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REVIEW

The Role of Novel Small Molecule Drugs in the Management of Inflammatory Bowel Disease

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Abstract

Treatment algorithms have traditionally been based on biological therapy when conventional therapy was not successful in controlling inflammatory bowel disease (IBD). Novel small molecule drugs (SMDs) for IBD include the Janus Kinase (JAK) inhibitors Tofacitinib, Filgotinib and Upadactinib and the sphingosine-1 phosphate (S1P) inhibitors Ozanimod and Etrasimod. SMDs have advantages over biologics, such as oral administration, lack of immunogenicity, and rapid onset of action. All agents are effective in treating ulcerative colitis, while Upadactinib is the only SMD for Crohn's disease. There is growing interest in the use of JAK inhibitors for acute severe colitis. However, safety profiles are distinct from biologics. Clinicians need to be aware of the need for additional lipid monitoring for JAK inhibitors. S1P inhibitors require pre-treatment electrocardiograms to reduce the risk of bradycardia and retinal exams at least in high-risk patients to avoid macular oedema. In this review we highlight the key evidence on efficacy and safety for general hospital physicians.

Key words: inflammatory bowel disease; ulcerative colitis; Crohn's disease; small molecule drugs; JAK inhibitors

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Introduction

Inflammatory bowel disease (IBD) encompassing Crohn's disease (CD) and ulcerative colitis (UC) affects over 500,000 individuals in the UK with a global incidence ranging from 1.2 to 20.3 cases per 100,000 persons per year and peak age at diagnosis of 15–30 years with a second peak after age of 60 (Abraham and Cho, 2009; Ng et al, 2017).

CD and UC present with a relapsing-remitting course and can have overlapping symptoms, including bloody diarrhea, abdominal pain, urgency, fever, and weight loss. Anatomically, CD more commonly affects the terminal ileum and colon, although it can involve any part of the gastrointestinal tract, usually in a non-contiguous pattern, in contrast to the uniform distribution seen in UC. The transmural and granulomatous nature of CD leads to a variable phenotype, ranging from inflammation to penetrating disease or structuring due to fibrosis (Lamb et al, 2019). In contrast, UC affects solely the rectum in close to 20% of cases but can extend to involve the entire colon, resulting in pancolitis in about 15% of cases (Lamb et al, 2019).

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Extra-intestinal features of IBD include arthritis, uveitis, and various forms of cutaneous inflammation. Additionally, IBD is associated with an increased risk of complications, including venous thromboembolism (VTE), colorectal cancer, and cardiovascular disease (Lamb et al, 2019). These complications lead to extensive morbidity, reduced quality of life, recurrent admissions and surgical interventions (Follin-Arbelet et al, 2023; Selinger et al, 2014). As the therapeutic landscape for has rapidly changed with more choice for clinicians and patients there is a need to understand the advantages and disadvantages of the various therapeutic options. We therefore describe the traditional treatment pathways with biologics and then comprehensively review the oral small molecule drug choices for IBD.

Treatment Pathway

The paradigm of disease management in IBD focuses on inducing and maintaining remission, considering the type of IBD, severity of disease, and patient preferences (Denesh et al, 2021). Corticosteroids are reserved for acute flares. Aminosalicylates, administered through various methods, are used for remission induction and maintenance in UC. Immunomodulators, including azathioprine, which is effective in both UC and CD, and methotrexate, mainly for CD, are used for maintenance due to their prolonged onset of action (Lamb et al, 2019). When these measures fail to induce and maintain remission, advanced medical therapies or surgical resections will be considered (Lamb et al, 2019).

Biologics

The introduction of biologic therapies 20 years ago revolutionised IBD management. Anti-tumour necrosis factor (TNF) biologics, such as infliximab and adalimumab, are associated with clinically significant outcomes, including mucosal healing (Selinger et al, 2018). Other biologics including gut-specific anti-integrin biologics (vedolizumab), anti-interleukin (IL)12/23 biologics (ustekinumab), anti-IL23 biologics (Risankizumab) have since been introduced allowing for greater choices in disease management (Fig. 1) (Kapizioni et al, 2024). While classic treatment algorithms follow a step-up approach from mesalazine (UC only) to immunomodulators and onto biologics, top-down approaches with early initiation of immunomodulator/biologic therapy show superior outcomes for patients with moderate to severe phenotypes disease (Noor et al, 2024).

However, biologic therapy presents its own challenges, ranging from response variability to safety concerns. While one-third of patients do not respond to anti-TNF agents (primary non-response), another third lose response over time (secondary loss of response), often due to immunogenicity and neutralizing anti-drug antibodies (Chanchlani et al, 2024; Papamichael et al, 2015). Moreover, biologics are variably associated with rare but serious adverse effects, including infections, autoimmune reactions and an increased risk of malignancy (Kapizioni et al, 2024). Therefore, there is an unmet need for novel anti-inflammatory therapies that are effective, maintain long-term remission, and are well tolerated.

Small Molecule Drugs

Small molecule drugs (SMDs) are compounds with a low molecular weight (<1 kDa) that are capable of modulating biochemical processes (Ngo and Garneau-Tsodikova, 2018). SMDs can bind to a wide range of targets such as proteins (enzymes, receptors, ion channels), RNA/DNA and lipids. Due to their size and permeability, they can cross biological barriers, such as the blood-brain barrier, to access intra-cellular targets (Beck et al, 2022).

In contrast to biologics, SMDs have a well-defined, stable structure with good oral bioavailability and generally do not require special storage conditions. Immunogenicity is not a problem with SMDs, which may reduce the risk of secondary loss of response. Currently, two major classes of SMDs have been approved for the treatment of IBD, including JAK inhibitors and Sphingosine-1 phosphate receptor modulators.

JAK Inhibitors

Janus Kinase inhibitors (JAKis) were first licensed in 2018 for moderate to severe IBD in the UK. Cytokine signalling within the gastrointestinal (GI) tract plays a crucial role in the inflammatory immune responses seen in IBD. JAKs are tyrosine kinase proteins pivotal to multiple pro-inflammatory signalling pathways involved in the dysregulated immune response seen in IBD (Salas et al, 2020). There are four main JAK isoforms (JAK1, JAK2, JAK3, and tyrosine kinase 2 (TYK2)) that are specific for certain cytokines, some of which are highly implicated in the pathogenesis of IBD (Table 1; Fig. 1) (Nemeth et al, 2017). Tofacitinib is selectively for JAK1 and/or JAK3 over JAK2; Upadacitinib is ~60 fold selective for JAK1 over JAK2, and >100 fold selective over JAK3 in cellular assays.

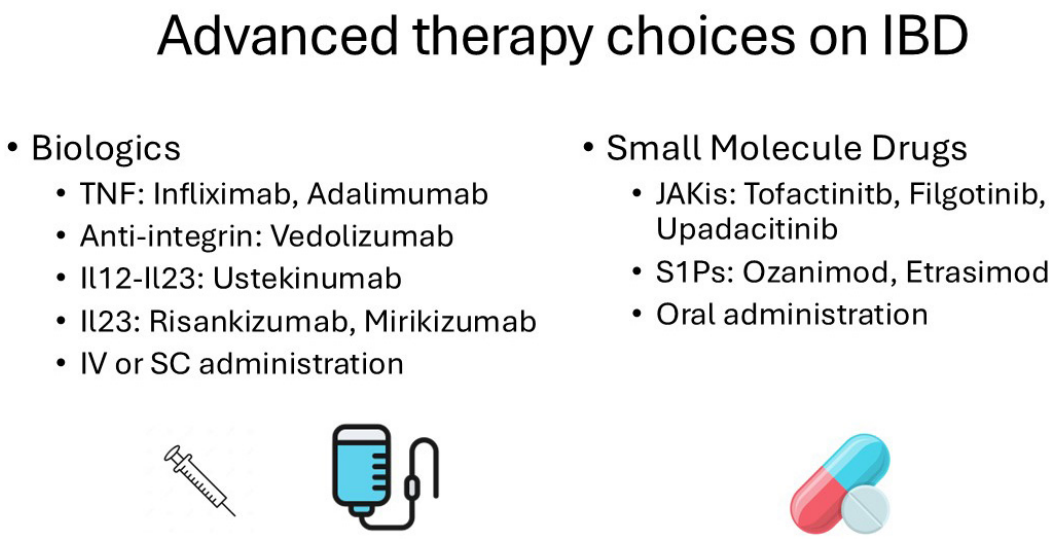

Fig. 1. Advanced therapy choices on inflammatory bowel disease (IBD). Figure drawn on Microsoft PowerPoint (Version 2108, Microsoft Corporation, Redmond, WA, USA). TNF, tumour necrosis factor; JAKis, Janus Kinase inhibitors; IL, interleukin; IV, intravenous; SC, subcutaneous; S1P, sphingosine-1 phosphate.

Table 1. JAK inhibitors.

	Tofacitinib	Filgotinib	Upadacitinib
UC license	Yes	Yes	Yes
Key UC studies	Octave 1 & 2	Selection	U-ACHIEVE U-ACCOMPLISH
CD license	No	No	Yes
Key CD studies	Not applicable	Not applicable	U-EXCEL, U-EXCEED
Induction dose	10 mg BD	200 mg OD	45 mg OD
Maintenance dose	5 mg BD	200 mg OD	15 mg or 30 mg OD

UC, ulcerative colitis; CD, Crohn's disease; BD, twice daily; OD, once daily.

Tofacitinib

Tofacitinib (Xeljanz, Pfizer, New York, NY, USA) is a first generation nonselective JAKi licensed for the treatment of moderate to severe UC since 2018 and is also widely used for rheumatoid arthritis and psoriatic arthritis. The key evidence stems from the OCTAVE trials (Sandborn et al, 2017). The OCTAVE Induction trials were two randomised, double-blind placebo-controlled trials that recruited over 1000 patients with moderate-severe UC, unresponsive to conventional or biologic therapy, who were randomised to either twice daily 10 mg doses of Tofacitinib or placebo for 8 weeks. Tofacitinib was superior to placebo in inducing clinical remission at week 8 in OCTAVE Induction 1 (18.5% vs 8.2, $p = 0.007$) and OCTAVE Induction 2 (16.6% vs 3.6%, $p = 0.001$) (Sandborn et al, 2017). Clinically responsive patients were randomized in the OCTAVE Sustain trial to maintenance therapy with 5 mg or 10 mg twice daily, or placebo, for an additional 52 weeks. Both Tofacitinib doses showed significantly higher rates of both clinical remission at 52 weeks and steroid free remission compared to placebo (Sandborn et al, 2017).

Real world evidence complements clinical trial data and provides important safety and effectiveness data relating to use in clinical practice. Real world data are however subject to bias especially by patient selection and incomplete data collection. A recent meta-analysis of real word studies (Taxonera et al, 2022) supports the clinical trial data of the effectiveness of Tofacitinib for moderate to severe UC, with remission achieved in 34.7% of patients at week 8, 47% at weeks 12 to 16 and 38.3% at month 6 (Taxonera et al, 2022). Currently, Tofacitinib is licensed with a standard induction regimen of 10 mg twice daily for 8 weeks, which can be extended if necessary, followed by 5 mg twice daily for maintenance.

In contrast, two phase IIb randomised controlled trials (RCTs) for induction and maintenance therapy in CD did not reach their primary efficacy endpoints (Panés et al, 2017).

Filgotinib

Filgotinib (Jyseleca, Galapagos NV, Mechelen, Belgium) is a once daily JAK1 inhibitor first licensed for moderate to severe UC with intolerance/failed response to conventional or biologic therapy in 2022. The phase IIb/III SELECTION trial recruited patients with moderate to severe UC, who were randomly assigned to in-

duction therapy in two studies with either 200 mg Filgotinib, 100 mg Filgotinib, or placebo in a 2:2:1 ratio, with clinical responders then re-randomised to the maintenance study (Feagan et al, 2021). By week 10, patients who received 200 mg had a higher rate of clinical remission than those given a placebo; however, the results were not statistically significant in the 100 mg group (Feagan et al, 2021). At week 58 in the maintenance study, efficacy of the 200 mg group vs placebo was maintained (37.2% vs 11.2%, $p < 0.0001$) with a significant difference also seen in the Filgotinib 100 mg arm (23.8% vs 13.5%, $p = 0.0420$) (Feagan et al, 2021). Furthermore, the long-term extension SELECTIONLTE showed that 4 years of Filgotinib treatment was effective at maintaining remission. Emerging real-world data corroborate effectiveness of Filgotinib for UC (Gros et al, 2023). However, like Tofacitinib, large phase II and III trials in patients with moderate to severe CD have shown failure for Filgotinib to meet primary endpoints (Vermeire et al, 2017).

Upadacitinib

Currently, Upadacitinib (Rinvoq, AbbVie, Chicago, IL, USA) is the only JAK inhibitor licensed for use in both UC and CD as of 2023. National Institute for Health and Care Excellence (NICE) guidelines advise Upadacitinib for patients with UC when conventional or biological therapy is ineffective or not tolerated, while for CD patients must have previously used a biologic treatment or were unable to due to contraindications (National Institute for Health and Care Excellence, 2023a; National Institute for Health and Care Excellence, 2023b). The pivotal phase III U-ACHIEVE induction (UC1), U-ACCOMPLISH (UC2) and U-ACHIEVE maintenance (UC3) studies demonstrated efficacy and safety for UC (Danese et al, 2022). For induction, patients with moderate to severe UC were randomised to Upadacitinib 45 mg daily and placebo for 8 weeks. There was a 21.6% and 29% difference (UC 1 and UC 2 respectively, $p < 0.001$) in remission rates compared to placebo (Danese et al, 2022). For maintenance, induction responders were then re-randomised to 15 mg, 30 mg or placebo for a further 52 weeks. The maintenance study demonstrated superior remission rates compared to placebo (30.7% for Upadacitinib 15 mg and 39% for Upadacitinib 30 mg vs 12% placebo, $p < 0.001$) (Danese et al, 2022). For CD, the U-EXCEL and U-EXCEED induction studies of Upadacitinib 45 mg daily for 12 weeks demonstrated significant clinical response compared to placebo (in U-EXCEL, 49.5% vs 29.1%; in U-EXCEED, 38.9% vs 21.1%). In the U-ENDURE maintenance study, significantly higher clinical remission rates were observed in both the 15 mg and 30 mg maintenance arms compared to placebo (Loftus et al, 2023).

Furthermore, improvement of symptoms including rectal bleeding and faecal urgency was seen as soon as 24 hours in UC and 2 weeks in CD. Subsequently, two recent network-meta-analyses ranked Upadacitinib highest for UC remission, endoscopic improvement, and for maintenance in CD (Barberio et al, 2023; Lasa et al, 2022).

Safety Profile

Trial data for JAKi have shown a largely favourable safety profile. Most side effects are mild including upper respiratory tract infections (Honap et al, 2023). Notably, there is a dose dependent increased risk of herpes zoster infection, which can be mitigated with prior varicella vaccination (Colombel, 2018). As with biologic therapy, patients should be screened for hepatitis B/C, HIV, and tuberculosis before initiating therapy. Mild cytopaenias and derangements in liver function tests are often transient or resolve on drug cessation (Herrera-deGuise et al, 2023).

The ORAL SURVEILLANCE randomised patients with rheumatoid arthritis aged ≥55 years who had at least one cardiovascular risk factor, to receive Tofacitinib 10 mg or TNF therapy (Ytterberg et al, 2022). There was an increased risk of VTE, major cardiovascular events and malignancy for patients receiving Tofacitinib (Ytterberg et al, 2022). This led to the Medicines and Healthcare products Regulatory Agency (MHRA) issuing guidance in April 2023 advising clinicians to avoid use of JAKi unless viable alternatives are unavailable in patients with an increased risk of cancer, VTE and cardiovascular disease (Medicines and Healthcare products Regulatory Agency, 2023). In contrast, meta analyses of IBD studies have failed to show a significantly increased risk of these events compared to placebo (Olivera et al, 2020; Olivera et al, 2023; Yates et al, 2021). Whether the findings of the ORAL SURVEILLANCE are applicable to IBD and whether they apply to more selective JAK inhibition remains unclear. Clinicians should follow the strict guidance in those selected high-risk groups when there are suitable alternative therapies available. The MHRA guidance will be reviewed in 2025 and recommendations may change as real-world evidence grows.

Sphingosine-1 Phosphate (S1P) Receptor Modulators

Altered leukocyte recruitment is recognised as a contributor in the pathogenesis of inflammatory bowel disease. Sphingosine-1 phosphate (S1P) is a signalling molecule that acts on cell-surface G protein-coupled receptors (S1P1-S1P5 receptors). The interaction between S1P and S1P receptor 1 regulates the lymphocyte movement from the spleen and lymph nodes into the systemic circulation and sites of inflammation. S1P receptor modulators lead to the internalisation of receptors resulting in reduced lymphocyte trafficking, decreased inflammation and tissue damage (Brinkmann et al, 2004).

The first-generation non-selective S1P modulator Fingolimod used for multiple sclerosis was associated with serious adverse events due to its non-selective nature (Calabresi et al, 2014), which prompted the development of S1P modulators with greater selectivity and improved safety profiles.

Two selective S1P receptor modulators licensed in the UK for the treatment of moderate to severe ulcerative colitis, are oral, rapid-acting, once daily tablets (Table 2; Fig. 1).

Table 2. S1P Inhibitors.

	Ozanimod	Etrasimod
UC license	Yes	Yes
Key UC studies	Touchstone	ELEVATE UC
CD license	No	No
Key CD studies	Not applicable	Studies ongoing
Induction dose	0.92 mg OD	2 mg OD
Maintenance dose	0.92 mg OD	2 mg OD

Ozanimod

Ozanimod (Zeposia, Bristol Myers Squibb, Princeton, NJ, USA) is selective for S1P1 and S1P5 subtype receptors located in endothelial cells and oligodendrocytes respectively. The phase 2 TOUCHSTONE trial comparing two dosing regimens of Ozanimod with placebo showed Ozanimod 0.92 mg to be superior to placebo in inducing and maintaining remission in patients with UC (Sandborn et al, 2016).

The phase 3 True North trial showed clinical remission at week 10 was higher in 0.92 mg Ozanimod 18.4% vs placebo 6.0% ($p < 0.0001$). After induction Ozanimod treatment, efficacy in maintenance therapy at week 52 was 37% for Ozanimod vs 18.5% for placebo ($p < 0.0001$) (Sandborn et al, 2021). In patients who had prior TNF inhibitor exposure, the delta between Ozanimod and placebo for clinical remission and response was similar to the delta seen in unexposed patients (Sandborn et al, 2021).

The development program for CD has been halted after the primary endpoint for the induction study in the Phase 3 placebo-controlled YELLOWSTONE did not meet the primary endpoint.

Etrasimod

Etrasimod (Velsipity, Pfizer, New York, NY, USA) is selective for S1P4, in addition to S1P1 and S1P5. The Phase 3 ELEVATE UC 52 trial compared once daily 2 mg Etrasimod with placebo over a 12-week induction followed by a 40-week maintenance period (Sandborn et al, 2023). Symptomatic improvement (rectal bleeding and stool frequency sub scores) was seen as early as week 2. At week 12, clinical remission was 27% in Etrasimod vs 7% in placebo ($p < 0.0001$), and this was maintained at 52 weeks. All patients with remission at week 52 were corticosteroid free for at least 12 weeks. This trial showed that Etrasimod 2 mg is effective as an induction and maintenance therapy for patients with moderately to severe active UC (Sandborn et al, 2023).

There are ongoing phase 2/3 studies evaluating efficacy and safety in moderately to severely active CD.

Side Effects and Pre-Treatment Screening

Most side effects observed with S1P receptor modulators were mild or moderate, and they resolved upon cessation of treatment (Sandborn et al, 2016; Sandborn et al, 2023).

The TOUCHSTONE trial showed that patients had a mean reduction in their lymphocyte counts by 49%, which is consistent with the proposed mechanism of action (Sandborn et al, 2016). Furthermore, open label extension of TOUCHSTONE showed no long-term safety signals associated with Ozanimod and despite reduction in lymphocyte counts, there was no increased risk of serious or opportunistic infections (Sandborn et al, 2016). In ELEVATE 52, there were similar incidences of serious and opportunistic infections between the Etrasimod treatment group and placebo (Sandborn et al, 2023). With Etrasimod, 80% of patients' lymphocyte count returned to normal range within 2 weeks of cessation.

First-degree atrioventricular block and sinus bradycardia occurred in several patients in the Ozanimod and Etrasimod trials, all of whom had prior evidence of atrioventricular block and none required interventional treatment (Sandborn et al, 2016; Sandborn et al, 2020). Ozanimod requires a 7-day up-titration regime reaching full dose on day 8 to mitigate the bradycardia risk. Etrasimod does not require an up-titration regime.

Common side effects of Ozanimod include headaches, hypertension, nasopharyngitis, arthralgia and increase in liver enzymes (Sandborn et al, 2021). S1P receptor modulators have been associated with an increased risk of macular oedema (1 patient with Ozanimod; 2 patients with Etrasimod) which resolved after discontinuation (Sandborn et al, 2021; Sandborn et al, 2023).

Across the ELEVATE trials, 4 patients develop herpes zoster events that were mild or moderate (Sandborn et al, 2023).

Pre-Treatment Screening

Based on this data, pre-initiation screening is recommended, including full blood count, electrocardiogram to screen for conduction abnormalities, liver function tests, and confirmation of varicella immunity (with vaccination if serology is negative). For Ozanimod, ophthalmic evaluation is only required for those with prior history of diabetes, macular oedema or uveitis, while all patients treated with Etrasimod require macular examination within 3 months of starting treatment. Treatment is contra-indicated in those with recent heart problems or known atrioventricular block.

Special Situations

Acute Severe Ulcerative Colitis

Acute severe ulcerative colitis (ASUC) as defined by Truelove and Witts criteria ($\geq$6 blood stools per day with tachycardia, fever, anaemia and/or erythrocyte sedimentation rate/C-reactive protein (ESR/CRP) rise) is a potentially life-threatening, medical emergency (Truelove and Witts, 1955). Patients with ASUC require admission to a specialist unit for combined medical and surgical care to receive intravenous corticosteroids as initial treatment, but 30–40% of patients fail steroid therapy. Standard rescue therapy for steroid-refractory ASUC is infliximab or cyclosporine and trials have shown no significant difference between these two treatments in frequency of colectomy or quality-adjusted survival (Williams et al,

2016). When treatments fail, colectomy becomes the option, with rates around 20% during the first admission for ASUC. Therefore, there is a need for more medication treatment options.

There has been increasing interest to use the JAK inhibitors Tofacitinib and Upadacitinib in ASUC, given their rapid absorption and clearance, low immunogenicity and reduced susceptibility to drug loss (Dowty et al, 2014). JAKis may be positioned as rescue therapy or concomitant with iv steroids as an adjunct to first line treatment. A retrospective case-control study showed that Tofacitinib induction in biologic-experienced patients was protective against colectomy at 90 days compared to controls. This benefit was only observed in patients receiving 10 mg doses three times daily (Berinstein et al, 2021). A systematic review of pooled data for Tofacitinib as rescue therapy found colectomy-free survival rates of 85% at 30 days, 86% at 90 days and, 69% at 180 days (Steenholdt et al, 2023). In a systematic review of 55 patients using Upadacitinib as rescue therapy for ASUC showed a colectomy rate of 16.3% at 90-day. Among those who did not undergo colectomy, 80% achieved steroid-free remission at follow-up (Damianos et al, 2024).

A single-centre randomised controlled trial from India showed that Tofacitinib (10 mg thrice daily) used concomitantly with iv steroids as an adjunct first line treatment reduced the need for rescue therapy (odds ratio 0.27, 95% confidence interval 0.09–0.78, $p = 0.01$) (Singh et al, 2024).

Taken together, the data suggest Tofacitinib and Upadacitinib may be effective as rescue therapies for ASUC and may have a place in the treatment algorithm. However, this requires further investigation in randomised controlled trials.

Pregnancy and Breastfeeding

The peak incidence of IBD coincides with the peak age of fertility in young adults, which raises important considerations when selecting IBD treatments. Active IBD disease is associated with adverse pregnancy outcomes including intrauterine growth restriction, miscarriage and stillbirth (Lee et al, 2020). Additionally, there is an increased risk of relapse of ulcerative colitis during pregnancy and the post-partum period (Pedersen et al, 2013). This highlights the importance of achieving remission prior to conception and throughout pregnancy. However, many pregnancies are not planned and this needs to be accounted for when managing treatment for women of childbearing age.

Biologics with a large immunoglobulin structure cannot cross the placenta in the first trimester but are actively transported during the second and third trimesters (Cuffe and Selinger, 2024). Large-scale observation studies looking at the perinatal safety of biologics have shown good maternal and infant outcomes for infliximab, adalimumab, vedolizumab and Ustekinumab (Mahadevan et al, 2021). Biologic transmission into breast milk is minimal, with no observed negative effects on the infant (Torres et al, 2023). These biologics have been classed as low risk during pregnancy making them a good choice for women of childbearing age.

In contrast, due to their small size, SMDs passively cross the placenta at all stages of pregnancy and into breast milk (Honap et al, 2023). Animal studies showed the in-utero exposure to Filgotinib, Upadacitinib and Ozanimod led to loss

of pregnancy and was associated with significant teratogenicity (Monfared et al, 2023). This raises concern for exposure in unplanned pregnancies. There is very limited data on SMD exposure in pregnancy, but the available data has not shown the worrying safety signals from the animal models with 40% of pregnancies exposed to SMDs resulting in a healthy live birth (Monfared et al, 2023). However, this data mostly comes from accidental exposure in clinical trial settings which led to drug cessation and therefore minimal exposure. Therefore, until more data on pregnancies with significant exposure emerge, SMDs remain contra-indicated in pregnancy and breastfeeding. They should be avoided in patients wishing to conceive in the next 12 months given there are more appropriate alternatives such as biologics (Cuffe and Selinger, 2024).

Conclusion

SMDs provide effective alternatives to biologic treatment for patients with UC, while Upadacitinib is the only effective SMD for CD. Clinicians need to be aware that while there are similarities in safety profiles and screening, notable differences exist compared to biologics. With that in mind, SMDs provide a useful extension of the medical treatment options for patients with IBD.

Key Points

- SMDs provide an oral alternative medication to patients with IBD requiring advanced therapies.
- In contrast to biologics, and especially anti-TNF therapy, loss of response due to immunogenicity is not an issue with SMD therapy.
- SMDs, especially JAK inhibitors, have a rapid onset of action, often allowing for the avoidance of steroids during induction.
- JAK inhibitors have a unique safety profile and current regulator guidance requires consideration of cardiovascular, thromboembolic and malignancy risks prior to initiation.
- SMDs have been shown to be teratogenic in animal studies and are contraindicated during pregnancy and lactation.

Availability of Data and Materials

Not applicable.

Author Contributions

EG, NE, EMSO, KS and CS reviewed the literature. EG and NE wrote the draft article. EMSO, KS and CS critically reviewed the article. All authors contributed to important editorial changes in the manuscript. All authors read and approved the final version of the paper. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

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Conflict of Interest

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All other authors declare no conflict of interest.

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