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REVIEW ARTICLE

Novel pharmacological developments in the management of paediatric inflammatory bowel disease: Time for guideline update – A narrative review

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Aim: The incidence of paediatric inflammatory bowel disease (IBD) continues to increase in both adults and children across the globe, with more than one third of the patients not responding to anti-tumour necrosis factor biologics and immune modulators. This narrative review provides an overview of novel pharmacological developments in the management of paediatric IBD, including new biological therapies.

Methods: A PubMed Medline search was performed to include randomised controlled trials, retrospective and prospective observational studies, and relevant case reports of children with IBD published between 2018 and January 2023. Guidelines and protocols from relevant paediatric and adult gastroenterology societies, such as the European Society for Paediatric Gastroenterology, Hepatology and Nutrition and the European Crohn's and Colitis Organisation, were also included. Non-pharmacological treatments including therapeutic diets and faecal microbiota transplantation were outside the scope of this work.

Results: Early real-world evidence suggests that newer biologics and small molecules, such as anti-integrins, interleukin-12 and/or interleukin-23 inhibitors, Janus kinase and signal transducer and activator of transcription proteins inhibitors, are safe and effective in adult patients with IBD, with promising growing evidence for paediatric IBD.

Conclusion: While many developments have been achieved with novel pharmacological treatments to manage IBD, ongoing research is required to confirm their effectiveness and safety in the paediatric age. Extending the licence of novel treatments to children will be crucial to tackle the increasing loss of response to conventional treatments. International guidelines will require timely updating to incorporate novel treatments within the existing protocols.

Key words: biologic therapy; children; Crohn's disease; inflammatory bowel disease; novel treatments; ulcerative colitis.

Key Points

1 The incidence of paediatric inflammatory bowel disease (IBD) is rising globally, with more than a third of the patients not responding or losing response to conventional treatments of immune-modulators and anti-tumour necrosis factor biologics. Therefore, novel, safe and efficacious alternative treatment options are needed.
2 The use of newer pharmacological management options such as biological therapies and small molecules is expanding in adult IBD and is being explored for the management of paediatric IBD with preliminary encouraging data.
3 International guidelines and protocols will require timely updating to incorporate and re-position the expanding array of novel treatment options within the established protocols based on conventional treatments.

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Inflammatory bowel disease (IBD) is a chronic condition characterised by remitting and relapsing inflammation of the gastrointestinal tract. While IBD is increasingly understood to encompass a spectrum of phenotypes, the three main recognised categories that can be distinguished by their clinical presentation and how they affect the gastrointestinal tract are Crohn's disease (CD), ulcerative colitis (UC) and IBD-unclassified (IBD-U).[1] The aetiology of IBD is complex, with aspects such as altered immune responses, microbiota, environmental triggers and genetic factors understood to play a role.[2]

Incidence rates of childhood-onset IBD are dramatically increasing across the globe, with up to 25% of patients with IBD presenting before the age of 20.[3] Furthermore, special considerations must be given to patients who present with IBD during childhood, including growth, nutritional status, bone health, puberty and aspects related to mental health.[4]

Although the number of drugs approved by the US Food and Drug Administration (FDA) and the European Medicines Agency for adult IBD management has increased rapidly in recent years, it can take many more years until the same pharmacological agents are approved in children. This time lag means that there are fewer options for children with IBD compared to adults.[5]

Of the biological therapies available for use in adults with IBD, only infliximab and adalimumab are licensed for use in children. With up to one third of children with IBD not responding or losing response to anti-tumour necrosis factor (anti-TNF) biologics, randomised controlled trials and observational studies are currently under way to delineate the efficacy and safety of other, novel treatments in children and adolescents with IBD.

This narrative review aims to summarise the novel pharmacological developments in the treatment of paediatric IBD, reflecting the fast-paced advances in adult IBD from the past 5 years. This work is also an opportunity to update paediatricians on a changing landscape that will soon be leading to modifications of the existing international guidelines.

Materials and Methods

A PubMed Medline search using the key words 'paediatric/children', 'inflammatory bowel disease', 'Crohn's disease', 'ulcerative colitis', 'management', 'treatment', 'therapy', 'biologic', 'anti-integrin', 'IL-12 inhibitor', 'IL-23 inhibitor', 'JAK–STAT inhibitor', 'sphingosine-1-phosphate receptor modulator', 'immunosuppressant', 'diet', 'nutrition' and 'faecal microbiota transplantation' was performed.

Overall, 25 randomised controlled trials, 18 retrospective and prospective clinical observational studies, and 1 case report involving patients diagnosed with IBD aged <18 years published in English between January 2018 and January 2023, were included (Table S1). This research interval was chosen to enable a narrower focus that highlights the most recent changes in the pharmacological management options of paediatric IBD. Guidelines and protocols from relevant paediatric and adult gastroenterology societies, including the European Society for Paediatric Gastroenterology, Hepatology and Nutrition and the European Crohn's and Colitis Organisation, were included.

Where relevant, systematic reviews, meta-analyses, studies conducted prior to the inclusion period, and ongoing registered clinical trials, were also reviewed, such as studies involving adult IBD patients included to supplement information where paediatric data were limited.

Novel pharmacological management options

Non-anti-TNF biologics licensed in adults, such as vedolizumab and ustekinumab, are being increasingly used off-label in the management of IBD in children. Novel biologics and pharmacological therapies are also being explored in phase 2 or 3 trials in adults and are likely to become more commonly used in paediatric IBD in the near future. Nonetheless, data on safety, efficacy and pharmacokinetics of these therapies in the paediatric population remains limited. This section aims to highlight the key data and updates on various novel treatments that are unlicensed but increasingly used in the management in paediatric IBD.

Anti-integrins

Vedolizumab

Vedolizumab is a humanised monoclonal anti-integrin antibody that selectively blocks lymphocyte trafficking in the gastrointestinal tract without interfering with lymphocyte trafficking in the central nervous system (Fig. 1). Its mode of action involves inhibiting the $\alpha_4\beta_7$ integrin, a cell-surface glycoprotein expressed on B and T lymphocytes that interacts with mucosal addressin-cell adhesion molecule 1 (MAdCAM-1) expressed on endothelial cells.[6,7]

Vedolizumab was the first anti-integrin therapy specifically designed for gastroenterological use. Its safety in adult patients with IBD was demonstrated by the GEMINI trials and vedolizumab was approved for use in adult IBD in 2014.[8] Vedolizumab is also commonly used as an unlicensed therapy in paediatric-onset IBD, representing up to 9% of the biologics used in children with UC and 6% of those used in paediatric CD, with increasing understanding of its safety and efficacy in the paediatric population.[9]

The Phase 2 HUBBLE trial included 89 children with IBD and demonstrated the safety and efficacy of IV vedolizumab in inducing remission.[10] However, limitations to the methods and sample size meant the variance was too great to determine appropriate dosing, with further studies required to elucidate aspects related to paediatric dosing.[10]

The VEDOKIDS study by Atia *et al.*,[11] a prospective, multicentre, cohort study completed in 17 centres across 6 countries and including 142 children, investigated the real-life short and long-term safety, effectiveness, and dosage of vedolizumab as induction therapy in children with IBD. The outcomes and rates of clinical remission were better in UC compared to CD, in biologic-naïve children compared to the biologic-exposed group, and in those with lower baseline disease activity, in line with the data available from adult cohorts. No cases of death, malignancy, or progressive multifocal leukoencephalopathy were observed.

Overall, the VEDOKIDS study confirmed that vedolizumab is well-tolerated, has minimal serious side effects, and is effective in inducing remission of IBD in children, particularly in those with UC.[11] The same has also been confirmed by multiple retrospective cohort studies of children with IBD refractory to anti-TNF biologics.[7,11] Despite its gut-selectivity, studies assessing the effect of vedolizumab on the extra-intestinal manifestations of adult patients with IBD are mixed and remain unclear, with both positive and negative effects reported.[12]

Other anti-integrins

Etrolizumab is a gut-specific anti-β7 integrin monoclonal antibody that targets α4β7 and αEβ7 integrins. Various clinical trials, such as the GARDENIA, HIBISCUS I and II, LAUREL, HICKORY and BERGAMOT trials, have provided early evidence that etrolizumab is generally well-tolerated and is superior to placebo at inducing clinical remission in adults with CD and UC.[13,14] The same was confirmed by a phase 1 open-label trial of 24 children with moderate-to-severe UC and CD[15].

A small number of clinical trials have also assessed the effectiveness and safety of abrilumab, which targets α4β7, and AJM300, an oral α4 integrin antagonist, in adult patients.[16,17] More studies are needed to explore the role of these anti-integrin agents in paediatric IBD.

Interleukin (IL)-12 and IL-23 inhibitors

Ustekinumab

Ustekinumab is a monoclonal antibody that binds to the p40 subunit of interleukin (IL)-12 and IL-23, both of which are

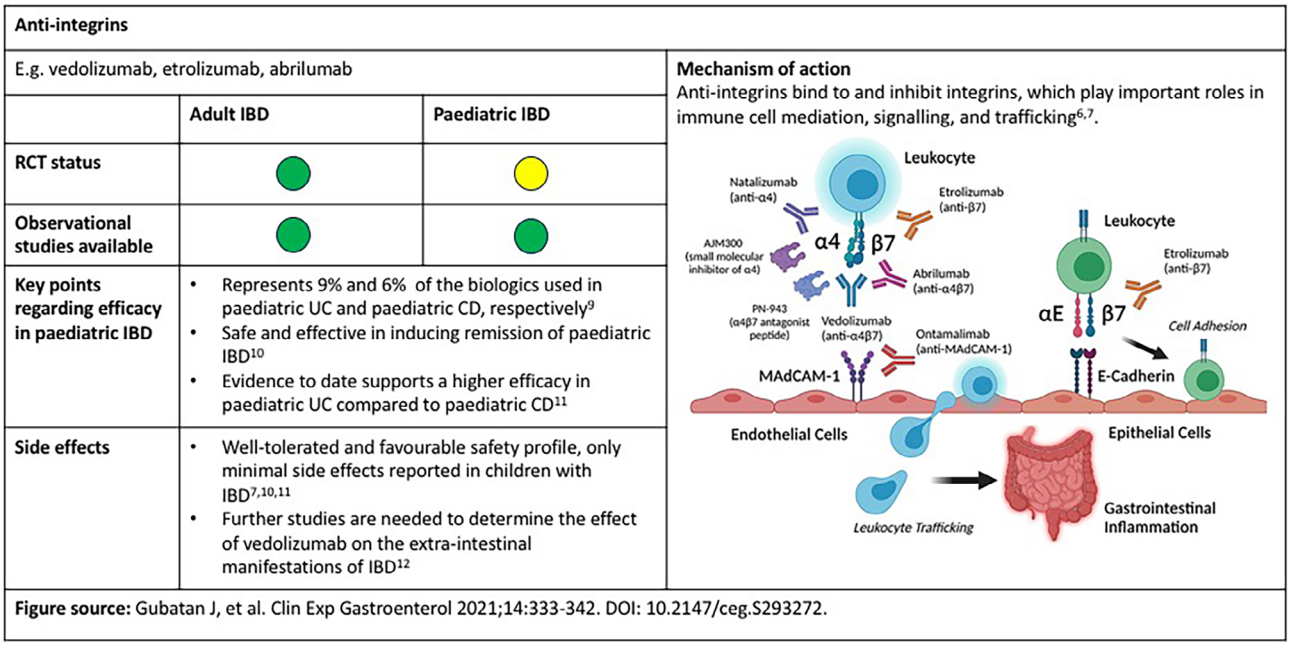

Fig. 1 A summary of the mechanism of action of anti-integrins and the current available evidence. (●), Studies completed and results published; (●), studies in progress, final results unpublished.

pro-inflammatory cytokines that modulate lymphocyte function and are associated with the pathogenesis of IBD (Fig. 2).[18] Ustekinumab is currently approved for use in adults with IBD who are refractory to anti-TNF therapy. The double-blind, placebo-controlled phase 3 UNITI and UNIFI trials demonstrated its safety and efficacy in inducing and maintaining clinical remission in adult patients with moderate-to-severe CD and UC, respectively.[19,20]

A multicentre retrospective cohort study by Chavannes *et al.*[21] evaluating the response of 44 children with refractory CD to ustekinumab, provided early evidence on its effectiveness in the paediatric age. Improvements in weight and BMI *Z*-scores at 12 months were also reported among children with growth failure at the time of starting ustekinumab therapy. Mild adverse events were reported in six patients (14%), including migraines, flares of scalp psoriasis, non-persistent bilateral feet paraesthesia and chronic rhinitis.[21]

Additionally, a phase 1 multicentre, double-blind clinical trial by Rosh *et al.*[22] undertaken to examine the safety, pharmacokinetics and efficacy of ustekinumab in 44 children with moderate-to-severe CD, identified lower ustekinumab concentrations in children weighing <40 kg.

Overall, current evidence suggests that ustekinumab has a favourable safety profile, with similar tolerability to adults with CD and psoriasis.[23] Clinical trials examining the safety and efficacy of ustekinumab on children with CD (UNITI Jr., REALITI)[24,25] and UC (UNIFI Jr.),[26] as well as trials investigating its long-term safety (UNITED)[27] and pharmacokinetics (STELARA)[28] are currently underway and will provide further data and insight in the near future.

Other IL-12 and IL-23 inhibitors

Other drugs with similar mechanisms of action to ustekinumab have more recently been developed. While ustekinumab targets p40, a molecule found on both IL-12 and IL-23, newer drugs, such as risankizumab, mirikizumab and guselkumab, target the p19 molecule found only on IL-23 and not IL-12 (Fig. 2). Although data remains preliminary, current early evidence, including randomised and placebo-controlled phase 2 and 3 trials, suggests that risankizumab,[29,30] guselkumab,[31] and mirikizumab[32,33] are well-tolerated and effective in inducing and maintaining remission in adults with moderate-to-severe IBD. Data related to the paediatric age remains limited.

Small molecules

Janus-kinase signal transducer and activator of transcription (JAK–STAT) inhibitors

The Janus-kinase signal transducer and activator of transcription (JAK–STAT) pathway plays an important role in the immune system, particularly the T helper cells.[34,35] JAK–STAT inhibitors are a class of immunomodulating agents that inhibit the activity of one or more of the JAK family of enzymes to interfere with the JAK–STAT pathway in lymphocytes (Fig. 3).[34,35]

Different JAK–STAT inhibitors have specific selectivities.[34] Table 1 summarises the key JAK–STAT inhibitors being used in the management of IBD and other immune-mediated conditions, and their targets.

Tofacitinib

Tofacitinib is a reversible competitive JAK inhibitor that targets the JAK1 and JAK3 pathways, and to a lesser extent the JAK2 pathway. It is currently licensed for use in adult patients with rheumatoid arthritis and UC. Tofacitinib is the first oral JAK–STAT inhibitor licensed for use in the USA, UK and Europe for adults with moderate-to-severe UC who are anti-TNF refractory,

IL-12 and IL-23 inhibitors

E.g. ustekinumab, risankizumab, guselkumab, mirikizumab

	Adult IBD	Paediatric IBD
RCT status	●	●
Observational studies available	●	●
Key points regarding efficacy in paediatric IBD	• Early evidence suggests ustekinumab may be effective in improving weight and BMI in children with IBD[21] • Clinical trials examining the safety and efficacy of ustekinumab on children with IBD are underway	
Side effects	• Early evidence suggests ustekinumab has a favourable safety profile in children with IBD[21-23] • Only mild adverse events reported in early clinical trials of children with IBD receiving ustekinumab[21]	

Mechanism of action

IL-12 and IL-23 inhibitors bind to the p40 subunit of IL-12 and IL-23, both of which are pro-inflammatory cytokines that modulate lymphocyte function and are associated with the pathogenesis of IBD[16].
Additionally, the p19 subunit can be specifically blocked by selective anti-p19 compounds[16].

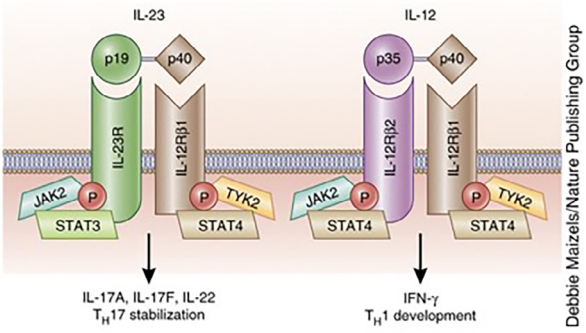

Figure source: Teng MW, et al. Nat Med 2015;21(7):719-29. DOI: 10.1038/nm.3895.

Fig. 2 A summary of the mechanism of action of IL-12 and IL-23 inhibitors and the current available evidence. (●), Studies completed and results published; (●), studies in progress, final results unpublished.

with data suggesting lower effectiveness in patients with CD.[36–38] Some of the advantages of tofacitinib include its short half-life of 3 h, which enables both a rapid onset of action and elimination, as well as the absence of an immunogenicity risk.[34–38]

The OCTAVE clinical trials provided further evidence of the safety and efficacy of tofacitinib in inducing and maintaining remission of UC.[38,39] In the OCTAVE Sustain trials of 593 participants, 34.3% of patients taking 5 mg BD of tofacitinib, and

Small molecules: JAK-STAT inhibitors

E.g. tofacitinib, filgotinib, upadacitinib, peficitinib, brepocitinib, TD-1473

	Adult IBD	Paediatric IBD
RCT status	●	●
Observational studies available	●	●
Key points regarding efficacy in paediatric IBD	• Early evidence suggests tofacitinib is safe and effective in delaying the need for colectomy and eliciting steroid-free remission in children with UC[40,41] • Currently limited data regarding the use of other JAK-STAT inhibitors in paediatric IBD[44-47]	
Side effects	• Further studies of the safety profile of tofacitinib are needed: while some studies report a favourable safety profile, others have described increased incidence of adverse events e.g. infections, cardiovascular events, and increased lipid levels[37-39]	

Mechanism of action

JAK-STAT inhibitors inhibit the activity of one or more of the JAK family of enzymes, interfering with the JAK-STAT pathway in lymphocytes[34,35]

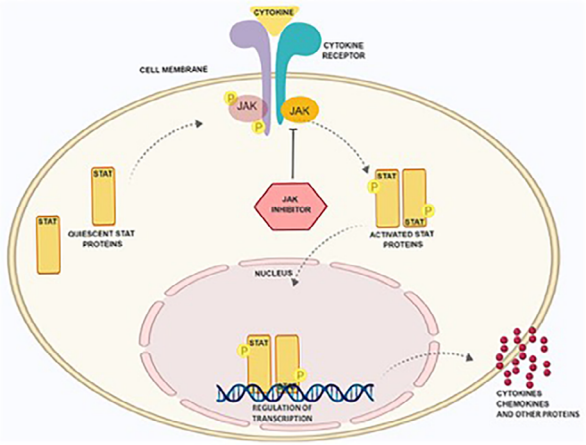

Figure source: Solimani F, et al. Front Immunol 2019;10:2847. DOI: 10.3389/fimmu.2019.02847.

Fig. 3 A summary of the mechanism of action ofJAK–STAT inhibitors and the current available evidence. (●), Studies completed and results published; (●), studies in progress, final results unpublished.

Table 1 Janus kinase and signal transducer and activator of transcription proteins (JAK–STAT) inhibitors used for inflammatory bowel disease and other immune-mediated conditions, and their specific targets[34]

JAK inhibitor	Target enzyme
Tofacitinib	JAK1, JAK3 JAK2 (lesser extent)
Filgotinib	Highly selective JAK1
Upadacitinib	JAK1
Peficitinib	JAK1, JAK3 JAK2 (lesser extent)
Brepocitinib	Tyk, JAK1
TD-1473	Pan-JAK

40.6% of those taking 10 mg BD achieved clinical remission at week 52, compared to 11.1% in the placebo group.[38]

While several studies report a favourable safety profile of tofacitinib, others have described an increased incidence of adverse events including increased rates of infections, herpes zoster, non-melanoma skin cancer, cardiovascular events and increased lipid levels.[37–39] Further studies of adverse events linked with tofacitinib are warranted.

A limited but growing amount of real-world evidence on the use of tofacitinib in children with UC is becoming available.[40,41] Two single-centre retrospective studies reported the safety and rapid efficacy of tofacitinib in corticosteroid- and anti-TNF-refractory children with UC in delaying the need for colectomy and eliciting a clinical response and/or steroid-free remission.[40,41] In addition, a small number of case reports of children with anti-TNF refractory moderate-to-severe UC successfully treated with 5 mg BD tofacitinib is available.[42,43]

Other JAK–STAT inhibitors

In addition to tofacitinib, other JAK–STAT inhibitors have recently completed or are currently undergoing clinical trials in adults with IBD, with preliminary or extrapolated data for children. Filgotinib is an oral JAK1-selective inhibitor that is administered once daily. The FITZROY phase 2 trial demonstrated that filgotinib had an acceptable safety and induced clinical remission in patients with moderate-to-severe CD at week 10.[44,45] The subsequent SELECTION phase 2b/3 trial showed that filgotinib was well-tolerated and effective in inducing and maintaining remission in patients with moderate-to-severe UC[45].

Upadacitinib is another oral selective JAK1 inhibitor with promising results from the initial studies. A phase 2, randomised, double-blind trial by Sandborn *et al.*[46] showed that upadacitinib was well-tolerated and successfully induced endoscopic remission in adults with CD. Studies investigating the use of upadacitinib in adults with moderate-to-severe UC also showed that upadacitinib was effective in inducing remission at week 8, with a favourable safety profile.[47]

Initial results regarding the use of JAK–STAT inhibitors are promising. As more data from adult IBD studies become available, paediatric studies evaluating the role of filgotinib, upadacitinib and other JAK–STAT inhibitors in children are now to be prioritised.

Sphingosine-1 phosphatase receptor modulators

Sphingosine-1 phosphatase (S1P) is a phospholipid produced by the phosphorylation of sphingosine by sphingosine kinase-1 or -2 (SphK1/2) that regulates cellular responses and contributes to the pathogenesis of inflammation in IBD. S1P receptor

Small molecules: Sphingosine-1 phosphatase receptor modulators

E.g. tofacitinib, filgotinib, upadacitinib, peficitinib, brepocitinib, TD-1473

	Adult IBD	Paediatric IBD
RCT status		
Observational studies available		
Key points regarding efficacy in paediatric IBD	• There is currently limited data regarding the use of sphingosine-1 phosphatase receptor modulators in paediatric IBD, however initial results from clinical trials of adults with IBD are promising[48]	
Side effects	• As more data from adult IBD studies become available, further data of the safety profiles of sphingosine-1 phosphatase receptor modulators in paediatric IBD will likely become available in the future	

Mechanism of action

Sphingosine-1 phosphatase (S1P) receptor modulators bind to and indirectly antagonise the S1P receptors expressed on the surface of lymphocytes to reduce the immune response

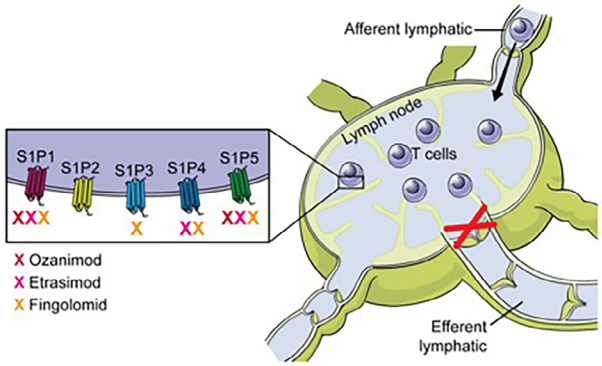

Figure source: Shukla T, et al. Curr Gastroenterol Rep 2019;21(5):22. DOI: 10.1007/s11894-019-0689-2.

Fig. 4 A summary of the mechanism of action of anti sphingosine-1 phosphate receptor molecules and the current available evidence. (●), Studies completed and results published; (●), studies in progress, final results unpublished; (●), data unavailable.

modulators are a class of biologics that bind to and indirectly antagonise the S1P receptors expressed on the surface of lymphocytes to sequester the lymphocytes within lymph nodes, thus dampening the immune response (Fig. 4). Currently used in the management of multiple sclerosis, the use of S1P receptor modulators, such as ozanimod, fingolimod, etrasimod and laquinimod, is currently being explored in clinical trials and studies for various autoimmune and inflammatory conditions, including IBD, with promising initial results in adults.[48] Studies to assess their safety and efficacy in children are also underway.

Discussion

Despite important, fast paced developments in the pharmacological management of adult IBD in the recent years, there remains a great need for safer and more effective treatments in children. The increasing incidence of paediatric IBD, the limitations of the current management options with up to one-third of the patients not responding or losing response to anti-TNF biologics, and the effects of uncontrolled disease and treatments on physical health and mental well-being, make developing new treatments for the paediatric age even more a key priority nowadays. While some medications are increasingly used off-licence in paediatric IBD, such as vedolizumab and ustekinumab, clear guidance regarding their use and appropriate dosing are often left to the physicians' discretion. Recent guideline review papers and position papers have included some of the newer biologics (i.e. anti-integrins and anti-IL12 and IL-23) in the management paediatric IBD. However, while their use is currently mainly recommended following loss of response or non-response to anti-TNF agents, the positioning of these newer agents is likely to change over time as more data becomes available.[49–52]

The time lag between when adult IBD therapies are eventually approved for use in children is mainly due to the challenges associated with conducting clinical trials in children compared to adults, such as smaller eligible patient cohorts, parental reluctance to enrol their children in clinical trials, and ethical concerns around using placebos.[5,53] The Paediatric IBD Network, a group of international paediatric IBD experts who met to publish a consensus process on how to best facilitate and optimise clinical drug trials for children with IBD, has provided specific recommendations to tackle these limitations.[53]

Moreover, as IBD is a lifelong condition with a relapsing and remitting course, children with IBD will eventually transition to adult care and will require ongoing care and management from the adult IBD multidisciplinary team. Updated, patient-centred guidelines on the optimal ways of transitioning patients from child to adult IBD care have become increasingly important as the number of children with IBD increases and therapeutic options expand.

Conclusion

This narrative review provides an overview of the novel pharmacological developments in the management of paediatric IBD. Tackling the time lag between the approval of new drugs for adult patients and licensing for the paediatric age is an absolute priority. With an expanding array of newer pharmacological agents becoming rapidly available, a timely update of the international guidelines will be required to incorporate recommendations based on the new evidence available within the conventional treatment protocols already in use.

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Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's web-site:

Table S1. Please scan the QR code above to access a table summarising the clinical trials and cohort studies of the pharmacological and non-pharmacological therapies used in paediatric IBD included in this narrative review.