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REVIEW ARTICLE

Safety of Janus Kinase Inhibitors in Inflammatory Bowel Diseases

Paulina Núñez[1] · Rodrigo Quera[2] · Andres J. Yarur[3]

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Abstract

In recent years, better knowledge of the pathophysiology of inflammatory bowel diseases (IBD) has led to a relevant expansion of the therapeutic arsenal for these conditions. Janus kinase (JAK) inhibitors are a family of small molecules that block one or more of the intracellular tyrosine kinases, including JAK-1, JAK-2, JAK-3 and TYK-2. Tofacitinib, a non-selective small molecule JAK inhibitor, and upadacitinib and filgotinib, which are selective JAK-1 inhibitors, have been approved by the US Food and Drug Administration (FDA) for moderate-to-severe active ulcerative colitis. Compared to biological drugs, JAK inhibitors have a short half-life, rapid onset of action, and no immunogenicity. Both clinical trials and real-world evidence support the use of JAK inhibitors in the treatment of IBD. However, these therapies have been linked with multiple adverse events (AEs) including infection, hypercholesterolemia, venous thromboembolism, major adverse cardiovascular events, and malignancy. While early studies recognized several potential AEs, post-marketing trials have shown that tofacitinib may increase the risk of thromboembolic diseases and major cardiovascular events. The latter are seen in patients aged 50 years or older with cardiovascular risk factors. Hence, the benefits of treatment and risk stratification need to be considered when positioning tofacitinib. Novel JAK inhibitors with a more selective effect on JAK-1 have proven to be effective in both Crohn's disease and ulcerative colitis, offering a potentially safer and efficacious therapeutic option to patients, including those with previous non-response to other therapies such as biologics. Nevertheless, long-term effectiveness and safety data are required.

Key Points

Stratifying risks for adverse events when positioning therapies is critical. Younger patients with no cardiovascular risk factors are good candidates for JAK inhibitors.

Considering that adverse events to JAK inhibitors are dose dependent, the lowest effective dose should be used during the maintenance phase of treatment.

Even though novel, more selective JAK inhibitors potentially offer a better safety profile, long-term data are needed.

✉ Andres J. Yarur
andres.yarur@cshs.org

[1] Department of Gastroenterology, Hospital San Juan De Dios-Universidad de los Andes, Digestive Disease Center, Clínica Universidad de los Andes, Universidad de Chile Santiago, 7620157 Santiago, Chile

[2] Universidad de los Andes, Digestive Disease Center, Clínica Universidad de los Andes, 7620157 Santiago, Chile

[3] Cedars-Sinai Medical Center, 8730 Alden Dr.Thalians 2E, Los Angeles, CA 90048, USA

1 Introduction

In the past 2 decades, the advent of biologic agents that target specific components of the immune response has greatly improved outcomes of patients with inflammatory bowel diseases (IBD). However, patients may not respond (primary non-response) or lose response after experiencing a benefit (secondary non-response) to biologic therapy. Furthermore, some patients develop adverse events (AEs) that often lead to treatment discontinuation [1, 2]. Thus, several new compounds have been in development with the goal to further improve the efficacy, while maintaining or improving the safety profile seen with current drugs. Although most of the approved drugs for IBD are biologics, novel small molecules have been introduced and have been approved or in the late phases of development.

Among those novel therapies, we find multiple small-molecule drugs (SMDs). This "new generation" of SMDs have several potential benefits over biologics. Small-molecule drugs have a molecular weight of less than 1kDa [3]. Due to their metabolism and binding to plasma proteins, SMDs usually have a short serum half-life when compared to biologics [4]. The lack of immunogenicity of SMDs is

another benefit over biologics and can potentially provide sustained efficacy and increase drug persistence [4].

Janus kinase (JAK) inhibitors have emerged as a novel strategy to modulate downstream cytokine signaling in immune-mediated diseases. The four members of the JAK family (JAK-1, JAK-2, JAK-3, and tyrosine kinase 2) are part of transmembrane cytokine receptor complexes that are activated upon binding of a ligand, leading to recruitment, phosphorylation, and activation of signal transducers and activators of transcription [5].

The JAK-signal transducer and activator of transcription (STAT) pathway plays an important role in innate immunity, adaptive immunity, and hematopoiesis, participating in cellular processes such as cell growth, survival, differentiation, and migration [6]. Based on this, inhibition of the JAK pathway has been studied for the treatment of numerous autoimmune diseases [7]. Tofacitinib was the first JAK inhibitor to be introduced to market, demonstrating clinical efficacy in rheumatoid arthritis (RA) as monotherapy in patients on non-biologic disease modifying drugs (DMARDs) or inadequate response to biologic treatment [8, 9].

Both ulcerative colitis (UC) and Crohn's disease (CD) share common pathogenesis mechanisms, including a dysregulated JAK pathway. Hence, targeting the JAK pathway in patients with IBD offers a promising therapeutic option. Three of these JAK inhibitors are already approved for UC and others are currently being trialed in Phase 2 and 3 programs for several indications including CD.

The aim of this review is to assess the available data on the risk of AEs in patients undergoing treatment with JAK inhibitors. We will briefly describe the efficacy in both, clinical trials and real-world studies followed by a review of the evidence on safety that is currently available. An electronic literature search was carried out using PubMed, EMBASE and clinicaltrials.gov looking for randomized controlled articles and case–control studies published up to October 2022. The keywords used were "adverse reaction"," small molecules", "Janus kinase inhibitors", "tofacitinib", "upadacitinib", "filgotinib", "inflammatory bowel disease", "ulcerative colitis" and "Crohn's disease" "Real-world". Reference lists and conference abstracts were also searched to identify additional studies.

2 Efficacy of Janus-Kinase Inhibitors

2.1 Tofacitinib

Tofacitinib is a pan-JAK inhibitor with more action on JAK-1 and -3 and, to a lesser extent, JAK-2 and tyrosine kinase 2 (TYK-2). Initially approved in 2012 for the treatment of moderate-to-severe RA [10], in 2017 for psoriatic arthritis (PsA) [11], in 2018 for UC and more recently was approved for the treatment of active ankylosing spondylitis [12].

This drug has been shown to be effective in inducing and maintaining remission in patients with moderate-to-severe UC and was approved for the treatment of moderate-to-severe UC for patients who had failed standard therapies and/or biologic agents [13].

Tofacitinib was evaluated in a Phase 2 randomized and placebo-controlled trial of patients with moderate-to-severe UC. The primary endpoint, clinical response at Week 8, was achieved by a higher proportion of patients receiving tofacitinib 15 mg twice daily (BID) (38/49, 78%) compared to placebo (20/48, 42%; $p < 0.01$) [14]. Based on these results, two subsequent Phase 3 double-blinded-placebo controlled induction trials, (the OCTAVE 1 and OCTAVE 2 studies) were performed in 598 and 541 patients, respectively [15]. The patients were randomly assigned to receive 10 mg of tofacitinib BID or placebo for 8 weeks. The rate of clinical remission at Week 8 was significantly higher in the tofacitinib group compared with placebo (OCTAVE 1: 18.5% vs 8.2% [$p = 0.01$] and OCTAVE 2: 16.6% vs 3.6% [$p < 0.01$]). Table 1 summarized the data reported for clinical trials for tofacitinib and other JAK inhibitors.

Subsequently, the OCTAVE SUSTAIN trial was performed in 593 patients who achieved clinical response after the induction therapy. Being randomly assigned to receive either tofacitinib as maintenance therapy (5 mg or 10 mg BID) or placebo for 52 weeks. The rate of clinical remission at Week 52 was higher in both tofacitinib groups compared with placebo (5 mg: 34.3% or 10 mg: 40.6%, $p < 0.01$ vs placebo 11.1%). Mucosal healing was achieved in a higher proportion of patients who received tofacitinib (5 mg BID: 37.4%, 10 mg BID: 45.7% vs placebo 13.1% $p < 0.01$) [16]. The long-term open-label extension (OLE) of the OCTAVE studies assessed dose de-escalation of tofacitinib 10 mg BID to 5 mg BID in patients who had previously achieved and maintained clinical remission after 52 weeks. In the de-escalation group, 53 of 63 patients (84.1%) maintained clinical response and 47 (74.6%) maintained clinical remission [17].

In patients with moderate-to-severe CD, tofacitinib showed no significantly better clinical remission or response rates when compared to placebo [18]. In another study mostly including patients with previous anti-tumor necrosis factor (TNF) non-response, results were also rather disappointing, with remission rates not reaching a significant difference when compared to placebo [19]. It is plausible that the failure to meet the primary endpoint in the Phase 2 trial and the high rate of placebo response may be a result of high proportion and prolonged taper of corticosteroid use. Another important limitation of the study was a lack of endoscopic central reading [20].

In 2020, Fenster et al conducted a retrospective cohort study to examine the real-world efficacy and safety of the

Table 1 Efficacy of Janus kinase inhibitors in pivotal randomized controlled trials in ulcerative colitis or Crohn's disease

Target	Drug	Clinical trials	Primary endpoint	Outcomes
Ulcerative colitis				
Pan JAK[a] inhibitor	Tofacitinib	Phase 2 (induction) OCTAVE I [16]	Clinical response at 8 weeks	The clinical response to tofacitinib was 0.5 (32%), 3 (48%), 10 (61%), and 15 mg (78%) compared with 42% of the placebo group
		OCTAVE II [16]	Clinical remission at 8 weeks	18.5% of the patients in the tofacitinib group versus 8.2% in the placebo group
		OCTAVE Sustain [16]	Clinical remission at 52 weeks	5 mg BID (34.3%) and tofacitinib 10 mg BID (40.6%) vs placebo (11.1%) ($p < 0.001$)
JAK[a] selective inhibitor	Filgotinib	Phase 2b/3 SELECTION trial (induction) [32]	Clinical remission at 10 weeks	Filgotinib (47%) versus placebo (23%; $p = 0.0077$) 26.1% vs 15.3%, $p = 0.0157$) and biologic-experienced (11.5% vs 4.2%; $p = 0.0103$) placebo
		Phase 2b/3 SELECTION trial (maintenance) [32]	Clinical remission at 58 weeks	Filgotinib 100 mg (19.1% biologic naive and 9.5% biologic experienced) and 200 mg (26.1% biologic naïve and 11.5% biologic experienced) were in clinical remission compared to placebo (15.3% biologic naive and 4.2% biologic experienced)
	Upadacitinib	Phase 2b U-ACHIEVE (induction) [28]	Clinical remission at 8 weeks	Higher clinical remission rates were noted in the treatment arm compared with none in the placebo arm (7.5 mg: 8.5%, $p = 0.052$; 15 mg: 14.3%, $p = 0.013$; 30 mg: 13.5%, $p = 0.011$; and 45 mg: 19.6%, p=0.002)
		Phase 3 U-ACCOMPLISH (induction) [29]	Clinical remission at 8 weeks	Higher proportion of patients receiving upadacitinib 45 mg daily 33.5% versus placebo 4.1% ($p < 0.001$)
		Phase 3 (maintenance) [29]	Clinical remission at 52 weeks	Patients receiving 15 mg and 30 mg versus placebo achieved clinical remission (42.3% and 51.7% vs 12.1%)
Crohn's disease				
Pan JAK[a]	Tofacitinib	Phase 2 (induction) [18]	Clinical response at 4 weeks	No statistically significant differences were noted in clinical response between the tofacitinib and placebo
		Phase 2b (induction) [19]	Clinical remission at 8 weeks	
		Phase 2b (maintenance) [19]	Clinical remission at 26 weeks	
JAK[a] 1 selective inhibitor	Filgotinib	Phase 2b FITZROY (induction) [35]	Clinical remission at 10 weeks	Higher proportion of patients receiving filgotinib compared with placebo in both the biologic-naive (26.1% vs 15.3%, $p = 0.0157$) and biologic-experienced (11.5% vs 4.2%; $p = 0.0103$) arms
		Phase 3 DIVERSITY trial (induction)	Clinical remission at 10 weeks	Pending results
		Phase 3 DIVERSITY trial (maintenance)	Clinical remission at 58 weeks	Pending results
	Upadacitinib	Phase 2 CELEST trial (induction) [30]	Clinical remission at 16 weeks	Clinical remission was achieved by 13% of patients receiving 3 mg upadacitinib, 27% of patients receiving 6 mg upadacitinib ($p < 0.1$ vs placebo), 11% of patients receiving 12 mg upadacitinib, and 22% of patients receiving 24 mg upadacitinib twice daily, and by 14% of patients receiving 24 mg upadacitinib once daily vs 11% of patients receiving placebo
		Phase 2, CELEST trial (maintenance) [31]	Clinical remission at 52 weeks	Efficacy was maintained for most endpoints through Week 52

BID twice daily, *JAK* Janus kinase

Table 2 Effectiveness of tofacitinib in real-world observational studies in ulcerative colitis and IBD IBD inflammatory bowel disease undetermined (when noted)

Study	Number	Endpoints	Proportion of patients achieving the endpoint at the specified time point			
			Induction (8 weeks)	Weeks 12–16	Week 26	Week 52
Taxonera et al [23] Systematic review and meta-analysis	1162	Clinical response	62%	64%	51%	42%
		Clinical remission	35%	47%	38%	
		Steroid-free remission	38%	35%	34%	31%
		Mucosa healing	42%	66%		
Chaparro et al [24] Eneida Registry Prospective multicenter study	113	Clinical response	40%	60%	57%	
		Clinical remission	16%	31%.	32%	
Biemans et al [25] ICC registry Prospective multicenter study	123	Clinical response		56%		
		Clinical remission		41%		
		Endoscopic response		36%		
		Endoscopic remission		21%		
Honap et al [22] LEO IBD Research consortium Retrospective multicenter study	134 [118 UC-5 IBD-U]	Clinical response	74%	66%	53%	
		Clinical remission	57%	51%.	45%	
		Steroid free remission	48%	49%	44%	
Ungaro et al [26] Retrospective multicenter study	123	Clinical response	61%	55%		
		Clinical remission	14%	49%		
		Mucosa healing			65%	
Avni-Biron I et al [27] Retrospective multicenter study	73	Clinical response			65%	
		Clinical remission			22.5%	
		Steroid-free remission			20%	

off-label use of tofacitinib in unclassified IBD and CD patients who had been previously treated with biologic therapy. Within the cohort, 48.7% have had non-response to at least two biologic agents [21]. Seventy-six patients were followed for a median of 7.6 months. Clinical response at Week 8/16 was 46.6%; 15.1% had achieved clinical remission. Male sex was associated with increased odds of achieving clinical response (adjusted odds ratio (aOR 5.4; confidence interval [CI], 1.9–15.5, $p = 0.002$). Another "real-world" cohort from the UK included a large patient population receiving tofacitinib. Among them, 80% had been previously treated with TNF inhibitors. By Week 8, 74% had achieved clinical response and by Week 26, 44% had achieved steroid-free remission. Primary nonresponse was independently associated with higher C-reactive protein (CRP) levels at baseline ($p = 0.004$) and with younger age ($p = 0.014$) [22]. Table 2 summarizes the real-world efficacy data that has been reported in the literature [23–27].

Despite the safety signals seen in long-term studies with tofacitinib, novel JAK inhibitors with a higher selectivity towards JAK-1 promise efficacy while potentially offering a better safety profile when compared to non-selective JAK inhibitors. Several compounds are in development; some have completed Phase 3 trials in IBD and two (upadacitinib and filgotinib) have been approved for UC.

2.2 Upadacitinib

In UC, a Phase 2b placebo-controlled trial (U-ACHIEVE) that included a total of 250 patients receiving upadacitinib at different doses (7.5 mg, 15 mg, 30 mg, 45 mg) or placebo showed that at Week 8, those patients receiving 45 mg daily of upadacitinib had better clinical remission rates when compared to placebo (19.6% vs none, respectively [$p = 0.002$]) [28]. The most common AEs were infections and elevated

serum lipoprotein levels. Serious AEs including death, stroke, and venous thromboembolism were rare, although larger clinical trials and registry studies with a longer follow-up are required to confirm the safety of upadacitinib.

In the Phase 3 program, two induction studies (U-ACHIEVE induction [UC1] and U-ACCOMPLISH [UC2]) and a single maintenance study (U-ACHIEVE maintenance) were performed. More patients achieved clinical remission with upadacitinib 45 mg (83 [26%] of 319 patients in UC1 and 114 [34%] of 341 patients in UC2) than in the placebo groups; $p < 0.0001$. In both induction studies, serious AEs and AEs leading to discontinuation of treatment were less frequent in the upadacitinib 45 mg group than in the placebo group.

In the maintenance study, clinical remission was more commonly achieved on those patients receiving upadacitinib (42% with 15 mg and 52% with 30 mg) versus those receiving placebo (12%; $p < 0.001$). The proportion of serious AEs was similar than that in the placebo group. The most reported AEs were nasopharyngitis, acne, and UC exacerbation [29].

Upadacitinib is a selective JAK-1 inhibitor. Its efficacy was assessed in patients with moderate-to-severe CD who had failed to respond to or tolerate TNF inhibitors (CELESTE TRIAL) [30]. In a 52-week study, clinical remission rates were higher with upadacitinib 6 mg given BID versus placebo, (27% vs 11%, respectively) [30]. In the CELESTE OLE, 107 patients completed a 30-month follow up. Clinical remission was maintained between Week 0 and Month 30 in all groups (61% with 15 mg; 54% with 30 mg; and 55% of those patients who first received 15 mg and were dose escalated to 30 mg daily). Endoscopic response was similar in all cohorts (68%, 67% and 40%, respectively) [31].

2.3 Filgotinib

Filgotinib is also a selective JAK-1 inhibitor, which has shown effectiveness in IBD. In patients with moderate to severe active UC, a Phase 2b/3, double-blind, randomized, placebo-controlled trial (SELECTION) found that filgotinib 200 mg was well tolerated and had a great efficacy compared to placebo in inducing and maintaining clinical remission [32]. Long-term data from extension trials are pending. The AE profile of filgotinib in patients with IBD in the Phase 3 SELECTION and Phase 2 FITZROY studies was consistent with that of patients with RA and others JAK inhibitors.

Filgotinib received the European license in November 2021 for the treatment of adult patients with moderate-to-severe active UC who have failed or are intolerant to conventional or biologic therapy [33].

It has also shown effectiveness for induction of remission in CD [34]. In a Phase 2 study (FITZROY) that included 128 patients, those receiving filgotinib 200 mg achieved clinical remission at a higher rate when compared to those receiving placebo (47% vs 23%, respectively [$p = 0.0077$]). This difference was even higher in treatment-naïve patients (60% vs 13%) [35].

Multiple other studies that evaluated the safety and efficacy of filgotinib in CD patients with and without previous exposure to biologics are ongoing and include the DIVERSITY trial (NCT02914561) and DIVERSITY LTE (long-term extension) (NCT02914600. The DIVERGENCE 1 (NCT03046056) and 2 (NCT03077412) trials are specifically evaluating the efficacy of filgotinib in CD patients with perianal fistulizing, which is an important unmet need in clinical practice and may help to position the drug in the treatment algorithm.

2.4 Other Janus Kinase Inhibitor Molecules

Several other novel JAK inhibitors have been in development. Izencitinib (TD-1473) is an orally, non-selective and gut-selective Pan-JAK inhibitor. As expected, considering its gut-specificity, exposure in blood was very low, making it an attractive candidate drug to be used in IBD. Data from a Phase 1 FTIH trial [NCT2657122] study in healthy volunteers found izencitinib to be safe in a daily dose given for 14 days; no serious AEs were seen. Subsequently, a multicenter randomized placebo-controlled Phase 1b trial [NCT 02818686] evaluated three doses (20, 80 and 270 mg) given within a period of 28 days in patients with moderate-to-severe UC. The study showed numerical trends toward higher rates of clinical response, endoscopic response, and decreased CRP levels for all doses when compared to placebo [36]. However, in a Phase 2 trial, patients who received TD-1473 failed to achieve higher rates of remission at Week 8 when compared to placebo [37]. The program was discontinued, leaving an unmet need for development of effective gut-selective JAK inhibitors.

Brepocitinib is a dual oral TYK-2/JAK-1 inhibitor that binds to the active sites in the catalytic domains of TYK-2 and JAK 1 [38]. Two Phase 2 trials are evaluating the efficacy and safety of oral brepocitinib in patients with moderate-to-severe UC (NCT02958865) and CD (NCT0399515). The former having already finished the recruitment process and the latter currently recruiting subjects. These studies will evaluate both endoscopic improvement at Week 12 and safety for up to Week 68. Other compounds selectively blocking the TYK-2 are in early development. Table 3 summarizes the most relevant JAK inhibitors that have been under development [39–43].

3 Safety of Janus Kinase Inhibitors

One of the biggest barriers to initiating immuno-suppressive therapy are safety concerns. It is critical to discuss the safety profile of each drug, the risks and benefits and to create

Table 3 Other Janus kinase inhibitors evaluated in ulcerative colitis or Crohn's disease patients

Target	Therapeutic agent	Trial number	Phase	Status
Ulcerative colitis				
Pan-JAK Inhibitor	Peficitinib[a] (ASP015K)	NCT01959282	Phase 2b induction therapy	No efficacy seen in moderate to severe UC and development was discontinued [85]
	Izencitinib (TD-1473)	NCT03758443	Phase 2b/3	Terminated early based on interim results
JAK-1 selective inhibitor	Ivarmacitinib (SHR0302)	NCT05181137	Phase 3	Recruiting
JAK-3 selective inhibitor	Ritlecitinib (PF-06651600)	Eudra CT2021-003702-42	Phase 3	Ongoing (positive results were reported in a Phase 2 study NCT02958865 [86])
TYK-2 selective inhibitor	Deucravacitinib (BMS-986165)	NCT04613518 and NCT 03934216	Phase 2 and open label	Recruiting
	Brepocitinib (PF-06651600)	NCT02958865	Phase 2b	Program discontinued despite positive Phase 2 study [86]
Crohn's disease				
Pan-JAK inhibitor	Izencitinib (TD-1473)	NCT03635112	Phase 2	Terminated early based on interim results
JAK-3 selective inhibitor	Ritlecitinib (PF-06651600)	NCT03395184	Phase 2a	Active, not recruiting
TYK-2 selective inhibitor	Deucravacitinib (BMS-986165)	NCT04877990	Open label	Recruiting
	Brepocitinib* (PF-06651600)	NCT03395184	Phase 2a	Active (unclear if will undergo further development)

JAK Janus kinase, *TYK-2* tyrosine kinase 2, *UC* ulcerative colitis

[a]The development of peficitinib and brepocitinib in inflammatory bowel disease indications has now been discontinued

awareness of the implications of these therapies in the shared decision-making process when selecting a therapy with a patient. Janus kinase inhibitors have gained attention due to the report of several AEs seen in post-marketing studies. This has ultimately led to a change in prescription drug labeling for those JAK inhibitors that are currently available in the market. The US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) added multiple prescription safety warnings to JAK inhibitors between 2019 and 2022), noting risks of blot clots and heart events and death (Table 4).

3.1 Mortality

Long-term extension (LTE) studies of tofacitinib included patients with RA, PsA, UC and psoriasis. Exposures of between 3 and 9.5 years demonstrated a consistent safety profile over time. A total of 13,567 patients received tofacitinib and were included in the study. All-cause mortality risk was similar across cohorts. The common cause of death within the 28-day risk period was cardiac related. Age-adjusted and sex-adjusted standardized mortality ratios (95% CI) were as follows: 0.2 (0.2–0.3) for RA, 0.2 (0.0–0.4) for PsA, 0.1 (0.0–0.5) for UC and 0.2 (0.1–0.4) for psoriasis [40].

In a recent systematic review and meta-analysis, comprising 66,159 patients with immune-mediated diseases who were exposed to a JAK inhibitor, mortality was not increased when compared to placebo (relative risk [RR]: 0.72; 95% CI 0.40–1.28). Overall mortality among those exposed to JAK inhibitors was 0.37 per 100 person-years [44].

3.2 Infections

In the Phase 2 tofacitinib trial performed in UC patients, the most common infectious AEs were influenza ($n = 6$) and nasopharyngitis ($n = 6$). Two patients experienced serious infectious AEs (SAEs). In a 4.4-year follow-up, Sandborn et al, found the incidence rate for serious infections to be 2.0 cases per 100 patient-years (PYs) [47] (95% CI 1.4–2.8). The incidence of serious infections was higher among those using tofacitinib in the induction phase versus placebo, while rates were lower and remained equivalent between treatment groups in the maintenance phase [45].

A worldwide tofacitinib post-marketing surveillance database that analyzed 4426 UC case reports from May 2018 to August 2020 and included 12,103 AEs, of which 1839 were labeled as SAEs [46], the most frequently reported AEs of interest were infections (RR: 3.28 per 100 PY), vascular disorders (1.26 per 100 PY) and respiratory disorders

Table 4 Adverse effects in patients with IBD receiving Janus kinase inhibitors; real-world data

Study	Number of patients/ reports	Distribution by Indication	Drug(s)	Exposure (mean in years)	AEs reported
Burmester et al. [40]	13,567	RA = 7964 PsA = 783 UC = 1157 PsA = 3663	Tofacitinib	RA = 2.1 PsA = 3.0 UC = 1.7 PsO = 2.4	AEs: IRs were highest for HZ in all groups
					SAEs: IRs (95% CI) were highest in RA 9.0 (8.6 to 9.4) vs 7.0 (5.8–8.2) for PsA, 8.5 (7.4–9.8) for UC, and 5.5 (5.0–6.0) for PsO
					Mortality: Age-adjusted and sex adjusted mortality ratios were ≤0.2 across cohorts. The IR for mortality was 0.1 (95% CI 0.0 to 0.3)
					Infections: The 3 more frequent infections were pneumonia, HZ, urinary tract infection
					Malignancies: IRs for all malignancies (excluding NMSC) were ≤0.1 for RA and PsA and highest with UC
Olivera et al. [44]	66,159 (MA)	UC/CD = 2077 RA = 10,706, AS = 214 PsO = 2210	Tofacitinib Filgotinib, Baricitinib Upadacitinib	8.7	AEs: Mean IR of AES was 42.69 per 100 PYE
					SAEs: Mean IR of SAES was 9.98 per 100 PYE
					Mortality: Relative risk vs patients receiving placebo or active comparator: 0.72 (95% CI 0.40–1.28)
					Infections: IR serious infection was 2.81 per 100 PYE. More risk HZ
					Malignancies: IR of NMSC was 0.51 per 100 PYE IR (excluding NMSC) was 0.75 per 100 PYE
Rubin et al. [47]	4226 reports	UC = 8916	Tofacitinib	2.2	AEs: 12,103 cases. The most reported was drug ineffectiveness (18.5%)
					SAEs: 1141 (27%). Of 18 fatal cases, 3 were related to tofacitinib
					Infections: 6.8% reported infections, of which 292 were serious The most frequent were nasopharyngitis and HZ
					Malignancies: 52 cases (1.2%) reported 56 neoplasms
Winthrop et al. [63]	3691	RA = 3691	Filgotinib	5.6	AEs: The most common were nasopharyngitis, upper respiratory tract infection and nausea
					SAEs: 5 patients reported a MACE. Patients who had MI or stroke all had ≥ 1 CV risk factor. Was observed 0.5 per 100 PYE (200 mg) vs 0.3 per 100 PYE (100 mg) and appeared to remain stable over time. All fatal and MI strokes occurred in patients with ≥1 CV risk factor
					Infections: Six SAEs of HZ were reported by 5 patients receiving filgotinib 200 mg and one receiving filgotinib 100 mg with 0.6 and 0.9 per 100 PYE for filgotinib 200 and 100 mg, respectively
					Malignancies: During the placebo-controlled period, one malignancy each was reported with filgotinib 100 mg (cervix carcinoma) and placebo (malignant glioma) Long term, of all non-NMSC malignancies for filgotinib 200 and 100 mg remained stable over time
Hoisnard et al. [84]	126,815 reports	Not reported	Tofacitinib Ruxolitinib Baricitinib	No data	AEs: Overall, 376,487 AEs were reported in the 126,815 safety reports
					SAEs: MACE and cerebrovascular events were not reported. Embolism and thrombosis were observed in 1803 patients (1.4%)
					Infections: The most frequently reported infections were viral: 3.3% HZ, 1.8% influenza (1.8%) and pneumocystis infections
					Malignancies: Hematopoietic neoplasms (excluding leukemias and lymphomas), skin neoplasm, and leukemias were the most reported neoplasms (0.65, 0.78 and 0.66%, respectively)

AE adverse event, *CV* cardiovascular, *PsA* psoriatic arthritis, *HZ* herpes zoster, *IBD* inflammatory bowel disease, *IR* incidence rate, *MA* meta-analysis, *MACE* major cardiovascular event, *MI* myocardial infarction, *NMSC* non-melanoma skin cancer, PsA psoriatic arthritis, *PsO* psoriasis, *PYE* patient years, *RA* rheumatoid arthritis, *RR* relative risk, *SAE* serious adverse event, *UC* ulcerative colitis

(0.74 per 100 PY). Overall, 16.8% (934) of cases reported an infection of which 292 were serious. This was observed more frequently in UC (3.28 per 100 PY) versus RA patients (2.57 per 100 PY). The most frequently reported infections were nasopharyngitis (134 [14.3%]) and herpes zoster (HZ) (127 [13.5%]). The most common serious infection events in UC were *Clostridioides* infections (51 [5.4%]), pneumonia (36 [3.8%]) and COVID-19 (12 [1.28%]). These results are consistent with those reported in tofacitinib clinical trials.

Among patients in the OCTAVE trials and the open-labeled extension, there was a clear signal towards a higher risk of developing HZ (5.6% of the study population). This association was dose dependent. In the induction cohort, HZ occurred in 0.6% (6) of patients receiving tofacitinib 10 mg BID, versus 0.4% (1) of patients receiving placebo [14]. In the overall cohort ($n = 1157$), 92 patients had HZ events at an incidence rate of 3.48 (95% CI 3.48 [2.79–4.30] and a median time to onset of 474 days (range 13–1799 days) [47]. Including all Phase 2/3/open-label extension studies involving patients with UC receiving tofacitinib, 65 (5.6%) patients developed HZ infection; among those, one patient developed encephalitis and 11 had multi-dermatomal involvement. Age $\geq$ 60 years, lower body weight, and prior TNF inhibitors exposure were identified as risk factor for herpes infections [48].

The risk of HZ has been reported for all JAK inhibitors that are either available or under development [49]. However, the incidence of serious HZ on those patients exposed to filgotinib has been very low, independently of the dose. Herpes zoster events observed after treatment with tofacitinib tended to be noncomplicated and in most cases did not result in permanent discontinuation of therapy nor additional HZ recurrence [50, 51]. For upadacitinib, three cases were reported during the CELEST trial [30]. Data from long-term follow-up registries and real-world data as well as the effect of systematic vaccination on these rates are needed.

Is important to mention that live vaccines are contraindicated in patients receiving JAK inhibitors and should be administrated at least four weeks before the start of treatment. However, recombinant vaccines can be safely used and are therefore preferred [52]. Figure 1, summarizes indications and schedules for patients initiating JAK inhibitor therapy [53–56].

An important question is how JAK inhibitors can affect the risk of developing COVID-19 or if they increase the risk of complications when compared to patients off immunosuppression. The SECURE-IBD registry is a global, collaborative registry established in March 2020 to understand COVID-19 outcomes in IBD patients [57]. Among patients with IBD enrolled in the registry, 37 were on treatment with tofacitinib. These patients did not have worse outcomes when compared to other therapies [58]. Furthermore, there were no significant differences between tofacitinib-treated patients and other therapies when looking at hospitalization rates (21.6% vs 23.3%), need for intensive care unit admission (5.4% vs 4.5%) and developing severe COVID-19 (6.2% in both groups) [59]. Is important to note that the number of patients on tofacitinib was low and the analysis was not powered to detect small differences. In a large cohort of patients with IBD and diverse exposure to immunosuppressive agents, the authors found that full vaccination (> 7 days after the second dose against SARS-CoV-2) but not partial vaccination, was significantly associated with a reduced rate of COVID-19 when compared to non-vaccinated patients (80.4%) [60].

In a follow-up publication that included a total of 6077 patients with IBD, RA and psoriasis, a higher risk for hospitalization or death was seen in patients receiving combination therapy with azathioprine/6-mercaptopurine (OR 1.74 [95% CI 1.17–2.58], $p = 0.006$) and JAK inhibitor monotherapy (OR 1.82; 95% CI, 1.21–2.74, $p = 0.004$) when compared with patient who received TNF inhibitor monotherapy [61]. In another systematic review and meta-analysis with 18 studies, tofacitinib was not associated with COVID-19-related hospitalization (RR = 0.81, 95% CI 0.49–1.33, $p = 0.40$) [62].

In an integrated analysis of patients with RA receiving filgotinib for RA, there was a higher incidence of infections when compared to placebo and even though the overall rate was similar, patients receiving the higher dose (200 mg) had a higher rate of serious infections [63].

3.3 Hypercholesterolemia

In the tofacitinib UC trials, concentration of both LDL and HDL cholesterol increased after Week 8 of therapy with a total-to-HDL cholesterol ratio being stable and normalizing after drug discontinuation [64]. Serum lipids should be monitored within 2 months of starting tofacitinib. After long-term tofacitinib use, no significant changes were detected during a 61-week period and 4.4 years of follow-up [65]. The short- and long-term clinical significance of these findings are still unclear. A recent meta-analysis showed that all the JAK inhibitors approved for RA lead to increase in HDL 8.11 mg/dL (95% CI 6.65–9.58, $I^2 = 82\%$) and a mean increase of 11.37 mg/dL (95% CI 7.84–14.91, $I^2 = 88\%$) in LDL levels from baseline [66].

3.4 Malignancies

Among the tofacitinib UC clinical trials population, 22 patients had malignancies, 11 of which developed non-melanoma skin cancer (NMSC); six had a previous history of NMSC. Among those who developed NMSC, all had prior exposure to a thiopurine and 8 of 11 patients had been previously treated for a NMSC. Through the

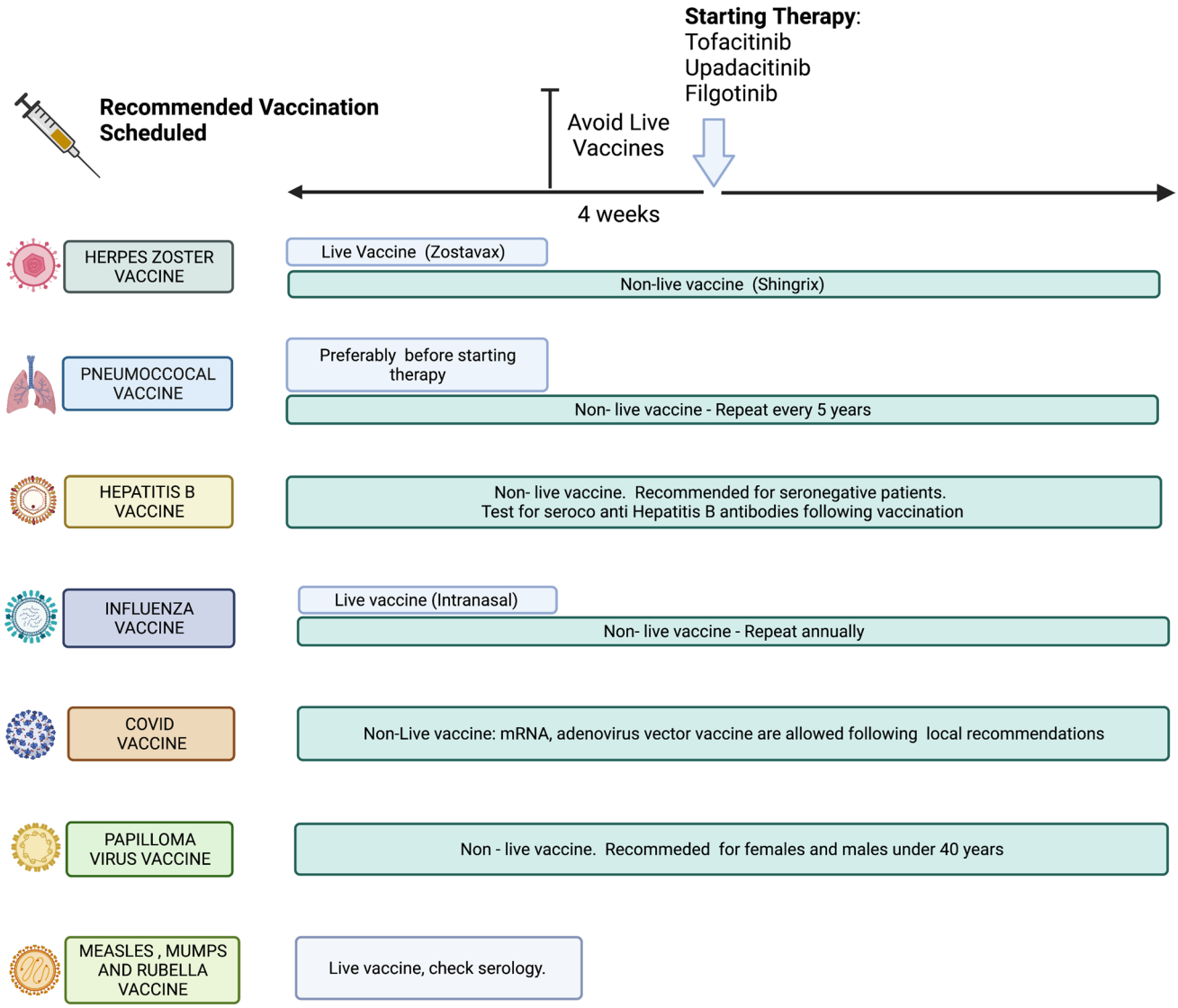

Fig. 1 Recommended immunization schedule in patients starting small molecules for inflammatory bowel disease *DILI* drug induced liver injury, *HDL* high density lipoproteins, *LDL* low density lipoproteins

OCTAVE trials, four deaths were recorded in the overall population, with 3 out of 4 cases being secondary to malignancies (hepatic angiosarcoma, acute myeloid leukemia, and cholangiocarcinoma) [14, 15]. In a recent publication, NMSC events were evaluated from 3 randomized, placebo-controlled studies that included patients with UC. Within the cohort, Cox regression models identified three significant risk factors: prior NMSC (hazard ratio [HR] 9.09; $p = 0.0001$), anti-TNF failure (3.32; $p = 0.0363$) and age (HR per 10-year increase: 2.03; $p = 0.0004$) as significant independent factors associated with the development of NMSC [67]. No patients developed malignancy during the maintenance trials in UC and CD. Furthermore, the risk of malignancies was similar to that observed in patients receiving tofacitinib with RA and psoriasis, even though that risk was comparable to that of patients on other biologics [68]. The ORAL Surveillance study (NCT02092467) was an open-label, randomized noninferiority and safety endpoint trial that enrolled patients with active RA who were aged 50 years and had at least one additional cardiovascular (CV) risk factor. Subjects were randomly assigned in a 1:1:1 ratio to receive tofacitinib at dose 5 mg or 10 mg BID or a TNF inhibitor [69]. Through a median follow-up of 4.0 years, the incidence of cancer was higher with tofacitinib (at any dose) (4.2% [$n = 122$]) versus those patients who received TNF inhibitors (2.9% [$n = 42$])—HR 1.48 (95% CI 1.04–2.09) [74] In another study, among 5671 patients with RA exposed to tofacitinib, 107 developed

malignancies (excluding NMSK); the most common were lung cancer (24 [22.4%]), breast cancer (19 [17.7%]) and lymphoma (10 [9.3%]) [70].

In the upadacitinib UC induction trials, one NMSC was reported in a patient receiving the 24 mg BID dose. All patients had prior exposure to azathioprine. During the maintenance phase, two malignancies were reported: one Hodgkin's lymphoma (the patient had been previously exposed to three biologics) and one malignant neoplasm of the thymus (with concomitant immunosuppressive therapy and previously exposed to two biologic agents) [29]. No malignancies were reported in the filgotinib trials and long-term studies have reported similar rates versus the overall RA population. Moreover, longer exposure doesn't seem to increase the risk further, even though registries with larger populations are needed [35]. Long-term real-world and safety registry data will be essential to better determine the risk of malignancies with the newer, selective JAK-1 inhibitors and how they compare to tofacitinib or anti-TNF agents.

3.5 Thrombotic Events

In July 2019, the FDA placed a "black box warning" on tofacitinib alerting of a possible higher risk for developing pulmonary embolism and increased risk of mortality [71]. This led to a change in indication and positioning of JAK inhibitors after anti-TNFs [72]. However, it is important to highlight that the greatest thrombotic risk has been seen in the RA population and when comparing tofacitinib 10 mg with anti-TNF (19 cases in 3884 patients-year vs 3 cases in 3982 PYs, respectively) [73]. As expected, a greater risk was observed in those patients with a history of malignancy, aged > 50 years and those with ≥ 1 CV risk factors. In a post hoc analysis of patients in the OCTAVE clinical trials who received at least one dose of tofacitinib, the overall risk of deep venous thrombosis (DVT) was 0.04 events/100 PYs of exposure (95% CI 0.00–0.23) and 0.16 PY (95% CI 0.04–0.41) for pulmonary embolism (PE). Real-world safety signals seen in patients on tofacitinib are similar to those reported during clinical trials. The incidence rates of SAEs were 10.0 (95% CI 8.9–11.2 per 100 PY of follow-up. Five patients developed HZ infection and two developed venous thrombo-embolism (VTE) (all were receiving 10 mg tofacitinib, BID) [72].

Because these events are relatively rare, large trials with long-term follow-up are needed. An analysis that included 12,410 tofacitinib-treated patients from development programs in RA, PsA, and psoriasis as well as the FDA Adverse Reporting System (FAERS), US Corona registries and the IBD MarketScan database showed that incidence rates of DVT, PE, and arterial thrombotic events were higher in patients with known baseline CV or VTE risk factors when compared to those with no previous history [73]. It is recommended to use the minimum effective dose to maintain remission and avoid its use in patients aged > 50 years with one or more CV risk factor [74, 75].

An important question—should extrapolate these results to other JAK inhibitors with a more selective effect on the JAK-1? Across the upadacitinib rheumatologic trials, 6 venous thromboembolic events were reported over 461 treatment-arm PYs, compared with one event in 366 placebo-arm PYs [74]. No thrombotic events have been reported with upadacitinib in RA, but the drug was only recently introduced to the market (in 2019) and long-term studies in larger populations are warranted [75].

In a Phase 2 study with upadacitinib in patients with UC, a patient on upadacitinib 45 mg developed a PE and DVT 26 days after drug discontinuation due to worsening of UC [30]. In another Phase 2 study in CD, one patient developed a mesenteric vein thrombophlebitis during the induction period (receiving a dose of 3 mg BID). No events of DVT or PE were observed [22]. We need to consider that Phase 2 studies are not powered to look into these types of AEs and further data will be needed.

3.6 Major Adverse Cardiovascular Events

Major adverse cardiovascular events (MACE), defined as any myocardial infarction (MI), cerebrovascular event (stroke), or CV death (defined as death caused by coronary, cerebrovascular, or cardiac events) represent one of the most common comorbidities in patients with RA. In the QUEST-RA study, the prevalence of CV morbidity in patients with RA was 9.3% for any CV event (MI, angina, coronary disease, or stroke) with considerable heterogenicity among countries. The overall prevalence for the whole cohort of lifetime MI was 3.2% and the prevalence of stroke was 1.9% [76]. In a post-marketing report of tofacitinib, 67 cases of MACE were reported. Of those, 45 were labeled as serious (estimated reporting rate: 0.50 per 100 PYs). The most reported MACE was acute MI, angina pectoris and pericarditis [47].

In a post hoc analysis of 2 long-term extension studies and 6 Phase 3 studies over 7 years that included patients with moderate-to-severe RA receiving tofacitinib, 52 cases MACE occurred in 4076 patients over 12,873 PYs of exposure (IR 0.4 per 100 PY). In subsequent multivariable analyses, aged > 49 years, with hypertension, and the total cholesterol to HDL cholesterol ratio remained significantly associated with a risk of developing a MACE [77].

Overall, tofacitinib trials for patients with UC have shown an increased risk of MACE compared to placebo (OR = 5 [CI 95% 1.7–10]) based on 4 cases (MI, acute coronary syndrome, aortic dissection, and hemorrhagic stroke) [66]. Likewise, 3 of 4 patients with a MACE had ≥ 4 predisposing

CV factors. An aortic dissection resulted in death of the patient and the other MACE resolved after tofacitinib discontinuation [45]. In upadacitinib, one MACE was reported in induction phase of CD, with no cases seen in the maintenance phase [30].

A post hoc analysis from ORAL Surveillance evaluated the risk of MACE with tofacitinib 5 and 10 mg versus TNF inhibitors in patients with RA. The highest risk was associated with age, > 50 years with at least one additional CV risk. In this patient population the recommendation is to use the lowest effective dose to maintain clinical response after 8 weeks of induction therapy [78].

In RA patients, approximately 2600 patients have been exposed to upadacitinib. Exposure-adjusted event rates of adjudicated MACE were not different across treatment groups and did not increase over time: 1.2 events/100 PY (95% CI 0.2–3.4) in placebo, 0.6 events/100 PY (95% CI 0.4–1.0) in upadacitinib 15 mg and 1.0 events/100 PY (95% CI 0.5–1.6) in upadacitinib 30 mg [79].

Data from filgotinib in RA have not shown a signal towards a higher rate of MACE, even when considering that risk factors in this patient population are relatively high. Long-term registries assessing the incidence of MACE events are warranted [63].

3.7 Pregnancy and Breastfeeding

As with other small molecules, the active metabolite of JAK inhibitors can cross the placenta during the first trimester. As with other novel compounds, there is always a concern for fetal exposure. Preclinical studies with tofacitinib showed that drug exposure at a much higher dose than the therapeutic dose (100 mg/kg/day), can cause fetal malformations (CV and bone malformations) [80].

In interventional studies with tofacitinib in RA and psoriasis, of 1821 female patients of child-bearing age, 47 women became pregnant, including 33 who were on tofacitinib monotherapy, 13 who received combination therapy with methotrexate, and one patient whose therapy was still blinded. No fetal deaths, one case of a congenital malformation (pulmonary valve stenosis) and 7 spontaneous abortions were reported [80].

A prospective registry study by Mahadevan et al described 11 cases of maternal exposure and 14 cases of paternal exposure to tofacitinib. No evidence of fetal or neonatal death was seen and no congenital malformations were reported [81].

The American Gastroenterology Association guidelines recommend avoiding tofacitinib use during lactation and at least in the first trimester of pregnancy, A 1-week washout period should be enough before attempting conception [82]. More data are needed before establishing recommendations for other JAK inhibitors but as of now, they should be avoided during pregnancy.

3.8 Other Adverse Events

In patients on tofacitinib, an initial decrease in hemoglobin, lymphocyte, neutrophil, and platelet counts were reported. However, they tended to be mild and reversible after drug discontinuation. As for filgotinib, there were no differences in hemoglobin levels or platelet counts [35]. In the SELECTION study, throughout Week 52, patients who received upadacitinib had no clinically meaningful changes from baseline in hemoglobin, leukocytes, neutrophils, transaminases, or creatinine concentrations across all treatment arms [30]. The proportion of patients with an abnormal increase of creatine kinase was higher in the filgotinib group versus placebo, with no association with rhabdomyolysis [83].

An open-label long-term extension of the OCTAVE trial followed patients on tofacitinib for up to 7 years. A total of 26 patients were evaluated for drug-induced liver injury; 7 patients administered tofacitinib 5 mg BID and 19 on 10 mg BID [17]. This adverse reaction has not been observed with filgotinib or upadacitinib. However, as with other less common potential AEs, larger, long-term studies are needed.

There have been reports of gastrointestinal perforation in patients receiving JAK inhibitors. From the WHO pharmacovigilance database, and among 126,816 reported AEs to tofacitinib, ruxolitinib and baricitinib, the risk is dose dependent. Gastrointestinal perforation with tofacitinib was greater with higher doses [84]. In patients with UC, two cases of intestinal perforations were reported. Both were in patients who had active IBD, which confounds these observations. Figure 2 summarizes the most common AEs associated with the use of JAK inhibitors and ways in which to monitor for them.

4 Conclusions

As JAK inhibitors make their way into the therapeutic landscape of IBD, more options become available to patients. Currently, tofacitinib, upadacitinib, and filgotinib are approved for treatment of patients with UC, and other JAK inhibitors are undergoing clinical trials for both UC and CD.

Even though the introduction of tofacitinib and other novel JAK inhibitors address an unmet need in the IBD therapeutic arsenal, safety concerns have positioned these drug classes lower in the therapeutic algorithm. While novel, selective JAK inhibitors aim to address these safety

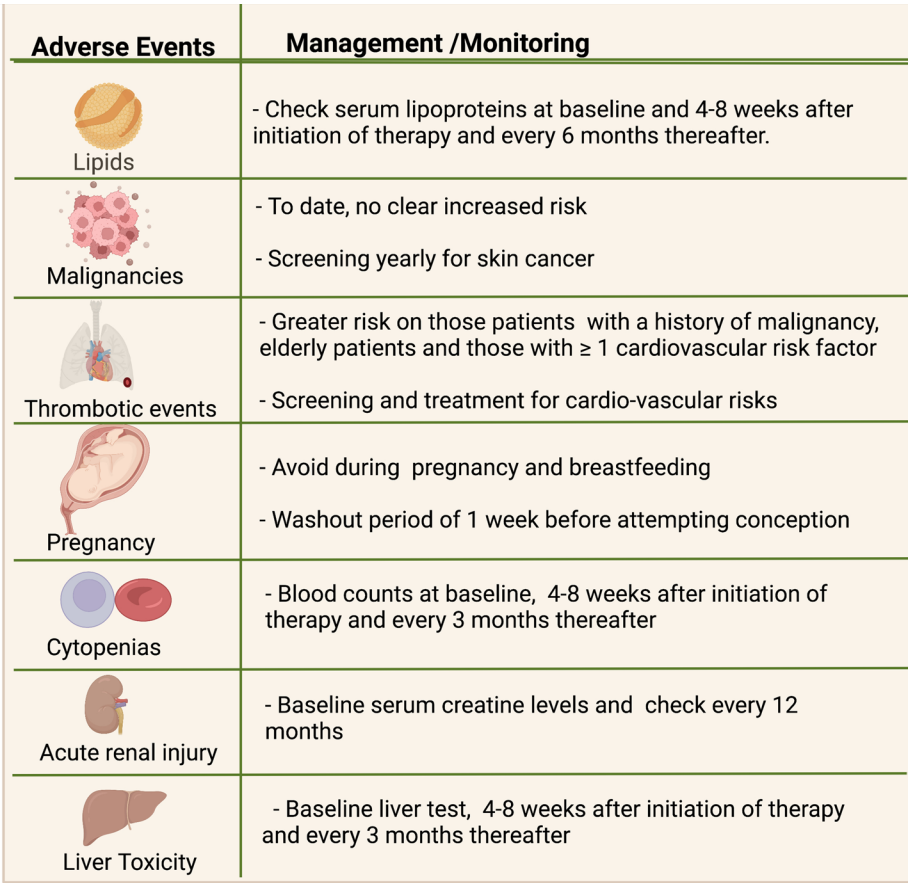

Fig. 2 Most frequently reported adverse events (AEs) with small molecules and ways in which to monitor for them

concerns, long-term data are needed. While as of now they are indicated in those patients who do not respond to other advanced therapies such as biologics, this represents a large population of patients with IBD in need of more effective therapies. Risk stratification, patient counseling, and adequate monitoring is pivotal. As of now, the recommendation is to use the minimal effective dose to maintain remission and to avoid their use in patients aged ≥ 50 years with one or more CV risk factor. However, we must consider that filgotinib is an effective and safe treatment of both biologic-naïve and biologic-experienced patients with moderate-to-severe UC with no associated risk of thrombosis and HS infections compared to other JAK inhibitors.

As with any other therapy, the risks and benefits should be discussed with each patient and treatment plans should be tailored on a case-by-case basis considering not only their IBD history, but also their complete medical history.

Declarations

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Conflict of interest PN has been a consultant for Janssen and Ferring, RQ has been a consultant for Jansen and AJY has been a consultant for Takeda, Pfizer, Bristol Myers Squibb, Arena pharmaceuticals, Prometheus Labs and Procise.

Ethics approval Not applicable

Consent to participate Not applicable.

Consent to publication Not applicable.

Availability of data and material Not applicable.

Code availability Not applicable.

Author contributions All authors contributed equally to this review with the conception and design of the study, literature review and analysis, drafting and critical revision and editing, and approval of the final version

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