Review

Therapeutic options for children and young people with moderate-to-severe ulcerative colitis

James Ashton [1], Kwang Yang Lee,[2] Anthi Thangarajah,[3] Astor Rodrigues,[4] Jochen Kammermeier [5]

[1]Paediatric Gastroenterology, University of Southampton, Southampton, UK
[2]Bristol Royal Hospital for Children, Bristol, UK
[3]Paediatric Gastroenterology, Chelsea and Westminster Hospital NHS Foundation Trust, London, UK
[4]Paediatric Gastroenterology, Oxford University Hospitals NHS Trust, Oxford, UK
[5]Pediatric Gastroenterology, Evelina London Children's Hospital, London, UK

Correspondence to
Dr Jochen Kammermeier; jochen.kammermeier@gstt.nhs.uk

Received 10 May 2024
Accepted 30 June 2024
Published Online First 13 July 2024

ABSTRACT

There are ever-increasing therapeutic options for patients with ulcerative colitis (UC), but licensing and availability for children and young people are often years behind those aged >18 years. 'Advanced therapies', including biologics and small molecules, now target numerous different inflammatory pathways but continue to have a therapeutic ceiling with only 30–60% of patients responding to initial therapies, although with patients achieving mucosal healing having improved long-term outcomes. Within this review, we synthesise the paediatric evidence for the medicines, including anti-tumour necrosis factor, anti-integrin, anti-interleukin-12/23 monoclonal antibodies, alongside Janus kinase (JAK)-inhibitors and Sphingosine-1-phosphate inhibitors, used in moderate-to-severe UC, and extrapolate the adult literature where paediatric data are lacking. Finally, we look at the potential for optimal use and sequencing of these therapies when they are used in an empirical algorithm and consider some of the longer-term implications of loss of response.

KEY POINTS

⇒ Conventional practice in paediatric ulcerative colitis is to escalate to an anti-tumour necrosis factor agent as first-line advanced therapy, with infliximab generally favoured over adalimumab.
⇒ Only two advanced therapies, infliximab and adalimumab, are licenced for use in patients with ulcerative colitis aged <16 years of age in the UK.
⇒ Recent UK data demonstrate widespread, but variable use of vedolizumab and ustekinumab in patients aged <18 years.
⇒ National funding for many other advanced therapies, including risankizumab and upadacitinib, is for post-pubertal children only, with some therapies not funded at a national level at all for those aged <16 years (ozanimod, etrasimod).
⇒ Careful consideration needs to be given to optimising therapies in paediatric onset patients, as they are likely to require 70+ years of treatment.
⇒ Sequencing of therapies remains challenging, with adalimumab, vedolizumab and ozanimod appearing to be less effective after previous infliximab exposure but ustekinumab, tofacitinib and upadacitinib remaining as effective.

INTRODUCTION

Over the last two decades, the therapeutic landscape for patients with ulcerative colitis (UC) has significantly evolved.[1] Since 2005, 11 biologics and novel small molecules have been licenced by the Food and Drug Administration and European Medicines Agency and are now endorsed by the National Institute of Clinical Excellence for use in adult patients with UC. Six of those were introduced over the last 5 years alone. This constitutes an opportunity for patients but also poses new challenges for physicians, particularly the sequencing of new drugs.[2] For paediatric inflammatory bowel disease (IBD) physicians, the access to novel IBD agents is significantly delayed, owing to the high, and sometimes unsurmountable thresholds set for paediatric licence approval.[3] To date, only two biologics (infliximab and adalimumab) are licenced for use in the paediatric population. This inequality has been raised by multiple stakeholders and paediatric-adjusted approaches to paediatric drug approval have been presented.[4] A recent UK-wide survey of the use of ustekinumab and vedolizumab in paediatric patients with IBD revealed significant variation in prescribing across different centres. It confirmed that overall

Check for updates

To cite: Ashton J, Lee KY, Thangarajah A, *et al*. *Frontline Gastroenterology* 2024;**15**:387–394.

Table 1 Summary of trials performed or underway in paediatric ulcerative colitis for medications within this review

Medication	Historical trial data	Planned/ongoing trials
Infliximab	IFX Kids (open-label phase 3)	
Adalimumab	ENVISION I (RCT)	
Golimumab	GOLI Kids (open label)	
Vedolizumab	HUBBLE (phase 2)	
Ustekinumab	None	A Study of Ustekinumab in Paediatric Participants With Moderately to Severely Active Ulcerative Colitis (UC)- NCT04630028
Mirikizumab	None	A Study of Mirikizumab (LY3074828) in Children and Teenagers With Ulcerative Colitis (UC)- NCT04004611
Tofacitinib	None	Evaluation of Oral Tofacitinib in Children Aged 2 to 17 Years Old Suffering From Moderate to Severe Ulcerative Colitis- NCT04624230
Upadacitinib	None	Study to Assess Adverse Events, Change in Disease Activity, and How Oral Upadacitinib Moves Through the Body of Paediatric Participants With Moderately to Severely Active Ulcerative Colitis- NCT05782907
Ozanimod/etrasimod	None	A Study Investigating Oral Ozanimod (RPC1063) in Paediatric Participants With Moderate to Severe Active Ulcerative Colitis- NCT05076175

off-label prescribing was highly prevalent, highlighting the unmet need to be able to access novel IBD drugs in paediatrics.[5] In 2018, the European Crohn's and Colitis Organisation (ECCO) and the Paediatric IBD Porto group of the European Society of Paediatric Gastroenterology, Hepatology and Nutrition published their latest reference guidelines for the management of UC in children.[6 7] The use of anti-tumour necrosis factor (TNF)-α biologics was reserved for patients with chronically active or steroid dependant UC failing to respond to 5-aminosalycilates and immunomodulators as well as in children with acute severe colitis and non-response after 5 days of intravenous steroid therapy. Vedolizumab was considered only in patients with prior anti-TNF-α failure.[6] We anticipate that over the next few years, multiple novel UC therapeutics will be licenced, or become widely available, for use in the paediatric population. Table 1 summarises the current landscape of paediatric trials for UC therapies.

In this review, we present advances in anti-TNF-α *therapies and discuss* emerging biologics and small molecules in the context of the available paediatric literature (figure 1). Furthermore, we explore where those novel drugs may be positioned in the therapeutic sequence of UC management in children, given that even recent adult guidelines have not commented on the positioning of therapies.[8]

Advances in anti-TNF-α therapeutics

Anti-TNF therapies are the best-established and most widely used biological agents in paediatric UC, consisting of infliximab (IFX), adalimumab (ADA) and golimumab (GLM). IFX is a chimeric (75% human and 25% murine) and ADA and GLM are fully human monoclonal antibodies. IFX was the first biologically licenced for inducing and maintaining remission in paediatric patients with UC but its usage is based largely on extrapolation of adult literature.[9] Among retrospective cohorts, Hyams *et al* reported corticosteroid-free remission, at 3, 6 and 12 months (26%, 27% and 28%, respectively).[9] Few studies addressed optimal IFX dosing for maintenance of remission in children with moderate-to-severe UC with the exception of Hyams *et al* who compared dosing intervals between 8 weeks and 12 weeks and concluding that 8 weekly dosing was more effective.[10] Additionally, the IFX Kids open-label, phase 3 trial of 60 patients confirmed the dosing of 5 mg/kg at 8 weeks was the most effective strategy, when compared with 12 weekly dosing.[11] In acute severe colitis, the indication for early use of IFX and dose intensification is established in paediatric practice.[7] In children, IFX increased clearance is associated with low body weight <40 kg, high body weight, low serum albumin, increased faecal loss, high inflammatory load and anti-drug antibodies.[12] After standard dosing, IFX drug levels in children can be 20–40% lower than in adult patients.[13] This is even more pronounced in younger children: In one study, 72% of patients younger than 10 years of age had suboptimal IFX trough levels (<5.4 µg/mL) at the start of maintenance (week 14) and were more likely to develop anti-drug antibodies within the first year.[14] Real-world data published so far has shown that subcutaneous IFX 2 weekly is as efficacious as intravenous IFX in adults, with more favourable pharmacokinetics, efficacy and improved quality of life.[15 16] Moreover, monotherapy subcutaneous IFX may provide comparable efficacy and immunogenicity to IFX-immunomodulator combination therapy, and lower prevalence of neutralising antibodies with no new safety signals.[15]

Results from the first ADA versus placebo randomised controlled trial (RCT) and the subsequent ULTRA 2 trial confirmed that ADA was superior to placebo in inducing and maintaining remission in anti-TNF-α naïve adult patients with moderate-to-severe UC.[17 18] Clinical remission rates were 21.3% versus 11% on

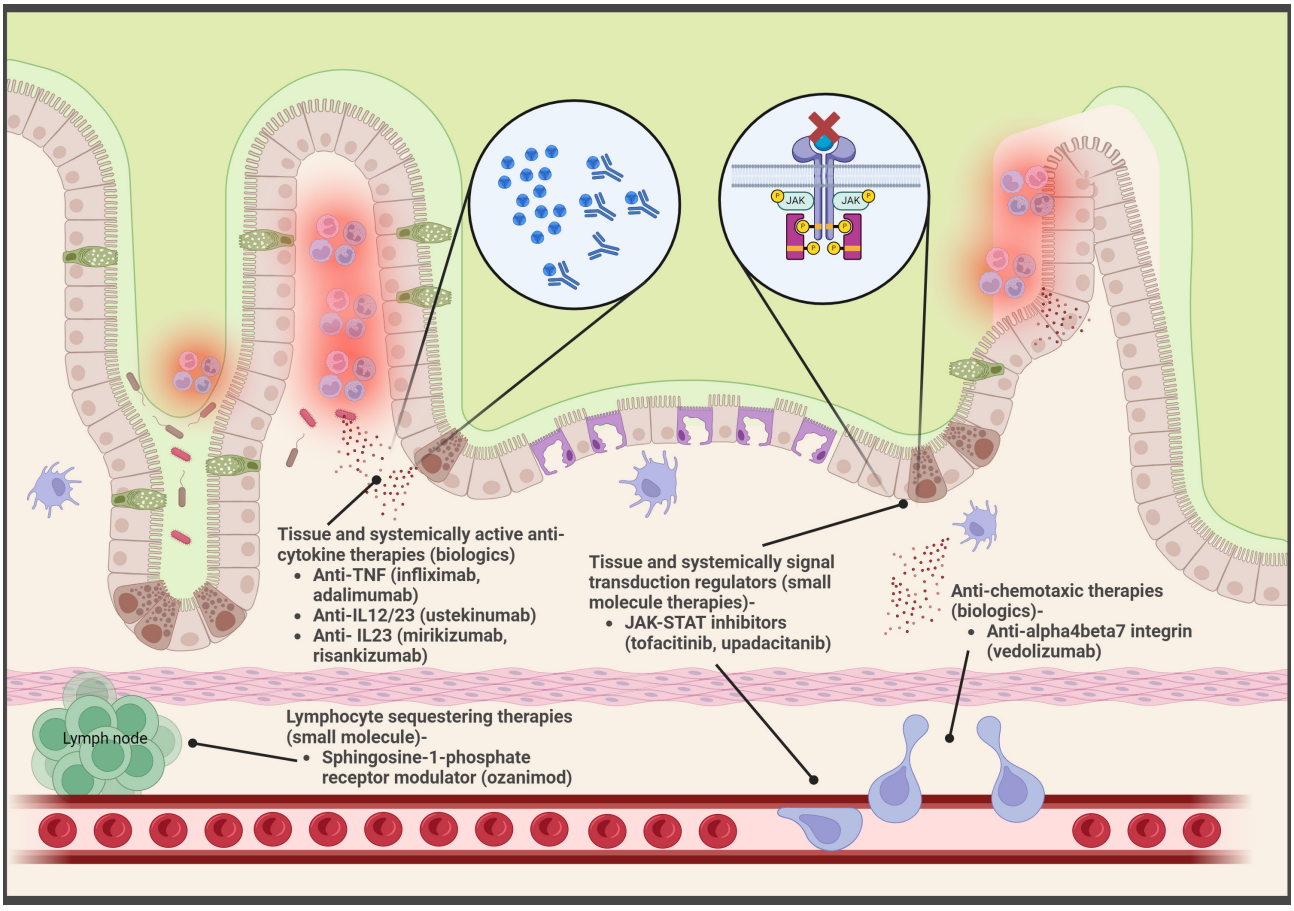

Figure 1 Schematic representation of the mechanism and site of action of the biological and small molecule therapies discussed within this article. Figure created with BioRender.com. IL, interleukin; JAK, Janus kinase; STAT, signal transducer and activator of transcription; TNF, tumour necrosis factor.

placebo at week 8 and 22% versus 12.4% at week 52. The SERENE UC trial evaluated the efficacy of high-dose ADA induction and maintenance regimens in adults with moderate-to-severe UC, with ADA responders at 8 weeks in the combined cohort more likely to achieve clinical remission at week 52 when treated with 40 mg every week (41%) versus every other week (30.1%).[19] ENVISION I is the only paediatric RCT of ADA in moderate-to-severe UC.[20] Children were randomised into high-dose or standard-dose induction. At week 8, high dose induction achieved significantly higher rates of patients in partial-mayo-score remission compared with placebo (60% vs 19.8%). Standard dosing versus placebo did not reach statistical significance (43% vs 19.8%, p=0.38). The full-mayo-score remission rate on high-dose maintenance at week 52 in children who were week 8 responders was 45% versus 18.4% of children on placebo. There have been no head-to-head trials of anti-TNF therapy in paediatric populations.

GLM has been the latest anti-TNF-*a* antibody available, licenced in 2013. There is very limited paediatric data on the use of GLM in children with UC: The PURSUIT PEDS PK long-term study led by Hyams et al studied GLM week 6 responders for 2 years.[21] Of 35 children, 21 responded at week 6 of whom 20 continued the long-term extension. At week 110, 50% of those were in clinical remission. The clinical remission rate of all enrolled patients at week 110 was 28.6%. Additional data from the GOLI Kids trial, an open-label phase 2 study demonstrated comparable pharmacokinetics to adult administration and response in biologically naïve patients.[22]

Advances in anti-integrin therapeutics

Vedolizumab is an anti-integrin $\alpha 4\beta 7$ monoclonal antibody that selectively blocks gut lymphocyte trafficking. It has been shown to be effective in UC in adults, with the GEMINI 1 study showing clinical remission in up to 44.8% of patients at week 52.[23] VARSITY, a head-to-head trial comparing vedolizumab with adalimumab in moderate-to-severe UC, showed higher rates of clinical remission at week 52 in the vedolizumab group compared with the adalimumab group (31.3% vs 22.5%).[24]

The use of vedolizumab in children is unlicensed, although use is common in UK paediatric IBD centres.[5] Evidence for efficacy in children is derived mainly from small retrospective and prospective cohort studies.[25–27] A systematic review of 10 retrospective cohort studies published in 2022 reported pooled clinical remission

rates of 36% at week 6, 48% at week 14 and 45% at week 52.[28] VEDOKIDS, a paediatric multicentre prospective cohort study, reported 42% steroid-free remission at week 14 and 60% at week 30 for paediatric patients with UC.[26 29] HUBBLE, a phase 2 randomised, double-blind, dose-ranging study, reported an overall clinical response rate (defined as a ≥20-point decrease from baseline in Paediatric Ulcerative Colitis Activity Index (PUCAI) score) of 63.4% and a clinical remission rate between 29.5% and 45.4% at week 14, in a small group of 44 paediatric patients with UC.[30]

In adults, switching from intravenous to subcutaneous vedolizumab has become an attractive option, saving time and travel expenses for patients, and freeing up capacity in day care units for hospitals.[31] This follows favourable results from the VISIBLE 1 study, showing subcutaneous vedolizumab to be effective maintenance therapy in UC. In this study, clinical remission was achieved at week 52 by 46.2%, 42.6% and 14.3% of patients in subcutaneous vedolizumab, intravenous vedolizumab and placebo groups, respectively.[32] As with the intravenous formulation, subcutaneous vedolizumab is also unlicensed in children, and there are so far no published reports of its use in children.

Vedolizumab has a well-established safety profile with no concerning safety signals.[33] Concerns of progressive multifocal leucoencephalopathy, as previously seen with natalizumab, a less selective anti-integrin therapy, have been unfounded.[34]

Advances in anti-IL12/23 therapeutics

Ustekinumab is a monoclonal antibody that binds to the p40 subunit shared by both interleukin (IL)-12 and interleukin-23, and prevents their interaction with their cell surface receptor protein IL-12Rb1 thus effectively targeting IL-12 (Th1)-mediated and IL-23 (Th17)-mediated cellular responses.

Its effectiveness was proven through the seminal UNIFI trial in which adult patients with moderate-to-severe UC were randomly assigned to receive an 8-week induction (intravenous or placebo) dose and those that had responded were randomised to receive 44 weeks of maintenance therapy as subcutaneous injections at varying intervals (12 or 8 weekly, or placebo).[35] Clinical remission (defined as a total score of ≤2 on the Mayo scale and no subscore >1 on any of the four Mayo scale components) was the primary end point in the induction and the maintenance arms and was significantly higher among patients who received ustekinumab versus placebo—15.6% versus 5.3% for the induction trial, and 38.4%–48.3% versus 24% in the maintenance trial. There was no difference in the incidence of serious adverse events with ustekinumab compared with placebo. Currently, there are no head-to-head trials of ustekinumab comparing it with another biological agent in UC.

Paediatric RCTs are lacking currently, however, a phase 3 study UNIFI Jr involving open-label intravenous induction treatment followed by randomised double-blind subcutaneous ustekinumab maintenance in paediatric participants with moderately to severely active UC is currently underway, aiming to complete recruitment by the end of 2025.[36] Although unlicensed in children under 18 years, several prospective and retrospective studies have reported on its efficacy and safety and have corroborated the findings of the UNIFI trial, with steroid-free clinical remission rates of around 40–50% at 1 year in previously bio-exposed patients, and without notable side effects.[37–39]

Six centres from The Canadian Children IBD Network reported their experience with ustekinumab in UC involving 25 children with conventional and biological refractory disease.[37] The primary endpoint of steroid-free clinical remission with subcutaneous ustekinumab at 52 weeks (Paediatric Ulcerative Colitis Activity Index <10, no steroids ≥4 weeks) was achieved in 44% of cases on an intention-to-treat basis. Trough levels were greater with 4 versus 8 weekly dosing, but greater exposure was not associated with a superior rate of clinical remission. No adverse events were associated with the therapy.

In another observational cohort study, 52 children and young adults with IBD most of whom had failed >1 biological therapy (81% anti-TNF refractory) initiating ustekinumab were analysed; 8% had UC and 11% IBD-unclassified (IBD-U), with the rest having Crohn's disease.[39] Patients were followed for a minimum of 12 months with the primary end point being steroid-free remission on subcutaneous ustekinumab. 50% (bio-exposed) and 90% (bio-naïve) were in steroid-free remission at the end of the year. Two infusion reactions, but neither serious adverse events nor serious infections were observed.

Similarly, the French multi-centre Paediatric GETAID studied 53 patients with IBD resistant to anti-TNF therapy, of which 5 (9.4%) had UC.[38] The average PUCAI at induction was 47 (25–65), 25 (15–40) at 3 months of treatment and 18.3 (0–35) at the last follow-up. No severe side effects were observed.

Fang *et al* conducted a systematic review evaluating the efficacy and safety of ustekinumab in paediatric IBD; 11 studies, comprising 370 patients were included.[40] For UC (UC)/IBD-U, the pooled steroid-free clinical remission rates were 24% (6/25) at 26 weeks and 46% (16/35) at 1 year with endoscopic remission of 63.6%. Serious adverse events were reported in 3.5% of patients. They concluded that according to low-quality evidence mainly from cohort studies and case series, approximately one-half of patients with UC/IBD-U achieved remission at 1 year, and that ustekinumab has a reasonable safety profile but dose optimisation is frequently required.

Mirikizumab is a biological therapy with selective targeting of the p19 subunit of IL-23. In a recently

published adult RCT mirikizumab demonstrated superiority to placebo at 12 and 40 weeks' follow-up, with remission rates of 24.2% versus 13.3% and 49.9% versus 25.1%, respectively.[41] No paediatric data are available. Risankizumab, a humanised monoclonal IgG1 class antibody, also acts by targeting the p19 subunit of IL-23. It is approved as an option for induction and maintenance therapy in patients over 16 years with moderately to severely active Crohn's disease following compelling data from RCTs.[42] Preliminary data from the head-to-head SEQUENCE trial appears to suggest the superiority of risankizumab over ustekinumab in patients with TNF-treated Crohn's disease.[43] The phase 3 INSPIRE (induction) and COMMAND (maintenance) trials for adults with UC are underway (ClinicalTrials.gov ID NCT03398135).

Advances in Janus kinase inhibition

The advent of small molecules that inhibit Janus kinase (JAKi) for treatment of IBD has seen rapid progression from a single approved agent for adults with UC to three agents with varying selectivity for the different JAK receptors. Tofacitinib, filgotinib and upadacitinib are now in widespread use for moderate-to-severe UC following positive initial RCT data.[44–46] Steroid-free remission rates at 1 year ranged from 27.2% to 68%, with upadacitinib reporting the best remission rates.[44–46] Data from these trials, and subsequent observational studies, demonstrates some of the potential advantages of these agents including no immunogenicity (no anti-drug antibody formation), rapid action of onset (1–3 days to response) and the ability to treat numerous co-existing autoimmune comorbidities (inflammatory arthritis, dermatological manifestations).[47] Data has begun to emerge on the efficacy of these agents to treat acute severe colitis, with comparable efficacy to steroids.[48]

These therapies are not without risk, and concerns around cardiovascular events and herpes zoster activation have been present since approval for rheumatoid arthritis.[49] However, according to ECCO, these data may be overstated in IBD populations, and close selection of (younger) patients and monitoring of additional cardiovascular risk factors should allow for safe use.[50]

None of these medicines are yet approved for use in paediatric UC, with trials ongoing in tofacitinib and upadacitinib.[47] There are retrospective reports of successful use of tofacitinib and upadacitinib in populations aged <18 years, demonstrating the ability of these drugs to induce and maintain remission in 40–92% of patients who had lost to response to conventional biological therapy.[51 52] No safety signals have been reported in the small studies published to date, but patient numbers are low. It appears that JAKi are an extremely promising class of therapy, with use beginning to lead to positive reports within paediatric age groups. Their current role as last-line rescue medicines may well progress to more front-line use, depending on trial and safety data, but for now, these seemingly effective drugs are reserved for the more/most severe paediatric cases.

Advances in sphingosine-1-phosphate receptor modulation (ozanimod, etrasimod)

These therapies target leucocyte trafficking by binding to sphingosine-1-phosphate receptors and preventing lymphoid cells moving from lymph tissue into the blood. Initially used as a therapy for relapsing multiple sclerosis, ozanimod has now been adopted for use in UC following positive RCT data published in 2021. This study reported induction of remission rates of 18.4% and maintenance of remission at 37%, with clinical response rates reported to be higher (47.8% and 60%, respectively).[53] Open-label extensions have demonstrated a good safety profile for this therapy, and added further evidence of longer-term stable response to these first-in-class medications.[54]

There is a paucity of data on the use of ozanimod in paediatric UC, with no reports in the literature to date. An RCT (ClinicalTrials.gov ID NCT05076175) has commenced but will not be imminently be reporting findings. Real-world data is likely to emerge prior to RCT evidence, but currently ozanimod would be seen as a final option in desperate

Table 2 Adverse effects and risks with different ulcerative colitis treatments

Medication	Observed side effects	Long-term risks/concerns
Anti-TNF therapy	Infusion reactions, headache, upper respiratory tract infection, diarrhoea, arthralgia.	Lymphoma, paradoxical psoriasis, tuberculosis or viral hepatitis reactivation, infections.
Anti-integrin therapy	Headache, upper respiratory tract infection, arthralgia.	Very few reported.
Anti-IL12/23 therapy	Infusion reactions, headache, upper respiratory tract infection, diarrhoea, arthralgia.	Infections.
JAK inhibitors	Temporary worsening of diarrhoea, headache.	Varicella reactivation, hypercholesterolaemia, infections, increased risk of cardiovascular events.
S1P receptor modulators	Nausea, arthralgia, headache.	Liver function abnormalities.

IL, interleukin; JAK, Janus kinase; S1P, sphingosine-1-phosphate; TNF, tumour necrosis factor .

situations for children with UC, although which patient cohorts would most likely benefit from this therapy remains to be seen.

Time to change our therapy approach in paediatric patient with moderate-to-severe UC?

In paediatric UC management, anti-TNF remains the first-line 'advanced therapy'. Contemporary approaches to optimisation of therapy, including proactive therapeutic drug monitoring and the potential for subcutaneous delivery of IFX are likely to provide further opportunities for outcome improvement.

Despite this, extrapolation from adult head-to-head trials are beginning to add uncertainty as to the optimal sequencing of advanced therapies. Although currently unlicenced in paediatric populations, vedolizumab has demonstrated superiority over adalimumab in achieving clinical remission (31.2% vs 22.5%), although the adalimumab dosing may have been too conservative for a true comparison.[24]

Indirect comparison of therapies, through network meta-analysis, may also reveal some insights into the potential head-to-head efficacy, although some caution should be exercised as trials are often extremely heterogeneous. In recent work from Burr *et al*, upadacitinib and infliximab appeared to be superior at inducing and maintaining clinical and endoscopic remission, although vedolizumab had the best safety profile and was mid-ranked for efficacy.[55] We have summarised the main safety considerations in table 2. An additional consideration in sequencing of therapies is the potential to capture remission after prior use of other advanced therapies. Paediatric patients with UC having been frequently exposed to anti-TNF therapy and data extrapolated from adult studies indicate that adalimumab, vedolizumab and ozanimod are less effective after prior anti-TNF (infliximab) exposure but ustekinumab, tofacitinib and upadacitinib were not less effective.[2] If we were to consider adult guidelines as a basis for paediatric practice, the American Gastroenterology Association recommends infliximab or vedolizumab as the first line, but the European Crohn's and Colitis Organisation does not favour a specific treatment.[56 57] Beyond simple sequencing of therapies, the possibility of quick-acting JAKi as bridges to more stable and safe biologics may be a future consideration, thus providing a steroid-sparing therapy in children in whom growth and nutrition need optimisation.[47] We have not discussed the role or place of dual advanced therapies, or the UC exclusion diet, in this work, but interest and evidence will begin to emerge to better understand the role of these experimental treatment strategies.

It appears increasingly clear that there are suboptimal remission rates for almost all advanced therapies, likely related to the underlying immunogenetic drivers of disease in an individual patient.[58] We are not yet at the point to personalise therapeutic agents for a patient, but neither is the evidence clear about which empirical treatment algorithm we should follow. The best use of treatments is also constrained by paediatric licensing and availability issues, where we lag behind adult colleagues in accessing therapies for our patients. To optimise patient outcomes, we must advocate for high-quality paediatric evidence, incorporate children into head-to-head trials and attempt to standardise treatment algorithms to better interpret real-world data.

X James Ashton @James_Ashton

Contributors JA, KYL, AT, AR and JK wrote sections of the article and conducted the literature review. JA and JK finalised the article. JA produced the tables and figures. All authors approved the final article. JK/JA act as guarantor of the article.

Competing interests JA is a scientific advisory board member of Orchard Therapeutics. No other conflicts are declared.

Patient consent for publication Not applicable.

Ethics approval Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

ORCID iDs
James Ashton http://orcid.org/0000-0003-0348-8198
Jochen Kammermeier http://orcid.org/0000-0002-6046-8727

REFERENCES

1 Baumgart DC, Le Berre C. Newer biologic and small-molecule therapies for inflammatory bowel disease. *N Engl J Med* 2021;385:1302–15.
2 Bressler B. Is there an optimal sequence of biologic therapies for inflammatory bowel disease. *Therap Adv Gastroenterol* 2023;16.
3 Crowley E, Ma C, Andic M, *et al*. Impact of drug approval pathways for paediatric inflammatory bowel disease. *J Crohns Colitis* 2022;16:331–5.
4 Croft NM, de Ridder L, Griffiths AM, *et al*. Paediatric inflammatory bowel disease: a multi-stakeholder perspective to improve development of drugs for children and adolescents. *J Crohns Colitis* 2023;17:249–58.
5 Auth MK-H, Ashton JJ, Jones KDJ, *et al*. Variation in access and prescription of vedolizumab and Ustekinumab in paediatric patients with inflammatory bowel disease: a UK-wide study. *Arch Dis Child* 2023;108:994–8.
6 Turner D, Ruemmele FM, Orlanski-Meyer E, *et al*. Management of paediatric ulcerative colitis, part 1: ambulatory care-an evidence-based guideline from European Crohn's and colitis organization and European society of paediatric gastroenterology. *J Pediatr Gastroenterol Nutr* 2018;67:257–91.
7 Turner D, Ruemmele FM, Orlanski-Meyer E, *et al*. Management of paediatric ulcerative colitis, part 2: acute severe colitis-an evidence-based consensus guideline from the European Crohn's and colitis organization and the European society of Paediatric Gastroenterology,Hepatology and nutrition. *J Pediatr Gastroenterol Nutr* 2018;67:292–310.
8 Lamb CA, Kennedy NA, Raine T, *et al*. British society of gastroenterology consensus guidelines on the management of inflammatory bowel disease in adults. *Gut* 2019;68:s1–106.
9 Hyams JS, Lerer T, Griffiths A, *et al*. Outcome following Infliximab therapy in children with ulcerative colitis. *Am J Gastroenterol* 2010;105:1430–6.
10 Hyams J, Damaraju L, Blank M, *et al*. Induction and maintenance therapy with Infliximab for children with

moderate to severe ulcerative colitis. *Clin Gastroenterol Hepatol* 2012;10:391–9.
11 Adedokun OJ, Xu Z, Padgett L, *et al*. Pharmacokinetics of Infliximab in children with moderate-to-severe ulcerative colitis: results from a randomized, multicenter, open-label, phase 3 study. *Inflamm Bowel Dis* 2013;19:2753–62.
12 Dotan I, Ron Y, Yanai H, *et al*. Patient factors that increase Infliximab clearance and shorten half-life in inflammatory bowel disease: a population pharmacokinetic study. *Inflamm Bowel Dis* 2014;20:2247–59.
13 Fasanmade AA, Adedokun OJ, Blank M, *et al*. Pharmacokinetic properties of Infliximab in children and adults with Crohn's disease: a retrospective analysis of data from 2 phase III clinical trials. *Clin Ther* 2011;33:946–64.
14 Jongsma MME, Winter DA, Huynh HQ, *et al*. Infliximab in young paediatric IBD patients: it is all about the dosing. *Eur J Pediatr* 2020;179:1935–44.
15 Schreiber S, Ben-Horin S, Leszczyszyn J, *et al*. Randomized controlled trial: subcutaneous vs intravenous Infliximab CT-P13 maintenance in inflammatory bowel disease. *Gastroenterology* 2021;160:2340–53.
16 Smith PJ, Critchley L, Storey D, *et al*. Efficacy and safety of elective switching from intravenous to subcutaneous Infliximab [CT-P13]: a multicentre cohort study. *J Crohns Colitis* 2022;16:1436–46.
17 Reinisch W, Sandborn WJ, Hommes DW, *et al*. Adalimumab for induction of clinical remission in moderately to severely active ulcerative colitis: results of a randomised controlled trial. *Gut* 2011;60:780–7.
18 Sandborn WJ, van Assche G, Reinisch W, *et al*. Adalimumab induces and maintains clinical remission in patients with moderate-to-severe ulcerative colitis. *Gastroenterology* 2012;142:257–65.
19 Panés J, Colombel J-F, D'Haens GR, *et al*. Higher vs standard adalimumab induction and maintenance dosing regimens for treatment of ulcerative colitis: SERENE UC trial results. *Gastroenterol* 2022;162:1891–910.
20 Croft NM, Faubion WA, Kugathasan S, *et al*. Efficacy and safety of Adalimumab in Paediatric patients with moderate-to-severe ulcerative colitis (ENVISION I): a randomised, controlled, phase 3 study. *Lancet Gastroenterol Hepatol* 2021;6:616–27.
21 Hyams JS, O'Brien CD, Padgett L, *et al*. Maintenance Golimumab treatment in pediatric UC patients with moderately to severely active UC: PURSUIT PEDS PK long-term study results. *Crohn's & Colitis 360* 2020;2:1–10.
22 Hyams JS, Chan D, Adedokun OJ, *et al*. Subcutaneous Golimumab in pediatric ulcerative colitis: pharmacokinetics and clinical benefit. *Inflamm Bowel Dis* 2017;23:2227–37.
23 Feagan BG, Rutgeerts P, Sands BE, *et al*. Vedolizumab as induction and maintenance therapy for ulcerative colitis. *N Engl J Med* 2013;369:699–710.
24 Sands BE, Peyrin-Biroulet L, Loftus EV Jr, *et al*. Vedolizumab versus Adalimumab for moderate-to-severe ulcerative colitis. *N Engl J Med* 2019;381:1215–26.
25 Ledder O, Assa A, Levine A, *et al*. Vedolizumab in Paediatric inflammatory bowel disease: a retrospective multi-centre experience from the Paediatric IBD Porto group of ESPGHAN. *J Crohns Colitis* 2017;11:1230–7.
26 Atia O, Shavit-Brunschwig Z, Mould DR, *et al*. Outcomes, dosing, and predictors of Vedolizumab treatment in children with inflammatory bowel disease (VEDOKIDS): a prospective, multicentre cohort study. *Lancet Gastroenterol Hepatol* 2023;8:31–42.
27 Hajjat TM, Mosha M, Whaley KG, *et al*. Vedolizumab experience in children and adolescents with inflammatory bowel disease: a multicenter observational study. *Crohn's & Colitis 360 -> Crohn's & Colitis 360* 2021;3:1–8.
28 Fang S, Song Y, Zhang C, *et al*. Efficacy and safety of Vedolizumab for pediatrics with inflammatory bowel disease: a systematic review. *BMC Pediatr* 2022;22:175.
29 Atia O, Shavit-Brunschwig Z, Quteineh A, *et al*. P774 maintenance treatment with Vedolizumab in children with inflammatory bowel disease: follow-up results from the prospective multicenter VEDOKIDS study. *J Crohns Colitis* 2023;17:i904–5.
30 Hyams JS, Turner D, Cohen SA, *et al*. Pharmacokinetics, safety and efficacy of intravenous Vedolizumab in paediatric patients with ulcerative colitis or Crohn's disease: results from the phase 2 HUBBLE study. *J Crohns Colitis* 2022;16:1243–54.
31 Ventress E, Young D, Rahmany S, *et al*. Transitioning from intravenous to subcutaneous Vedolizumab in patients with inflammatory bowel disease. *J Crohns Colitis* 2022;16:911–21.
32 Sandborn WJ, Baert F, Danese S, *et al*. Efficacy and safety of Vedolizumab subcutaneous formulation in a randomized trial of patients with ulcerative colitis. *Gastroenterology* 2020;158:562–72.
33 Loftus EV Jr, Feagan BG, Panaccione R, *et al*. Long-term safety of Vedolizumab for inflammatory bowel disease. *Aliment Pharmacol Ther* 2020;52:1353–65.
34 Honap S, Netter P, Danese S, *et al*. An update on the safety of long-term Vedolizumab use in inflammatory bowel disease. *Expert Opin Drug Saf* 2023;22:767–76.
35 Sands BE, Sandborn WJ, Panaccione R, *et al*. Ustekinumab as induction and maintenance therapy for ulcerative colitis. *N Engl J Med* 2019;381:1201–14.
36 A study of Ustekinumab in pediatric participants with moderately to severely active ulcerative colitis (UC) - full text view - Clinicaltrials.Gov. Available: https://classic.clinicaltrials.gov/ct2/show/NCT04630028 [Accessed 3 Apr 2024].
37 Dhaliwal J, McKay HE, Deslandres C, *et al*. One-year outcomes with Ustekinumab therapy in Infliximab-refractory paediatric ulcerative colitis: a multicentre prospective study. *Aliment Pharmacol Ther* 2021;53:1300–8.
38 Koudsi M, Martinez-Vinson C, Pigneur B, *et al*. Ustekinumab use in pediatric inflammatory bowel disease: a French multicenter study from the pediatric GETAID. *J Pediatr Gastroenterol Nutr* 2023;76:763–70.
39 Dayan JR, Dolinger M, Benkov K, *et al*. Real world experience with Ustekinumab in children and young adults at a tertiary care pediatric inflammatory bowel disease center. *J pediatr gastroenterol nutr* 2019;69:61–7.
40 Fang S, Zhang S, Zhang C, *et al*. Effectiveness and safety of Ustekinumab for pediatric inflammatory bowel disease: a systematic review. *Paediatr Drugs* 2023;25:499–513.
41 D'Haens G, Dubinsky M, Kobayashi T, *et al*. Mirikizumab as induction and maintenance therapy for ulcerative colitis. *N Engl J Med* 2023;388:2444–55.
42 D'Haens G, Panaccione R, Baert F, *et al*. Risankizumab as induction therapy for Crohn's disease: results from the phase 3 ADVANCE and MOTIVATE induction trials. *Lancet* 2022;399:2015–30.
43 Peyrin-Biroulet L, Bossuyt P, Regueiro M, *et al*. Dop10 Risankizumab versus Ustekinumab for the achievement of endoscopic outcomes in patients with moderate-to-severe Crohn's disease: results from the phase 3B SEQUENCE trial. *J Crohns Colitis* 2024;18:i90–1.
44 Sandborn WJ, Su C, Sands BE, *et al*. Tofacitinib as induction and maintenance therapy for ulcerative colitis. *N Engl J Med* 2017;376:1723–36.
45 Danese S, Vermeire S, Zhou W, *et al*. Upadacitinib as induction and maintenance therapy for moderately to severely active ulcerative colitis: results from three phase 3, multicentre, double-blind, randomised trials. *Lancet* 2022;399:2113–28.
46 Feagan BG, Danese S, Loftus EV Jr, *et al*. Filgotinib as induction and maintenance therapy for ulcerative colitis

(SELECTION): a phase 2B/3 double-blind, randomised, placebo-controlled trial. *Lancet* 2021;397:2372–84.
47 Honap S, Agorogianni A, Colwill MJ, *et al*. JAK inhibitors for inflammatory bowel disease: recent advances. *Frontline Gastroenterol* 2024;15:59–69.
48 Steenholdt C, Dige Ovesen P, Brynskov J, *et al*. Tofacitinib for acute severe ulcerative colitis: a systematic review. *J Crohns Colitis* 2023;17:1354–63.
49 Ytterberg SR, Bhatt DL, Mikuls TR, *et al*. Cardiovascular and cancer risk with tofacitinib in rheumatoid arthritis. *N Engl J Med* 2022;386:316–26.
50 Agrawal M, Kim ES, Colombel JF. JAK inhibitors safety in ulcerative colitis: practical implications. *J Crohns Colitis* 2020;14:S755–60.
51 Bergstein S, Spencer E. Single center experience with upadacitinib for refractory pediatric inflammatory bowel disease. Gastroenterol 2023;164:S79.
52 Moore H, Dubes L, Fusillo S, *et al*. Tofacitinib therapy in children and young adults with pediatric-onset medically refractory inflammatory bowel disease. *J Pediatr Gastroenterol Nutr* 2021;73:e57–62.
53 Sandborn WJ, Feagan BG, D'Haens G, *et al*. Ozanimod as induction and maintenance therapy for ulcerative colitis. *N Engl J Med* 2021;385:1280–91.
54 Sandborn WJ, Feagan BG, Hanauer S, *et al*. Long-term efficacy and safety of ozanimod in moderately to severely active ulcerative colitis: results from the open-label extension of the randomized, phase 2 TOUCHSTONE study. *J Crohns Colitis* 2021;15:1120–9.
55 Burr NE, Gracie DJ, Black CJ, *et al*. Efficacy of biological therapies and small molecules in moderate to severe ulcerative colitis: systematic review and network meta-analysis. *Gut* 2022;71:1976–87.
56 Raine T, Bonovas S, Burisch J, *et al*. ECCO guidelines on therapeutics in ulcerative colitis. *J Crohns Colitis* 2022;16:2–17.
57 Feuerstein JD, Isaacs KL, Schneider Y, *et al*. AGA clinical practice guidelines on the management of moderate to severe ulcerative colitis. *Gastroenterol* 2020;158:1450–61.
58 Raine T, Danese S. Breaking through the therapeutic ceiling: what will it take. *Gastroenterol* 2022;162:1507–11.