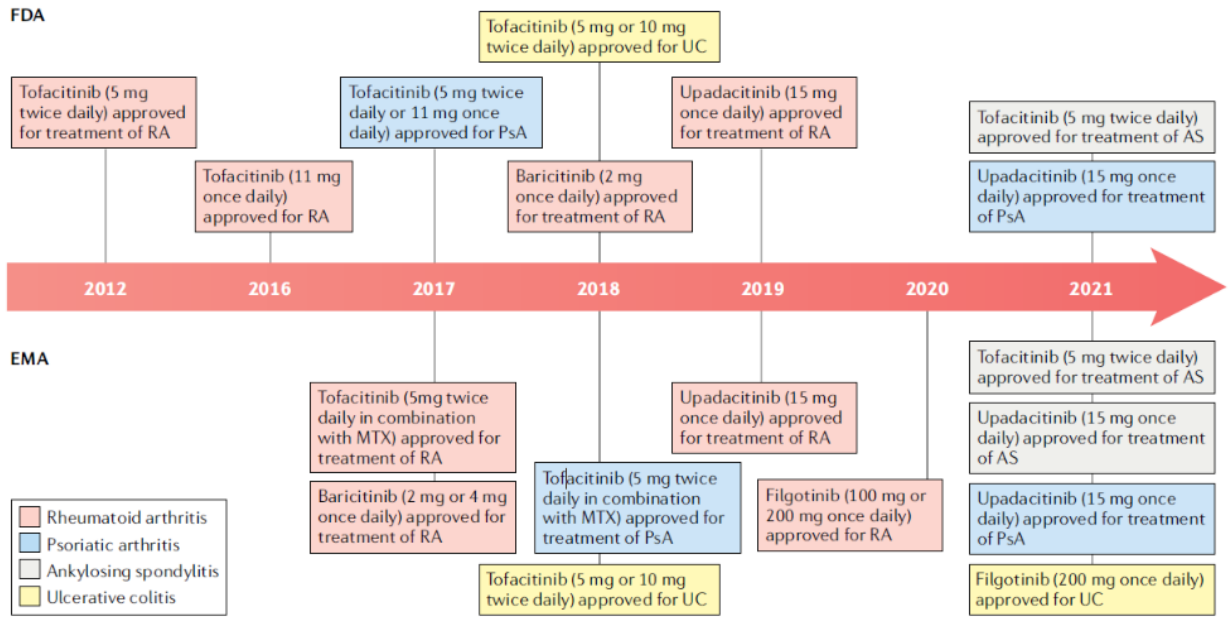


Fig. 1 | **Timeline of approved indications for Janus kinase inhibitors for rheumatic diseases.** In 2012 tofacitinib became the first Janus kinase (JAK) inhibitor to be indicated for a rheumatic disease, when the FDA approved its use in the treatment of rheumatoid arthritis (RA); EMA approval came in 2017. In addition to tofacitinib, other JAK inhibitors (baricitinib, upadacitinib and filgotinib) have also been approved for use in the treatment of RA, and the indications for JAK inhibitors have expanded to include psoriatic arthritis (PsA), ankylosing spondylitis (AS) and ulcerative colitis (UC). MTX, methotrexate.

B. ECCO Meta-analysis of placebo-controlled RCTs investigating tofacitinib in moderate to severe UC

SOF Table 14 (Tofacitinib versus placebo)

PICO question: Should treatment with tofacitinib be used for the induction of remission in patients with moderately-to-severely active UC?
P: Adult patients with moderately-to-severely active UC and with inadequate response to conventional therapy
I: Tofacitinib 10 mg PO bid
C: Placebo

No. participants (No. studies) Follow-up	Quality assessment						Summary of Findings				
							Study event rates		Risk Ratio (95% CI)	Anticipated absolute effects	
	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Quality of evidence	Risk with control group	Risk with intervention group		Risk with control group	Risk difference with intervention group
Clinical remission (critical outcome)											
N: 1220 (3 studies) 8 weeks	Not serious	Not serious	Not serious	Not serious	N/A	High	19/282 (6.7%)	175/938 (18.7%)	RR, 3.26 (1.95–5.43)	67 per 1000	152 more per 1000 (from 64 more to 298 more)
Clinical response (critical outcome)											
N: 1220 (3 studies) 8 weeks	Not serious	Not serious	Not serious	Not serious	N/A	High	92/282 (32.6%)	541/938 (57.7%)	RR, 1.79 (1.49–2.14)	326 per 1000	257 more per 1000 (from 160 more to 373 more)
Endoscopic response (important outcome)											
N: 1220 (3 studies) 8 weeks	Not serious	Not serious	Serious[1]	Serious[2]	N/A	Low	5/282 (1.8%)	72/938 (7.7%)	RR, 5.18 (2.12–12.69)	18 per 1000	74 more per 1000 (from 20 more to 207 more)
Serious adverse events, SAEs (critical outcome)											
N: 1812 (4 studies) 8–52 weeks	Not serious	Not serious	Not serious	Serious[3]	N/A	Moderate	31/480 (6.5%)	57/1332 (4.3%)	RR, 0.70 (0.45–1.08)	65 per 1000	19 fewer per 1000 (from 35 fewer to 5 more)

References:
Sandborn et al. N Engl J Med. 2012;367:616-24.
Sandborn et al. N Engl J Med. 2017;376:1723-36.

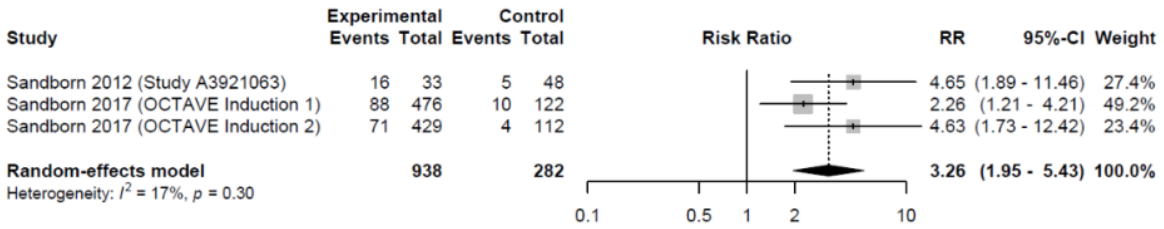
Footnotes:
[1] The evidence relies on an outcome definition (endoscopic remission) that is related to, but different from our outcome of interest (endoscopic response)
[2] Sparse data (77 events)
[3] Sparse data (88 events)

Comments: Evidence was sought also for biochemical remission; however, data were insufficient.

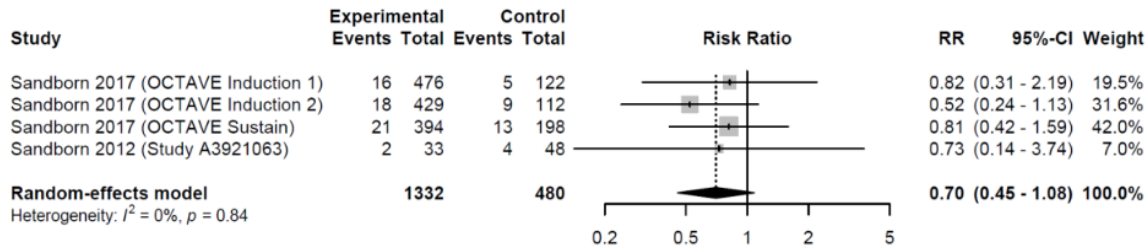
Abbreviations: UC, ulcerative colitis; PO, per os; bid, twice daily; RR, risk ratio; CI, confidence interval; N/A, not applicable.

Overall quality of evidence: Moderate.

Forest Plot 14.1 (Tofacitinib versus placebo) clinical remission



Forest Plot 14.4 (Tofacitinib versus placebo) serious adverse events



C. Summary of Recommendations of the AGA Clinical Guidelines Committee for the Management of Moderate to Severe Ulcerative Colitis

Recommendations	**Strength of recommendation**	**Quality of evidence**
1. In adult outpatients with moderate to severe UC, the AGA recommends using infliximab, adalimumab, golimumab, vedolizumab, **tofacitinib**, or ustekinumab over no treatment. (Medications are ordered based on year of approval by the US FDA.)	Strong	Moderate
2a. In adult outpatients with moderate to severe UC who are naïve to biologic agents, the AGA suggests using infliximab or vedolizumab rather than adalimumab, for induction of remission. Comment: Patients, particularly those with less severe disease, who place higher value on the convenience of self-administered subcutaneous injection, and a lower value on the relative efficacy of medications, may reasonably chose adalimumab as an alternative.	Conditional	Moderate
2b. In adult outpatients with moderate to severe UC who are naïve to biologic agents, the AGA recommends that **tofacitinib** only be used in the setting of a clinical or registry study. (No recommendation, knowledge gap) Comment: Updated FDA recommendations (July 26, 2019) on indications for use of **tofacitinib** in UC recommends its use only after failure of or intolerance to TNF-α antagonists.	No recommendation	Knowledge gap
2c. In adult outpatients with moderate to severe UC who have previously been exposed to infliximab, particularly those with primary nonresponse, the AGA suggests using ustekinumab or **tofacitinib** rather than vedolizumab or adalimumab for induction of remission.	Conditional	Low
3a. In adult outpatients with active moderate to severe UC, the AGA suggests against using thiopurine monotherapy for induction of remission.	Conditional	Very low
3b. In adult outpatients with moderate to severe UC in remission, the AGA suggests using thiopurine monotherapy rather than no treatment for maintenance of remission.	Conditional	Low
3c. In adult outpatients with moderate to severe UC, the AGA suggests against using methotrexate	Conditional	Low

Recommendations	Strength of recommendation	Quality of evidence
monotherapy for induction or maintenance of remission.		
4a. In adult outpatients with active moderate to severe UC, the AGA suggests using biologic monotherapy (TNF-α antagonists, vedolizumab, or ustekinumab) or **tofacitinib** rather than thiopurine monotherapy for induction of remission.	Conditional	Low
4b. In adult outpatients with moderate to severe UC in remission, the AGA makes no recommendation in favor of or against using biologic monotherapy or **tofacitinib** rather than thiopurine monotherapy for maintenance of remission.	No recommendation	Knowledge gap
5a. In adult outpatients with moderate to severe UC, the AGA suggests combining TNF-α antagonists, vedolizumab or ustekinumab with thiopurines or methotrexate rather than biologic monotherapy. Comment: Patients, particularly those with less severe disease, who place higher value on the safety of biologic monotherapy and lower value on the efficacy of combination therapy may reasonably chose biologic monotherapy.	Conditional	Low
5b. In adult outpatients with moderate to severe UC, the AGA suggests combining TNF-α antagonists, vedolizumab, or ustekinumab with thiopurines or methotrexate rather than thiopurine monotherapy.	Conditional	Low
6. In adult outpatients with moderate to severe UC, the AGA suggests early use of biologic agents with or without immunomodulator therapy rather than gradual step up after failure of 5-ASA. Comment: Patients, particularly those with less severe disease, who place higher value on the safety of 5-ASA therapy and lower value on the efficacy of biologic agents or **tofacitinib** may reasonably chose gradual step therapy with 5-ASA therapy.	Conditional	Very low
7. In adult outpatients with moderate to severe UC who have achieved remission with biologic agents and/or immunomodulators or t**ofacitinib**, the AGA suggests against continuing 5-ASA for induction and maintenance of remission.	Conditional	Very low

Recommendations	Strength of recommendation	Quality of evidence
8. In hospitalized adult patients with ASUC, the AGA suggests using intravenous methylprednisolone dose equivalent of 40–60 mg/d rather than higher doses of intravenous corticosteroids.	Conditional	Very low
9. In hospitalized adult patients with acute severe UC without infection, the AGA suggests against adjunctive antibiotics.	Conditional	Very low
10. In hospitalized adult patients with ASUC refractory to intravenous corticosteroids, the AGA suggests using infliximab or cyclosporine.	Conditional	Low
11. In hospitalized adult patients with acute severe UC being treated with infliximab, the AGA makes no recommendation on routine use of intensive vs standard infliximab dosing.	No recommendation	Knowledge gap

D. The strengths and weaknesses of real-world data sources (Crisafulli 2023) (13)

Table 1. Summary of the main strengths and weaknesses of real-world data sources.

Data Source	Strengths	Limitations
Claims Databases	• Wide population coverage • Comprehensive data on healthcare utilization and costs	• Limited clinical information • Potential for coding errors • Lack of information regarding privately purchased healthcare services
Electronic Health Records	• Large amount of high-quality patient-level data, including longitudinal data • Data on the indication of use of drugs is often recorded • If prescribed by GPs or FPs, also medications not reimbursed by the NHS are traced	• Potential for missing or inaccurate data, data privacy concerns • Selective data logging (e.g. selective registration of comorbidities and/or signs and symptoms) • Lack of standardized terminology • Presence of unstructured narrative information, which is often not relevant to patient care
Drug and disease registries	• They provide prospectively collected data on specific diseases or exposure to specific drugs • They can be linked to other healthcare databases • They are particularly relevant to study rare diseases and for the post-marketing monitoring of orphan drugs	• Limited generalizability • Potential for selection bias
Spontaneous reporting system databases	• They are the main RWD source for the identification of new potential safety signals • They cover all authorized medicines used in any setting and all reasons for use • The information concerning suspected ADRs rapidly available for analysis	• Under-reporting of ADRs • Clinical data are often missing or inaccurate • It is not possible to calculate incidence rates, due to the lack of information regarding the total number of drug users • Potential for reporting bias (e.g. Weber effect and notoriety bias) • Presence of duplicate records

Abbreviations: ADRs=adverse drug reactions; GPs=general practitioners; FP=family pediatricians; NHS=National Health Service.

E. Non RCT studies reporting serious harm data with tofacitinib, upadicitinib for UC

Study	Findings
	Randomized - extension
Panaccione 2024(17) Responders in prior UPAD induction trials rerandomized to maintenance phase of up to 52 weeks open-label	Patients without clinical response to 8 weeks' upadacitinib 45 mg once daily induction therapy in two induction trials were eligible for an additional 8 weeks of therapy. Patients achieving clinical response at Week 16 were subsequently rerandomised (1:1) to upadacitinib 15 or 30 mg once daily for 52-week maintenance therapy. 52 week – number and proportion of patient with treatment emergent adverse event (TEAE); Exposure-adjusted event rates, E (E/100PY) (95% CI) **Serious TEAE** UPAD 15mg daily – 1/35 (2.9%); 1 (4.1) (0.0-12.2) UPAD 30mg daily – 4/40 (10%); 7 (20.9) (5.4–36.4) **TEAE with reasonable possibility of being related to UPA** UPAD 15mg daily – 7/35 (20.0%); 16 (66.1) (33.7–98.5) UPAD 30mg daily – 13/40 (32.5%); 31 (92.6) (60.0–125.2)
Vermeire 2023 (18) Responders in prior UPAD induction trials rerandomized to maintenance phase of up to 52 weeks open-label	Of the 987 patients with moderately to severely active UC who were randomized to 8 weeks of UPAD 45 mg once daily induction therapy, those with a clinical response after 8 weeks were randomly reassigned to UPAD 15 mg once daily (n=225), UPAD 30 mg once daily (n=233), or placebo (n=223) to maintenance therapy representing a intention-to-treat population plus patients who received up to 44 weeks' maintenance therapy under earlier protocol amendments For adverse events of special interest (AESIs), the exposure-adjusted event rates (EAERs) of serious infection were 5·9, 5·0, and 3·2 events per 100 patient-years with placebo, UPAD 15 mg once daily, and UPAD 30 mg once daily, respectively. Four (1% of patients) malignancies (excluding non-melanoma skin cancer) were reported, all of which were considered serious; of these, three occurred in UPAD-treated patients, one invasive breast carcinoma in the UPAD 15 mg once daily group, one adenocarcinoma of the colon and one small cell carcinoma of the prostate in the UPAD 30 mg once daily group.

	No malignancies (excluding nonmelanoma skin cancer) with upadacitinib were considered by the investigator as having a reasonable possibility of being related to upadacitinib treatment. in the upadacitinib 30 mg once daily group … [there was] one case of herpes zoster with meningoencephalopathic involvement
	Randomized – open-label
Sandborn 2022(19) TOFA Open Extension trial with up to 7.0 yrs followup	In OCTAVE Open, 769 of 944 patients (81.5%) initially received TOFA 10mg BID Among all patients (2440.8 patient-years of exposure), Incidence Rates; (95% confidence intervals) deaths, 0.25 (0.09-0.54); serious infections, 1.61 (1.14-2.20); herpes zoster (non-serious and serious), 3.16 (2.47-3.97); opportunistic infections, 0.87 (0.54-1.33); major adverse cardiovascular events, 0.16 (0.04-0.42); malignancies (excluding non-melanoma skin cancer), 1.03 (0.67-1.52); non-melanoma skin cancer, 0.75 (0.45-1.19); deep vein thrombosis, 0.04 (0.00-0.23); pulmonary embolism, 0.21 (0.07-0.48).
	Observational - non-comparative
Kim 2024(20) National Korean database population based cohort study	Analysis by continued use 3947 JAKi users (RA 3540, UC 407) JAK inhibitors (TOFA 71.6% / baracitinib 28.4%) After a median of 0.95 years (IQR, 0.93–2.58) of exposure to JAK inhibitors, 611 (15.5%) patients developed HZ reactivation, with an incidence rate of 8.38 per 100 PY. There was no significant difference in the incidence rate of HZ reactivation according to the type of JAK inhibitor (tofacitinib: 8.27 per 100 PY; baricitinib: 8.92 per 100 PY; P = 0.84) Herpes zoster reactivation • **Total Serious 51/460 (11.1%)** • JAKi continuation 39/386 (10.1%) • JAKi discontinuation 12/74 (16.2%) Hospitalization was the criteria for seriousness
Lindsay 2023(21)	Analysis of remission and indicators of inadequate response

UK chart review	**35 of 408 patients (8%) had serious adverse events** Of those infections, there were 18 that met the criteria of serious adverse events (39% of all the infections) SAEs included cardiovascular events (3), neoplasm (1), pulmonary embolism (2), anemia (1) and other (9). There were 93 adverse events related to tofacitinib treatment (including 2 pulmonary thromboembolisms [in patients with risk factors] and 2 peripheral vascular thrombosis), and 29 led to tofacitinib discontinuation.
Ma 2023(22) REMIT-UC Canadian multicenter cohort study	334 consecutive adult (age 18 years or older) outpatients with Moderate-to-Severely Active UC treated with TOFA followed for 375 patient years. Incidence of serious infections, herpes zoster, and venous thromboembolism were 2.1 [0.9–4.2], 0.5 [0.1–1.9], and 1.1 [0.3–2.7], respectively. Adverse events by severity n (%) 36 (30.2%) **serious events** of 334 total events 9.6 (6.8-13.0) (event/100PY exposure (95% CI) 8 (6.7%) **serious infections** of 334 total events 2.1 (0.9-4.2) (event/100PY exposure (95% CI) 4 (3.4%) **venous thromboembolism** of 334 total events 1.1 (0.3-2.7) (event/100PY exposure (95% CI) 3 (2.5%) **malignancies** of 334 total events 0.8 (0.2-2.3) (event/100PY exposure (95% CI)
Deepak 2021(23) Analysis based on data obtained from Tofacitinib Real-world Outcomes in Patients with ulceratIve colitis and Crohn's disease consortium study	Data on 260 patients with UC treated with TOFA were obtained from an ongoing study **Thirteen of the 15 SAEs** occurred in patients on 10mg twice a day The rate of serious AEs was 10.0 [95%CI, 8.9– 11.2] per 100 PYF. The median age of patients with SAEs was 24.9 (IQR, 21.6 – 29.0), the majority were male (n= 11, 73.3%) and approximately half were non-Hispanic whites (53.3%) and were either past or current smokers (53.3%) Of the three that continued therapy after SAE, 2 patients had a VTE event ...

	One patient had a hospitalization related to group B streptococcus septic shock. He was maintained on the same dose of tofacitinib for 11 months until the end of study follow-up. Nine patients (69.2%) were on concomitants systemic corticosteroids.
Rubin 2021(24) Drug sponsors pharmacosurveillance data on TOFA in UC	4226 case reports for TOFA over first 27-month post market reporting period after approval for UC in May 2018 to August 2020 - 1839 SAEs Among the cases reported, 1141 (27.0%) included an SAE and 18 (0.4%) were fatal. The RR (per 100 PY) for SAEs of interest by Medical Dictionary for Regulatory Activities System Organ Class were: 3.28 for infections, 1.26 for vascular disorders, 0.74 for respiratory disorders, 0.55 for neoplasms and 0.50 for cardiac disorders.
Mahadevan 2019(25) Sponsors drug development research dataset including 5 UC trials to 2017 plus registry data	Pregnancy outcomes A total of 1157 patients (including 301 women of childbearing age) with 1612.77 patient-years of tofacitinib exposure were included in the tofacitinib UC interventional studies. A total of 25 cases of pregnancy were reported: 11 cases of maternal exposure were reported among the 301 women of childbearing age) and 14 cases of paternal exposure. There were 7 healthy newborns, 1 medical termination, no fetal or neonatal deaths, one congenital malformation, 3 spontaneous abortion and 33 or 45 were pending or lost to follow-up. There was 1 congenital malformation (pulmonary valve stenosis) in the newborn of a 32-year-old RA patient with hypertension treated with angiotensin II receptor antagonist losartan (50 mg QD), with diet-controlled gestational diabetes, and who received tofacitinib 5 mg BID.
	Observational – non-comparative – adverse event case reports
Lyman 2023(26) Case report	Case report of varicella zoster vasculopathy exacerbated by TOFA in UC patient
Verma 2023(27) Case report	Miliary Tuberculosis in a Patient With Ulcerative Colitis Treated With Tofacitinib This case report highlights the importance of screening for latent TB in patients receiving tofacitinib.

Weber 2023(28) Case report	Acute inflammatory disease (acute appendicitis) seen in the case of a patient undergoing immunosuppressive/anti-inflammatory treatment using a JAK-Inhibitor for ulcerative colitis
Charpy 2022(29) Case report	First case report of disseminated tuberculosis in patient treated with TOFA for UC
Sanchez 2022(30)	64-year-old female patient with proven disseminated cryptococcosis secondary to the use of tofacitinib
Wetwittayakhlang 2021(31) Case report	Rare biopsy-proven Kaposi sarcoma in a patient with complex biological-resistant ulcerative colitis after 2 years of treatment with tofacitinib. Kaposi sarcoma lesions spontaneously regressed after tofacitinib was discontinued.
Tominaga 2020a(32) Case report	On the 29th day after TOF administration, he developed a lung abscess with high fever. A chronic bulla was already present in his lung; therefore, the lung abscess was likely formed due to a combination of the bulla being present and the pharmacological effects of TOF. Our report is significant as it highlights the compounding association between TOF and PSL therapy and bulla presence with the rare adverse effect of developing an abscess
Tominaga 2020b(33) Case report	26-year-old man unable to maintain remission with alternate treatment started on TOFA. Day 44 with chest pain led to discover of multiple esophageal ulcers – a rare SAE
Verstockt 2020(34) Case report	53-year-old woman with invasive nocardiosis, disseminated varicella zoster reactivation, and pneumocystis jiroveci pneumonia associated with tofacitinib and concomitant systemic corticosteroid use in ulcerative colitis… She was discharged from acute care on day 145 (including 92 days on ICU), with a subsequent admission on a specialized ward for further rehabilitation of her critical illness neuropathy. She finally returned home 6 months after initial admission. More than 1 year after the acute event, she is at home but still has moderate dyspnea on exertion and has not been able to resume work.
	Observational – comparative
Russell 2024(35) Chart review of patients who underwent colectomy surgery at one centre	42 patients with TOFA exposure compared to 84 matched controls without TOFA exposure Nine (22.0%) tofacitinib exposed patients, and 7 (8.3%) unexposed patients, had a postoperative VTE within 90 days of surgery (p = 0.03) (Authors question power of the study to reach statistical significance)

Adimadhyam 2023(36) Retrospective cohort study using US health care insurers data	168 new users of tofacitinib vs 568 new users of vedolizumab. • all-cause hospitalization, adjusted hazard ratio, 1.23; 95% CI, 0.83-1.84; • total abdominal colectomy, adjusted HR, 1.79; 95% CI, 0.93-3.44;and • hospitalization for any infection, adjusted HR, 1.94; 95% CI, 0.83-4.52) Tofacitinib was associated with lower treatment persistence (adjusted risked ratio, 0.77; 95% CI, 0.60 -0.99)
Buisson 2023(37) Retrospective cohort study using French hospital clinical records	304 consecutive patients with UC ≥18 years old with partial Mayo score >2 and prior anti-TNF exposure, who started tofacitinib (n=126) or vedolizumab (n=178) between January 2019 and June 2021 'Severe' AE: TOFA 6/126 (4.8%) vs Vedolizumab 7/178 (3.9%) Cancer: TOFA 1/126 (0.8%) vs Vedolizumab 0/178 (0.0%) Heart stroke: TOFA 0/126 (0.0%) vs Vedolizumab 1/178 (0.6%)
Straatmijer 2023(38) Dutch National disease registry study	Patients with UC who failed anti-TNF treatment and initiated vedolizumab or tofacitinib treatment (switching study) Severe infections: 1 gastrointestinal (1.8 per 100 patient-years) TOFA vs 0 (0 per 100 patient-years) TNFi SAE – infusion -related malaise: 1 (1.8 per 100 patient-years) TOFA vs 0 1 (2.2 per 100 patient-years) TNFi Authors report underpowered to detect SAE
Cheng 2022(39) Analysis based on US commercial health insurance database	Subjects with UC (or Crohns) treated with TOFA vs TNFi were identified in a US commercial health insurance database 19,096, 2420, and **305** patients with inflammatory bowel disease initiating anti-TNF, UST, and tofacitinib therapy, respectively Infection-related hospitalizations TOFA - 6% anti-TNF - 7% ustekinumab (UST) - 4% The risk of infection-related hospitalizations (HR, 0.59; 95% CI, 0.27–1.05) was similar between patients on tofacitinib and anti-TNF
Kochar 2022(40) Retrospective cohort study using US claims database	New users of TOFA (305) or TNFi (19.096) were identified and an analysis of venous thromboembolism and cardiovascular events identified in these cohorts were analysed using propensity score-weighten Cox proportional hazards model was used to estimate hazard ratios and time to events outcomes. VTE occurred in 5% of patients treated with tofacitinib and 4% of anti-TNF users; in a [propensity score] PS-weighted cohort, tofacitinib did not confer a

	signifcantly elevated VTE risk compared with anti-TNF therapy (HR: 1.72, 95% CI: 0.74–3.01) A major CV event (MACE) occurred in 2% of tofacitinib users and 1% of anti-TNF users; tofacitinib also did not confer a signifcantly elevated risk for MACE (HR: 2.50, 95% CI: 0.37–6.18).
Seo 2022(41) Analysis based on Korean national health care database	Incidence of serious adverse events (SAEs) among 1,026 UC patients excluding those with prior history of adverse events of special interest The overall incidences (100 person-years; 95% confidence interval) of SAEs were 4.06 (1.63–8.36) and 6.30 (4.59–8.43) in the tofacitinib and anti-TNFi groups, respectively. No thromboembolic event occurred and major cardiovascular events occurred in only three patients (two unstable angina and one congestive heart failure) in the tofacitinib group. The incidence of herpes zoster and tuberculosis did not differ between the two groups. There was no difference in the overall incidence of SAEs, including thromboembolic events, between tofacitinib- and TNFi-treated UC patients.
	Pooled / subgroup analyses
Lee 2023(43) Post hoc subgroup analysis by Mayo endoscopic subscore (MES) in OCTAVE Sustain	Infection adverse events were less frequent among patients with baseline MES 0 versus 1. At Week 52 of OCTAVE Sustain, a numerically higher proportion of TOFA-treated patients achieved remission with OCTAVE Sustain baseline MES of 0 versus 1 (61.9% vs. 36.5% for TOFA 5 mg twice daily [BID] and 75.0% vs. 54.2% for TOFA 10 mg BID).
Lichtenstein 2023(44) Pooled data from manufacturer's research program database	Post hoc subgroup analysis by age stratification Data were from phase 2 and 3 induction studies, a phase 3 maintenance study, and an open-label, long-term extension study. Efficacy and/or safety outcomes were analyzed in the Induction, Maintenance, and Overall Cohorts (patients who received ≥ 1 dose of tofacitinib), stratified by age. SAEs were based on the Investigator's assessment. Patients were counted only once per treatment for each category. Severity counts were based on the maximum severity or grade of events. SAE Induction cohort 18 to < 30 yrs: PL 4/67 (6.0%); TOFA 10mg BID 6/216 (2.8%) 30 to <40 yrs: PL 8/80 (10.0); TOFA 10mg BID 12/251 (4.8%) 40 to <50 yrs: PL 1/51 (2.0); TOFA 10mg BID 10/210 (4.8%) 50 to ≤60 yrs: PL 2/44 (4.5); TOFA 10mg BID 0(0.0%) ≥60 yrs: PL 0(0.0); TOFA 10mg BID 0(0.0%) < 60 yrs: PL 0(0.0); TOFA 10mg BID 0(0.0%)

	≥60 yrs: PL 0(0.0); TOFA 10mg BID 0(0.0%) Maintenance cohort 18 to < 30 yrs: PL 0(0.0); TOFA 10mg BID PL 0(0.0%) 30 to <40 yrs: PL 0(0.0); TOFA 10mg BID (0.0%) 40 to <50 yrs: PL 0(0.0); TOFA 10mg BID (0.0%) 50 to ≤60 yrs: PL 0(0.0); TOFA 10mg BID 0(0.0%) ≥60 yrs: PL 0(0.0); TOFA 10mg BID 0(0.0%) < 60 yrs: PL 0(0.0); TOFA 10mg BID 0(0.0%) ≥60 yrs: PL 0(0.0); TOFA 10mg BID 0(0.0%)
Loftus 2023(47) Subgroup analysis of 4 RCT and open label extension	The overall cohort comprised 1157 patients who received ≥1 dose of tofacitinib 5 or 10 mg BID, with a total of 2814.4 patient-years of TOFA exposure and up to 7.8 years of treatment. Clostridium difficile infection investigated Two patients had events reported as serious due to hospitalization
Sandborn 2023(53) Pooled data from manufacturer's research program database up to 7.8 years follow-up	1157 patients received one or more dose of TOFA (mean duration: 946.9 days); 955/1157 [83%] received a predominant dose of 10 mg BID; 412/1157 [35.6%] received TOFA for >4 years. 244/1157 [21.1%] had serious AEs including: deaths, 0.23 [0.09–0.46]; serious infections, 1.69 [1.26–2.21]; herpes zoster [non-serious and serious], 3.30 [2.67–4.04]; opportunistic infections, 1.03 [0.70–1.46]; malignancies (excluding non-melanoma skin cancer [NMSC]), 0.84 [0.55–1.24]; NMSC, 0.73 [0.45–1.10]; MACE, 0.29 [0.13–0.55]; deep vein thrombosis, 0.03 [0.00–0.18]; pulmonary embolism, 0.19 [0.07–0.42]; gastrointestinal perforations, 0.10 [0.02–0.28]
Schreiber 2023(48) Pooled data from manufacturer's research program database	MACE analysis Of 1157 patients [2814.4 patient-years of exposure; ≤7.8 years' TOFA treatment], 4% had prior arthrosclerotic cardiovascular disease (ASCVD) and 83% had no prior ASCVD and low–borderline baseline 10-year ASCVD risk. Eight [0.7%] patients developed MACE; one had prior ASCVD. Incidence rates [unique patients with events/100 patient-years of exposure; 95% confidence intervals] for MACE were: 0.95 [0.02–5.27] in patients with prior ASCVD; and 1.81 [0.05–10.07], 1.54 [0.42–3.95], 0.00 [0.00–2.85], and

	0.09 [0.01–0.32] in patients without prior ASCVD and with high, intermediate, borderline, and low baseline 10-year ASCVD risk, respectively. For the 5/7 patients with MACE and without prior ASCVD, 10-year ASCVD risk scores were numerically higher [>1%] prior to MACE versus at baseline, primarily due to increasing age.
Straatmijer 2023(38) Dutch National registry study	Patients with UC who failed anti-TNF treatment and initiated vedolizumab or TOFA treatment (switching study) Severe infections: 1 gastrointestinal (1.8 per 100 patient-years) TOFA vs 0 (0 per 100 patient-years) TNFi SAE – infusion -related malaise: 1 (1.8 per 100 patient-years) TOFA vs 0 1 (2.2 per 100 patient-years) TNFi Authors report underpowered to detect SAE
Winthrop 2023a(49) Post hoc analysis of 4 trial cohorts pooled	Subgroup analysis of serious and non serious herpes zoster In both the Overall and Overall plus phase 3b/4 Cohorts, 7 of 1157 (0.6%) patients had serious HZ. There were no serious HZ events in either the Induction or Maintenance Cohorts
Winthrop 2023b(54) Post hoc analysis of 31 TOFA drug development program trials for 3 indications including UC, RA and PsA	Subgroup analysis of trial subjects experiencing an influenza adverse event Serious influenza AE in UC subgroup with influenza: 1/115 (0.9%) Of the 1157 patients in the UC Overall tofacitinib cohort, 115 patients (9.9%) reported combined influenza AEs, of which one (0.9%) was serious, and one (0.9%) had an SAE within 28 days of the onset of an influenza event (ureter obstruction caused by a blood clot). Of RA patients with serious influenza AEs, eight were hospitalized. Two hospitalized patients died; both had H1N1 infection.
Danese 2022(42) Pooled analysis using 3 trials from UPAD drug development program	UPAD SAE in 2 induction and 1 maintenance In both induction studies, serious adverse events … were less frequent in the upadacitinib 45 mg group than in the placebo group (serious adverse events eight [3%] vs nine (6%) in UC1 and 11 [3%] vs eight [5%] in UC2. No deaths were reported in the induction studies.

	Serious infections, were similarly reported in the upadacitinib 15 mg, 30 mg, and placebo groups (five [3%] vs four [3%] vs six [4%]). Maintenance: The proportion of serious adverse events () …was lower in both upadacitinib groups than in the placebo groups. No deaths were reported during the maintenance period.
Vavricka 2022(45) Subgroup analysis by corticosteroid use	Subgroup analysis of rerandomized responders in OCTAVE maintenance study to 52 weeks by corticosteroid use at baseline No apparent differences in AEs of special interest by steroid-free remission status.
Burmester 2021(55) Post hoc analysis using drug development program trial data for UC and 3 rheumatic conditions	SAEs within 28 days of last dose of drug IR (95% CI) (n/N) UC: 8.5 (7.4 to 9.8) (210/1157) RA: 9.0 (8.6 to 9.4) (1913/7964) PsA: 7.0 (5.8 to 8.2) (135/783) PsO: 5.5 (5.0 to 6.0) (484/ 3663) Mortality within 28 days of last dose of drug IR (95% CI) (n/N) UC: 0.1 (0.0 to 0.3) (2/1157) RA: 0.2 (0.2 to 0.3) (59/7964) PsA: 0.1 (0.0 to 0.3) (2/783) PsO: 0.2 (0.1 to 0.3) (17/ 3663) Authors interpretation: The data from this analysis of the RA, PsA, UC and PsO clinical programmes demonstrate a consistent safety profile across indications.
Farraye 2021(46) Drug development program trial data	Post hoc analysis by BMI in 3 pivotal RCTs reports data on serious infections over 3 pivotal trials Among patients receiving TOFA 10 mg b.d. in OCTAVE Induction 1 and 2, serious infections were numerically greater in the BMI ≥30 subgroup (3.2%) vs other subgroups (0.4%). Limitations included small patient numbers in the BMI ≥30 subgroup.
Lichtenstein 2021(50) Malignancies in 4 trials in drug development program data	The overall cohort consisted of patients who received at least 1 dose of tofacitinib at 5 or 10 mg twice daily, for up to 6.8 years, with an exposure of 2576.4 PY. Of the 1124 overall cohort tofacitinib-treated patients, 20 developed a malignancy (excluding NMSC; IR, 0.75; 95% confidence interval, 0.46–1.16), of which 17 occurred in patients treated with tofacitinib 10 mg twice daily; importantly, more than 80% of patients predominantly received this dose

Winthrop 2021(51) Post hoc analysis of 3 trial cohorts pooled	Subgroup analysis of trials subjects experiencing infectious adverse event In the Overall Cohort, 49 serious infection events occurred in 46 patients [including one event of severe cellulitis reported 61 days after the last dose of tofacitinib and not included in the proportion or IR calculations]. Of these, only anal abscess [four events], appendicitis [three events], herpes zoster [five events], ophthalmic herpes zoster [two events], sinusitis [two events], and Clostridium difficile infection [two events] occurred in ≥1 patient. The median [range] time to infection for serious infections was 433 [23–1742] days. IRs of serious infection in the Overall Cohort [tofacitinib all doses] were generally similar across age groups [Figure 2], with an IR [95% CI] of 1.19 [0.44–2.59] for patients ≥60 years old. No serious infections resulted in death.
Sandborn 2019(52) Pooled analyses from phase 2, 3, maintenance and manufacturer's TOFA drug development program for UC	Venous thromboembolic event analyses Data from 1157 patients (2404 patient-years' exposure; ≤ 6.1 years' tofacitinib treat- ment) were analysed in induction, maintenance and overall (patients receiving ≥ 1 dose of tofacitinib 5 or 10 mg b.d. in any phase 2, 3 or OLE study) cohorts. In the overall cohort, one patient had DVT (incidence rate [patients with events/100 patient-years; 95% CI]: 0.04 [0.00-0.23]); four had PE (0.16 [0.04-0.41]); all received predominant dose tofacitinib 10 mg b.d.; all had venous thromboembolism risk factors alongside UC.
	Not contributory to analysis
Dalal 2024	69 patients (too small)
Macaluso 2024	111 patients (too small)
Singh 2024	78 patients (too small) for 8 weeks (too short)
Viola 2024	67 patients (too small)
Belousova 2023 Russian national IBD registry analysis of IBD treatment	No SAE data A small number of cancelled treatment due to adverse events: for UC — 1 patient each on adalimumab, golimumab, and **tofacitinib**
Chaparro 2023(56)	73 patients (too small)

Dala 2023	Too small - 233 Spanish patients
Friedberg 2023	Too small - 105 patients were followed up for 8 weeks on upadacitinib - one serious AE that was not clearly drug-related
Giri 2023	Too small – 47 biologically naive cases from India
Herfarth 2023 US TOUR registry cohort analysis	Too small – 103 subjects Hospitalization due to UC flare - 4 patients (4.7%) 7 events Hospitalization other* - 1 patient (1.2%) 1 event
Komeda 2023	8 patients with steroid resistance (too small, sub population of interest)
Lichtenstein 2023	Too short – pooled 2 trials of 8 weeks
Long 2023	Too small – 98 patients
Mateescu 2023(57) Retrospective cohort analysis of advanced therapies in IBD	22 (3%) TOFA in advanced therapy group Frequency of adverse reactions Serious infection 7 (1%) Hospitalization 5 (0.7%) Life-threatening event 1 (0.1%) … Cancer 1 (0.1%) Surgery 11 (1.6%) Severe allergic reaction 4 (0.6%)
Moraliyska 2023	Too small – 41 patients
Parra-Izquierdo 2023	Too small – 34 subjects
Resal 2023(58)	Reports on ‘severe’ (12 of 391) not serious AE
Shin 2023	Too small - 148 asian patients - Adverse events (AEs) including herpes zoster and deep vein thrombosis occurred in 19 patients (12.8%) and serious AEs occurred in 12 patients (8.1%)
Traboulsi 2023	Too small – 12 subjects
Tursi 2023(36)	166 patients (too small) 3 SAE (1.8%)
Ussan 2023	Too small - 35 patient included in case series of ulcerative proctitis

Alayo 2022	Combination therapy - biologics and JAKi
Bokemeyer 2022	Too few - 3 TOFA pts in German UC treatment cohort analysis
Colombel 2022	142 patient subgroup analysis (too small)
Hyun 2022	95 patients (too small)
Matsuoka 2022	105 patient (too small) east asian cohort
Perin 2022	56 patients (too small) cohort
Straatmijer2022	100 patients (too small) cohort from national disease registry in netherlands
Avni-Biron 2021	73 patients (too small) Israeli with mod to sev UC
Chaparro 2021	Too small – 113 subjects
Dalal 2021	81 patients (too small) cohort
Jameshorani 2021	53 first treated Iranian patients (too small)
Martinez 2021	74 patients (too small) cohort
Straatmijer 2021	Too small – no identification of serious AE
Biemans 2020	Too small – 123 subjects – Netherlands
Hoffmann 2020	Too small – 38 subjects
Honap 2020	Too small – 134 patients
Kolar 2020	Too small – 24 patients, too short, 8 weeks
Antonelli 2019(59)	Search end date too old
Lair-Mehiri 2019	Too small – 38 subjects – France – 6 SAE
Weisshof 2019	Too small - 58 subjects
Motoya 2018	Too small - 121 East Asian subjects
Suzuki 2019	Too small – 62 Japanese patients in 2 OCTAVE trials
Winthrop 2018(60)	Too old – more recent herpes zoster analysis published

F. Importance of ORAL Surveillance (Ytterberg 2022)

ORAL SURV was a phase 3b trial required by FDA regulators concerned about abnormal **laboratory findings in the regulatory RCTs**.

ORAL SURV did not include blinding of clinicians or patients but its methodology included **independent blinded adjudication** of harmful events, particularly serious ones. That is, identification and adjudication of adverse events was not controlled by the research/drug sponsor. This contrasts with most RCTs, including the tofacitinib regulatory approval RCTs, where the sponsor and trialists judged whether to include an adverse event for evaluation and whether to attribute it to the drug under investigation. Most importantly, to protect against bias, all SAEs were included in the adjudication process.

Study events or measures that incorporate both benefit and harm are most important and prominent in ORAL SURV. For example: mortality. A reduction constitutes a benefit, an increase constitutes harm. Another example is **event-free survival (EFS).** EFS is defined as time from treatment initiation to a treatment failure event from any cause (i.e. inefficacy or intolerability). Either an adverse event or lack of effect of treatment constitute failure therefore EFS reflects both harm and benefit outcomes.

ORAL SURV compared TOFA with TNFa inhibitors, not other JAKi's. Nor have any other RCTs compared JAKis. Therefore, there is no valid scientific evidence whether ORAL SURV findings for TOFA represent a **drug class effect**. Nevertheless, in the absence of RCT evidence, regulators have assumed ORAL SRUV findings apply to all drugs in the class and have required manufacturers to include black box warnings on all JAKis for all indications.

ORAL SURV is a critically important study that demonstrates the necessity of independent, high quality RCTs as part of the drug approval process, especially for a new class of drugs. Otherwise, knowledge, essential for prescribing decisions, may take years, if ever, to emerge.

ORAL SURV demonstrated the power of independent adjudication of serious adverse events to reveal differences between treatment groups in the harm profile. Better understanding of the true harm profile can support future prescribing decisions. **Minimizing serious adverse** events depends on this type of analysis informing practice as well as clinical and public benefit decisions.

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