World Journal of Gastroenterology

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World J Gastroenterol 2017 August 14; 23(30): 5469-5485

DOI: 10.3748/wjg.v23.i30.5469

ISSN 1007-9327 (print) ISSN 2219-2840 (online)

MINIREVIEWS

Treating children with inflammatory bowel disease: Current and new perspectives

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Author contributions: Guariso G and Gasparetto M contributed equally to this work in respect to designing the review, contributing to the manuscript with intellectual content, writing the paper and final approval of the version to be published.

Conflict-of-interest statement: No potential conflicts of interest. No financial support.

Manuscript source: Invited manuscript

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Received: February 26, 2017
Peer-review started: February 28, 2017
First decision: April 7, 2017
Revised: June 2, 2017
Accepted: July 22, 2017
Article in press: July 24, 2017
Published online: August 14, 2017

Abstract

Inflammatory bowel disease (IBD) is a chronic inflammatory condition of the gut characterised by alternating periods of remission and relapse. Whilst the mechanism underlying this disease is yet to be fully understood, old and newer generation treatments can only target selected pathways of this complex inflammatory process. This narrative review aims to provide an update on the most recent advances in treatment of paediatric IBD. A MEDLINE search was conducted using "paediatric inflammatory bowel disease", "paediatric Crohn's disease", "paediatric ulcerative colitis", "treatment", "therapy", "immunosuppressant", "biologic", "monitoring" and "biomarkers" as key words. Clinical trials, systematic reviews, and meta-analyses published between 2014 and 2016 were selected. Studies referring to earlier periods were also considered in case the data was relevant to our scope. Major advances have been achieved in monitoring the individual metabolism, toxicity and response to relevant medications in IBD including thiopurines and biologics. New biologics acting on novel mechanisms such as selective interference with lymphocyte trafficking are emerging treatment options. Current research is investing in the development of reliable prognostic biomarkers, aiming to move towards personalised treatments targeted to individual patients.

Key words: Paediatric inflammatory bowel disease; Crohn's disease; Ulcerative colitis; Treatment; Therapy; Immunosuppressant; Biologic; Monitoring; Biomarker

Core tip: This narrative review summarises the current practice in treating children with inflammatory bowel disease (IBD) and explores the new advances and future aims. A particular focus of the review are the peculiarities of the paediatric age in respect to the standard practice in adult patients with IBD. Whilst the cause of this condition remains only partly understood, a significant proportion of children does not respond to the treatment options currently available. Developing

new treatments is therefore a key target. Major advances have already been achieved in therapeutic drug monitoring.

Guariso G, Gasparetto M. Treating children with inflammatory bowel disease: Current and new perspectives. *World J Gastroenterol* 2017; 23(30): 5469-5485 Available from: URL: http://www.wjgnet.com/1007-9327/full/v23/i30/5469.htm DOI: http://dx.doi.org/10.3748/wjg.v23.i30.5469

INTRODUCTION

Inflammatory bowel disease (IBD) is a chronic inflammatory condition of the gut characterized by alternating periods of remission and relapse[1].

It comprises Crohn's disease (CD), ulcerative colitis (UC) and IBD-Unclassified (IBD-U), and its incidence has increased steadily worldwide, particularly in Western countries[2-4]. The disease affects both children and adults, with current estimated prevalence of 2.6 million people in Europe and 1.2 million in North America[5]. Approximately 25% of IBD patients are diagnosed before the age of 18[6]. Given that a cure for IBD hasn't been developed so far, treatments currently available are mainly aimed to induce and maintain remission. Therapeutic options include corticosteroids which have shown up to 80% efficacy in inducing remission in patients with CD. Other immunomodulators used for the treatment of IBD include thiopurines [*i.e.*, azathioprine (AZA) and 6-mercaptopurine], methotrexate (MTX) and biological treatments such as anti-tumour necrosis factor (anti-TNFa) therapies like infliximab (IFX) and adalimumab (ADA)[5].

CD is characterized by focal, patchy, transmural and granulomatous inflammation and it can affect any part of the intestinal tract as well as extra-intestinal tissue[4]. Peak age of diagnosis of CD is between 12 and 25[7].

Due to its typical onset in the young age and to the chronicity of the disease, medical treatment remains the cornerstone in CD, with most patients requiring lifelong therapy[4]. Whilst for CD surgery is generally an option restricted to patients resistant to maximised medical treatments or with specific complications, approximately 75% of patients with CD will eventually undergo surgical resection[4,8]. Nevertheless, according to the current epidemiology data available, up to 73% of these patients will experience endoscopic recurrence of disease at one year post surgery and 22% to 55% will have a clinical relapse at five years[8].

UC mainly involves the large bowel mucosa, with inflammation extending proximally from the rectum in a continuous fashion. In approximately 80% of children, the disease extent is proximal to the splenic flexure, whereas in adults it's more frequently left sided. Prolonged severe inflammation of the colonic mucosa is a known risk factor for the development of colorectal carcinoma[9].

Currently, proven medical treatment of paediatric UC is limited to a few options, including amino-salicylates, corticosteroids and thiopurines. More recently, anti-TNF agents have been established for the management of patients with UC who are refractory to conventional medical treatment[10]. Choice of therapy is mainly based on disease extension and severity of inflammation. Up to 25% of the total patients with UC currently require a colectomy because of ongoing, severe inflammation, unresponsive to medical therapy, or when the disease is steroid-dependent[11].

When a child is diagnosed with IBD, achieving early remission has a positive impact on normal child growth and development, long-term remission and quality of life, thus reducing the psychological burden[2]. Children tend to present with a more aggressive course of IBD, therefore immunomodulators and biological treatments are used extensively[2].

Achieving satisfactory nutritional status and reaching growth target should be one of the focuses in paediatric IBD. In fact, nutritional concerns are still common in children with CD (up to 65%-75% of cases) who are often underweight at presentation[3,6,12]. Even in the longer term, despite current treatment strategies for CD including biologics, short stature and slow growth are still encountered in paediatric CD.

Whilst an early diagnosis is pivotal to minimize growth deficiency, the signs of CD onset vary and can easily go unnoticed, causing growth deficiency and pubertal delay to precede the intestinal manifestations of the disease[12].

Poor bone health, delayed puberty, and growth failure may go on to complicate these patients' clinical management[2,6,12].

The pharmacokinetics (PK) and pharmacodynamics of drugs in children are different from those in adults and the approach to paediatric drug dosing needs to be based on the physiological characteristics of the child and the pharmacokinetic parameters of the drug[13].

Current European Medicines Agency (EMA) and United States Food and Drug Administration (FDA) guidance recommends that dose selection for paediatric studies is based on extensive and detailed prior information, starting with what has been learnt in adult populations[14]. Paediatric pharmacometric approaches are increasingly being applied to drugs already in use, but that remain unlicensed and off-label in children[14]. There are multiple factors contributing towards the pathogenesis of IBD, and the whole mechanism is yet to be entirely defined in its complexity. Current hypotheses suggest the host's genetic profile, immune system and environmental factors such as the gut microbiota as possible key factors[3].

IBD may develop from a chain of events involving alteration in the microbiome, increase in intestinal permeability leading to bacterial translocation, and

subsequent activation of the adaptive immune response to cause tissue damage (a model known as "bacterial penetration cycle hypothesis")[15].

As a result of the uncontrolled activation of the mucosal immune system, the pro-inflammatory cytokines released cause chronic inflammation of the gastrointestinal tract[5]. In consideration of the crucial role played by cytokines in the development of intestinal inflammation, all current treatments for IBD target downstream events in the host inflammatory response[15].

Given the complexity and heterogeneity of IBD, a holy grail of current research is to be able to customize therapy to a patient's predictive biomarker profile, in order to personalise treatment and to maximise response[11].

Studies in adult patients with CD have shown that treatments capable of inducing and maintaining endoscopic mucosal healing (MH) have a positive impact on the disease course, by reducing the number of clinical relapses, hospitalizations and surgical interventions[16]. Therefore, the current aim in the care of IBD for all ages is achieving intestinal MH, *i.e.*, beyond the simple resolution of symptoms[3].

Based on this evidence, the strategy of early introduction of immunomodulators and biological therapies ("top-down") to induce deep remission (long-term intestinal healing) is increasingly used in high-risk paediatric patients (*e.g.*, children with extensive disease distribution, severe perianal disease, no response to standard medical options, growth retardation and delayed puberty) as an attempt to modify the clinical course of the disease by inducing and maintaining remission, reducing hospitalizations, surgeries, use of corticosteroids, as well as promoting growth and pubertal development[3].

Based on the recommendations above, the conventional "step up" approach for paediatric CD, based on amino-salicylates, corticosteroids, and immunomodulators, is increasingly outdated for patients at high risk of complicated disease[17,18].

This narrative review aims to summarise the most recent advances in treating children with IBD and to provide with an overview of the new treatments in this field.

LITERATURE SEARCH

A Medline search using the keywords "paediatric inflammatory bowel disease", "paediatric Crohn's disease", "paediatric ulcerative colitis", "treatment", "therapy", "immunosuppressant", "biologic", "monitoring" and "biomarkers" was carried out.

Retrospective and prospective clinical studies, systematic reviews and meta-analyses published between 2014 and 2016 were selected for this narrative review. Studies conducted earlier were also taken into consideration whenever the data outline was considered relevant to the scope of the review.

DIET, MICROBIOTA AND FAECAL TRANSPLANT

Diet has an impact on the composition of the intestinal microbiome and gut immune status and currently there is growing evidence that the microbiota has a relevant role in the pathogenesis of IBD[15].

"Dysbiosis", an imbalanced intestinal microbiota with pro-inflammatory microorganisms prevailing on the protecting ones, has been repeatedly reported in patients with IBD[19].

Dietary interventions in children with active CD have proved evidence of a link between diet and the disease[15]. Exclusive enteral nutrition (EEN) using a polymeric formula for 6-8 wk, is the first-line therapy to induce remission in children with active CD[20,21]. EEN is effective in inducing remission in approximately 80% of patients, with a clinical remission rate similar to corticosteroids[3]. However, as opposed to steroids, EEN provides significant nutritional benefit and is superior in achieving MH[3].

EEN also leads to early MH, and long-term benefits of EEN-induced MH are currently being looked into[16]. Grover *et al*[16] conducted a prospective cohort study on 54 children with new diagnosis of CD, to evaluate the impact of early EEN-induced MH on predicting sustained remission (SR) on immunomodulators, without need for additional therapy like steroids, biologics or surgery. Paediatric CD Activity Index (PCDAI), C-reactive protein (CRP) and endoscopic assessment at diagnosis were paired with those post 6 wk of EEN. Complete MH was observed in 33%, and near complete in 19%. SR was superior in children with complete MH *vs* those with active endoscopic disease at 1, 3 and 5 years of follow-up, therefore the authors conclude that following induction of remission with EEN, complete MH is superior to clinical and biochemical remission in predicting SR over and beyond 3 years on maintenance immunomodulators[16] (Table 1).

Partial enteral nutrition with allowance of free diet hasn't been proved effective yet. It is unclear whether this depends on the supply of specific nutrients within the polymeric formula or on the exclusion of dietary factors during the course of exclusive polymeric diet[15].

Recent studies have aimed to evaluate which of the excluded dietary components in EEN may be responsible for the effect, in order to look into ways to allow a safe whole food diet[15].

Sigall-Boneh *et al*[15] validated a dietary intervention that allows whole foods but reduces exposure to dietary components that have been shown to induce inflammation, affect the microbiome and the mucous layer, increase gut permeability or the adherence and translocation of bacteria in mouse or cell line models.

Table 1 Summary of the cohort studies mentioned in the review including reference, study design and population, main results, conclusions

Ref.	Study design	Population	Main results	Conclusion
Nutrition				
Sigall-Boneh *et al*[15] *Inflamm Bowel Dis* 2014	Prospective cohort study	47 patients = 34 children + 13 young adults Mean age 16.1 ± 5.6 yr Active CD (PCDAI > 7.5 or Harvey-Bradshaw Index ⩾ 4)	Post treatment with 6-wk exclusion diet: access to specific foods + 50% of calories from polymeric formula Response in 37 (78.7%) Remission in 33 (70.2%) Decrease in CRP and ESR Normalisation of CRP in 70% of patients entering remission	Dietary therapy involving PEN with an exclusion diet seems to lead to high remission rates in early mild-to-moderate luminal CD in children and young adults
Grover *et al*[16] *J Crohns Colitis* 2016	Prospective cohort study	54 children with CD Age < 16 At least 6 wk EEN	Post EEN: Clinical remission (PCDAI < 10) in 45/54 (83%) Biochemical remission (PCDAI < 10, CRP < 5) in 39/54 (72%) Complete MH in 18/54 (33%) Nearly complete MH in 10/54 (19%) SR superior in children with MH *vs* active endoscopic disease: P 0.003 at 1 yr P 0.008 at 2 yr P 0.005 at 3 yr	Only complete MH post EEN induction predicts more favourable SR for up to 3 yr
Thiopurines				
Stocco *et al*[23] *World J Gastroenterol* 2015	Retrospective cohort study	12 paediatric patients = 6 CD + 6 UC	NAT1 genotypes (fast enzymatic activity) were associated with reduced TGN concentration The effect of NAT1 on TGN persists even 1 mo after the interruption of the aminosalicylate No effect of the NAT2 polymorphism was observed	NAT1 genotype affects TGN levels in patients treated with thiopurines and aminosalicylates and could therefore influence the toxicity and efficacy of these drug
Biologics and biosimilars				
Sharma *et al*[7] *Inflamm Bowel Dis* 2015	IMAgINE-1 study Phase-3, randomized, Multicentre, double-blind	Paediatric CD population = 192	Strong positive association between serum ADA concentration and disease remission/response to treatment Higher body weight, baseline CRP, lower albumin, previous treatment with anti-TNF and presence of anti-IFX antibody were associated with increased ADA clearance	Positive association between serum ADA concentration and remission/response in paediatric patients with moderate/severe CD
Nuti *et al*[18] *J Crohns Colitis* 2016	Prospective cohort study	37 biologic-naïve paediatric patients with CD	Biological therapy with IFX + AZA was effective in achieving MH (based on change in PCDAI and SES-CD) Combination of biologics + immunomodulators was more effective than biological monotherapy Improvement of mucosal lesions at 2 yr follow-up was predictive of favourable outcomes	Biologics improve mucosal lesions, more effectively if given in combination with immunomodulators. MH predicts a better disease course
Fumery *et al*[33] *J Pediatr Gastroenterol Nutr* 2015	Retrospective population based study (EPIMAD registry)	27 paediatric patients with CD experiencing IFX failure	Effectiveness and safety of ADA: Clinical benefit: 19 (70%) measured by the physical global assessment score Significant decrease in CRP in children responding to ADA (9 *vs* 15 mg/L) Cumulative probability of failure to ADA treatment: 38% at 6 mo, 55% at 1 yr Primary failure: 8 (30%) Secondary failure: 5 (26%) Adverse effects: 11 (40%)	Treatment with ADA was safe and effective in two-thirds of patients with pediatric-onset CD and IFX failure

Frymoyer *et al*[38] *J Pediatr Gastroenterol Nutr* 2016	Monte Carlo simulation analysis constructed using a published population pharmacokinetic model based on data from 112 children in the REACH trial	1000 simulated children	Trough IFX concentration > 3 mg/mL was achieved at week 14 in 21% for albumin level of 3 g/dL *vs* 41% for albumin of 4 g/dL	Standard IFX maintenance dosing in children with CD is predicted to frequently result in inadequate exposure, especially when albumin levels are low.
Dziechciarz *et al*[34] *J Crohns Colitis* 2016	Systematic review of 14 studies	Efficacy and safety of ADA I paediatric patients with CD	Pooled remission rates: At 4 wk: 30% (n = 93/309) At 3 mo: 54% (n = 79/145) At 4 mo: 45% (n = 18/40) At 6 mo: 42% (n = 146/345) At 8 mo: 57% (n = 20/35) At 12 mo: 44% (n = 169/383) Primary non-responders: 6% (13/207) Severe adverse events: 12% (69/599)	According to low-quality evidence based mainly on case series, approximately half of children with CD on ADA therapy achieve remission during the first year of the therapy with reasonable safety profile
Conrad *et al*[39] *Inflamm Bowel Dis* 2016	Observational, single-centre, prospective cohort study	21 paediatric patients (16 CD, 5 UC) with refractory IBD who had previously failed anti-TNFa therapy	Clinical response post treatment with vedolizumab: 6/19 (31.6%) at week 6 11/19 (57.9%) at week 22 Steroid-free remission in 1/20 (5%) at week 6, 3/20 (15%) at week 14 and 4/20 (20%) at week 22.	
Singh *et al*[44] *Inflamm Bowel Dis* 2016	Retrospective review on the experience with vedolizumab	52 paediatric patients with IBD, 90% of whom had failed ⩾ 1 anti-TNF agent	Week 14 remission rates: 76% for UC, 42% for CD, 80% of anti-TNF naïve IBD Week 22 remission rates: 100% anti-TNF naïve *vs* 45% anti-TNF exposed	Clinical response to vedolizumab in children with moderate/severe CD increases from week 14 to week 22
Sieczkowska *et al*[46] *J Crohns Colitis* 2016	Prospective cohort study	39 paediatric patients: 32 with CD, 7 with UC Children were switched from IFX originator to its biosimilar All patients had PCDAI ⩾ 25 at the time of switching	Clinical remission: 88% for CD 57% for UC	No differences in treatment efficacy, after switching from IFX originator to its biosimilar
Thalidomide				
Lazzerini *et al*[49] *JAMA* 2013	Double-blind, placebo-controlled, randomized clinical trial	56 padiatric patients with active CD, randomised to receive either thalidomide or placebo Almost all had not responded to thiopurines and 35% had not responded to biologics	Clinical remission achieved by 13/28 (46.4%) of the children treated with thalidomide *vs* 3/26 (11.5%) of those who received placebo (P = 0.01) Responses were not different at 4 wk, but greater improvement was observed at 8 wk in the thalidomide group [75% response in 13/28 (46.4%)] *vs* 3/26 (11.5%)(P 0.01) Of the non-responders to placebo who began receiving thalidomide, 11 of 21 (52.4%) subsequently reached remission at week 8 (P = 0.01). Overall, 31 of 49 children treated with thalidomide (63.3%) achieved clinical remission Mean duration of clinical remission in the thalidomide group was 181.1 wk *vs* 6.3 wk in the placebo group (P < 0.001).	Thalidomide compared with placebo resulted in improved clinical remission at 8 wk of treatment and longer-term maintenance of remission.
Lazzerini *et al*[50] *Inflamm Bowel Dis* 2015	Multicenter, double-blind, placebo-controlled, randomized clinical trial	26 paediatric patients with active UC, randomised to receive thalidomide or placebo All patients had had thiopurines and 35% had received prior IFX treatment	Clinical remission at week in 10/12 (83.3%) of the children treated with thalidomide *vs* 2/11 (18.8%) of those who received placebo (P = 0.005) Of the non-responders to placebo who were switched to thalidomide, 8 of 11 (72.7%) subsequently reached remission at week 8 (P = 0.01) Clinical remission in the thalidomide group was 135 wk compared with 8 wk in the placebo group (P < 0.0001).	Thalidomide compared with placebo resulted in improved clinical remission at 8 wk of treatment and in longer term maintenance of remission.

New treatments				
Tew *et al*[11] *Gastroenterology* 2016	Retrospective analysis of two cohorts: 1. phase 2 placebo-controlled trial; 2. observational study at a separate site	110 patients with UC (cohort 1) and 21 patients including UC and controls (cohort 2)	Increased expression of T-cell associated genes in baseline biopsies of anti-TNF naïve patients who achieved clinical remission in response to etrolizumab Patients with high colonic integrin aE expression showed greater benefit GZMA expression was different post-treatment	Levels of GZMA and ITGAE mRNAs in colon tissues can identify patients with UC who are most likely to benefit from etrolizumab GZMA is a promising biomarker for etrolizumab response
Sandborn *et al*[51] *N Engl J Med* 2016	Double-blind, placebo-controlled, phase-2 trial	197 adult patients with moderate-severe UC	Clinical remission at 8 wk: 16% of patients who received 1 mg of Ozanimod *vs* 14% who received 0.5 mg *vs* 6% of those who received placebo Clinical remission t 32 wk: 21% *vs* 26% *vs* 6% respectively Drop in absolute lymphocyte count at week 8: 49% from baseline in the group who received 1 mg of Ozanimod 32% from baseline in the group who received 0.5 mg	Ozanimod at a daily dose of 1 mg resulted in a slightly higher rate of clinical remission of UC than placebo
Allez *et al*[52] *Gut* 2016	Randomised, double-blind, parallel group trial	78 adult patients with CD Age 18-75 Disease duration ⩾ 3 mo CDAI 220-450 CRP ⩾ 10 mg/L Endoscopic evidence of inflammation	No significant difference in change in CDAI from baseline to week 4, between NKG2D group and placebo group Significant difference in change in CDAI at week 12 (delta CDAI -55, $P \leqslant 0.1$) between NKG2D group and placebo group Significant improvement noted in the non-failure to biologic subgroup treated with anti-NKG2D from week 1	A single s.c. dose of 2 mg/kg anti-NKG2D did not reduce disease activity at week 4 *vs* placebo, but the difference was significant at week 12

ADA: Adalimumab; CD: Crohn's disease; CDAI: Crohn's disease activity index; CRP: C-reactive protein; EEN: Exclusive enteral nutrition; GZMA: Granzyme A; IFX: Infliximab; ITGaE: Integrin aE gene; MH: Mucosal healing; NAT: N-acetyl transferase; PCDAI: Paediatric Crohn's disease activity index; PEN: Partial enteral nutrition; s.c.: Subcutaneous; SES-CD: Simple Endoscopic Score for Crohn's Disease; SR: Sustained remission; TGN: Thioguanine nucleotides; UC: Ulcerative colitis.

They recruited 47 patients including 34 children and 13 young adults with active disease, who were treated with a 6-wk exclusion diet that allowed access to specific foods and up to 50% of dietary calories from a polymeric formula.

The diet consisted in elimination of or reduction in animal fat, dairy products, gluten, and emulsifiers whereas fibre from fruits and vegetables was allowed. Clinical response was observed in 78.7% and remission in 70.2%, alongside improvement in CRP (normalized in approximately 70%) and ESR. On the basis of these results, the Authors recommend the use of this elimination diet in patients with mild-moderate disease, as it allows access to specific foods improving palatability and compliance[15] (Table 1).

So far, efficacy of microbiome-based therapies like probiotics or antibiotics has been limited in IBD[19]. Nevertheless, the recent focus on dysbiosis as a plausible key factor in IBD pathogenesis, has led to a growing interest in faecal microbiota transplantation (FMT) as a novel potential treatment option in IBD.

FMT is the administration of faecal material from a donor into the intestinal tract of a recipient, with the aim to change the microbiota composition and restore mucosal health. Over the past few years, FMT has been used successfully for the treatment of recurrent Clostridium difficile infection (CDI) (efficacy of 80%-95%), and is now being evaluated in other diseases possibly driven by the microbiota, including IBD[19].

There are several studies and case reports on the use of FMT in UC, but only two randomized control studies published to date[19,20,22].

The success rate of FMT in treating UC has been much more limited (clinical remission in 35%) in respect to its success in treating recurrent CDI. However, studies so far have been small and heterogeneous, therefore clear conclusions are difficult to make[19].

Even less data is available for FMT in CD, with only isolated cases or heterogeneous small series reporting overall clinical remission in 60%-75%[19].

At present, evidence on FMT in IBD is not strong

enough to recommend its use as part of routine treatment. Preliminary results are promising and more studies are needed to define the best indications, optimal timing, frequency, mode of delivery, and the most appropriate donor for each patient[19].

AMINOSALYCILATES

5-aminosalicylic acid (mesalazine, 5-ASA) acts topically on the gastrointestinal mucosa, with minimal systemic effect. Even though its exact mechanism of action is yet to be understood in its complexity, the pathways that are known to be involved include the blockade of IL-1 production and TNF-α receptor, the inhibition of cyclooxygenase and 5-lipoxygenase, and the blockade of the pro-inflammatory prostaglandin E2 and leukotrienes. On top of the inhibition of multiple inflammatory pathways and the suppression of the nuclear factor kappa B as a main result, amino-salicylates also possess potent anti-oxidant and free-radical-scavenger properties[4]. Amino-salicylates are mainly used in the induction and maintenance of remission in UC[23].

In CD, their use is no longer recommended in view of limited efficacy. However, there are studies suggesting a possible role in the postoperative maintenance of remission, as well as in the subgroup of children with mild, localised ileal disease. In addition, adult studies suggest a protective role of 5-ASA in IBD against colon cancer in patients with colonic location[23].

Given that sulfasalazine is not tolerated in 30%-40% of patients, particularly slow acetylators, the use of its therapeutically active component 5-ASA has led to the development of new formulations, that deliver higher concentrations of 5-ASA without the dose-limiting side effects of sulfasalazine. A wide range of these formulations is available and comprises pH-dependent release coated drugs (targeting the ileum), time-dependent release micro-granules enclosed within a semi-permeable membrane of ethyl-cellulose (released in the whole small and large intestine), and azo-bonded formulations released throughout the colon[4].

CORTICOSTEROIDS

Corticosteroids are used as first-line therapy for induction of remission in UC, particularly in patients with non-response to 5-ASA or with severe presentation, as well as to induce remission in CD when EEN is not possible[3,9,24].

The mechanism of action of corticosteroids consists in inhibiting protein synthesis and transcription, which ultimately results in down-regulation of pro-inflammatory cytokines, such as NF-kappa B, TNF-α, interleukin-1 and interleukin-6[9].

Clinical remission rates for CD are up to 80%, similarly to EEN, whereas MH rates are significantly lower[3]. Corticosteroids improve rapidly and effectively the signs and symptoms of disease in CD, however they are ineffective, and inappropriate, for maintenance therapy[17].

In children with moderate-severe active luminal CD, oral prednisolone is given at 1 mg/kg, with a maximum of 40 mg/d, followed by a weaning course over 8-10 wk. Intravenous steroids may be initially needed for severe disease and include methylprednisolone (1-1.5 mg/kg, maximum: 60 mg/d) and hydrocortisone (2-4 mg/kg per dose, maximum 100 mg/dose, four times a day)[3].

Adverse effects like adrenal suppression, growth failure, cosmetic and behavioural effects, are dependent on dose and duration[3].

Budesonide (maximum of 12 mg/d, followed by weaning course over 2-4 wk) is a topically acting corticosteroid with high first pass hepatic metabolism, which reduces the likelihood of adverse effects[3,9].

Budesonide is particularly recommended for patients with mild to moderate CD involving the distal ileum and/or right colon, as it has been shown to be non-inferior to conventional oral steroids for inducing remission in this specific group. It has also proved to be an effective therapeutic option as enema formulation for distal UC[9].

There are currently three formulations of budesonide: two standard formulations including a controlled-release capsule and a pH-dependent capsule both designed to target the ileum and right colon; and a more recent Budesonide-MMX® capsule that releases the drug throughout the entire colon[9].

THIOPURINES

Thiopurines are purine analogues used for the maintenance of disease remission in patients with CD and UC; they include the prodrug AZA and the antimetabolite 6-MP[25,26].

AZA is non-enzymatically degraded to 6-MP which is then metabolised to its active component, 6-thioguanine nucleotide (6-TGN)[8]. 6-TGN inhibits the proliferation of T and B lymphocytes, which results in a decrease in the numbers of cytotoxic T cells and plasma cells[8].

These dugs are able to block the rapid cell proliferation involved in inflammatory processes, which results in immunosuppression[26].

For the treatment of IBD, thiopurines are used at relatively low dosages, so their anti-inflammatory effect is mainly produced by the inhibition of the small GTPase Rac1, leading to apoptosis of activated T-lymphocytes. When given at higher dosages, as in oncological treatments, thiopurines mainly inhibit DNA synthesis[26].

Thiopurines are steroid sparing agents and have been proven effective maintenance treatment in paediatric IBD: studies have shown significantly lower cumulative steroid doses and relapse rates at 18 mo in children on 6-MP compared with placebo (9% *vs* 47%) as well as a reduced need for surgery in CD[3,23]. Recommended doses are 1.0 to 2.5 mg/kg per day for AZA and 1 mg/d for 6-MP[25].

Thiopurines are also used effectively to maintain surgically-induced remission in CD, even though a systematic review by Gordon *et al*[8] pointed out that the results for efficacy outcomes between thiopurines and 5-ASA in this group of patients are uncertain.

Testing the activity of the enzyme thiopurine-S-methyltransferase (TPMT) is recommended to guide thiopurine dosing avoiding adverse events[26].

Genetic polymorphisms in the TPMT gene are associated with a reduced enzymatic activity and an increased production of the active metabolites TGNs[23].

A large prospective study with 1000 individuals established TPMT activity reference intervals, with normal activity associated with a level $\geqslant$ 25 nmol/h per gram Hgb[27].

According to the current data available, 1 in 300 patients have a very low to absent TPMT activity (homozygous mutant TPMT), 11% have intermediate TPMT activity (heterozygous) and 89% have normal to elevated activity (homozygous wild type TPMT)[27].

The use of thiopurines is limited by an extensive spectrum of adverse events in up to almost half of patients, particularly within the first twelve months of treatment. Adverse effects include myelotoxicity, hepatotoxicity, pancreatitis and gastrointestinal complaints[26].

Measuring TPMT activity levels (phenotype) or determining TPMT genotype before initiating thiopurine therapy, is recommended by the FDA to limit the likelihood of side effects[27]. However, it still remains possible to develop significant myelotoxicity despite normal TPMT activity.

The use of TPMT activity and 6-TGN level monitoring has the potential to avoid nearly a quarter of episodes of myelosuppression[27]. In addition, 6-TGN monitoring is helpful to detect non-compliance, under-dosing, and drug resistance or refractory states[27].

Blood levels of thiopurine metabolites correlate with the efficacy and toxicity of these drugs as follows: TGN levels higher than 235 pmol/8 $\times$ 10^8 red blood cells reflect an adequate therapeutic level, whereas methyl mercaptopurine nucleotides levels above 5700 pmol/8 $\times$ 10^8 red blood cells are indicative of hepatotoxicity[23].

AZA or 6-MP can be started at the full recommended dose of 2-2.5 mg/kg per day or 1-1.5 mg/kg per day, respectively, in patients with normal to high TPMT activity level. Patients with an intermediate TPMT activity should start, instead, with a daily dose reduced by 30%-70%. Alternative therapy should be offered to individuals with low or absent TPMT activity, or they should be started at 10% of the suggested dosing, given three times per week[27].

The results of a recent retrospective study by Benmassaoud *et al*[27] evaluating the safety and efficacy of starting thiopurines at low dose *vs* full dose in adult patients with CD and normal TPMT, suggest that AZA should be started on full dose in patients with normal TPMT, rather than starting on a lower dose and increasing slowly. This is mainly due to the fact that patients with normal TPMT level may still be exposed to side effects that are unrelated to the enzymatic activity[27]. Overall, almost half of the adults treated with thiopurines discontinue their treatment due to ineffectiveness or intolerance[26]. It has been hypothesized that prescribing thioguanine (TG) therapy instead of AZA/6-MP reduces the release of potentially toxic metabolites, as its metabolism is less complex with a more direct conversion to the therapeutically active metabolite 6-TGN[1].

In a systematic review, Meijer *et al*[1] describe how TG therapy can represent a valuable option in adult IBD patients intolerant to conventional thiopurine therapy, with efficacy in 65% of patients and short term adverse events in 20%. However, TG is currently only used as experimental or rescue therapy and should not be used outside highly controlled situations[1]. Thiopurines and amino-salicylates are often used in combination in the treatment of IBD[23].

An increase in mean TGN blood levels has been reported in patients on concomitant treatment with thiopurines and 5-ASA. Moreover, a higher rate of myelotoxicity was observed in this group of patients compared with those treated with the thiopurine alone[22]. A plausible explanation comes from *in vitro* studies showing that amino-salicylates and their metabolites can inhibit the activity of TPMT, even though this observation has not been yet replicated *in vivo*[23].

The enzymes N-acetyltransferases (NAT1 and NAT2, EC 2.3.1.5) are responsible for the N-acetylation of multiple drugs including the amino-salicylates. Subjects are classified as rapid, intermediate or slow acetylators based on the activity of NAT1 and NAT2 that is genetically determined[23].

Stocco *et al*[23] evaluated the variation of the level of TGN after 5-ASA cessation and the role of genetic polymorphisms of NAT 1 and 2, in a group of 12 children recruited at two tertiary level paediatric gastroenterology units (6 CD and 6 UC) (Table 1).

Rapid acetylators with NAT1 genotypes were found to have reduced TGN concentration, and the effect of NAT1 activity on TGN persisted up to one month after discontinuation of the 5-ASA. NAT2 polymorphism, instead, did not produce any effect. These results, though limited by the small number of patients, show that the NAT1 genotype affects TGN levels in patients treated with thiopurines and 5-ASA and it may therefore impact on the efficacy and toxicity of these drugs[23] (Table 1).

MTX

MTX, a dihydrofolate reductase inhibitor, has long been used effectively to treat rheumatoid arthritis until it was brought into the field of IBD to treat patients with

refractory CD. Nowadays, it has become one of the principal alternatives to thiopurines as maintenance treatment[28,29].

Efficacy of MTX, given at 15 mg/m^2 once a week for a maximum of 25 mg/wk subcutaneously, is reported as 50%-80% by retrospective cohort studies in children who failed to respond or were intolerant to thiopurines[3]. MTX is a first-line treatment option in patients who have concomitant inflammatory arthritis and it represents a valuable alternative to maintenance treatment with anti-TNF[3,29]. Adverse events associated with MTX include flu-like symptoms, transaminitis and, less frequently, myelosuppression, which may require dosage adjustment or drug withdrawal[3]. Nausea and vomiting have been reported in 11%-24% of patients, the majority of whom respond to antiemetic medication. Significant hepatocellular liver disease is rare. Contraception is essential[3].

Systematic reviews performed by MacDonald JW and by Patel *et al*[29] to assess the efficacy and safety of MTX for the treatment of active refractory CD in adults, show that intramuscular MTX is effective in inducing remission and acts as a steroid sparing agent allowing complete withdrawal from steroids[28,30,31]. Lower dose oral MTX does not appear to provide any significant benefit in respect to placebo or active comparator[28,31-33]. Though limited by the small size of the studies analysed, this review could not identify any additional benefit from combining MTX and IFX over IFX monotherapy[28,31].

BIOLOGICS AND BIOSIMILARS

TNF is produced by macrophages, adipocytes, fibroblasts and T cells and acts as a pleiotropic, pro-inflammatory cytokine by triggering a cascade of events that lead to tissue damage[5,7].

IFX, ADA and other anti-TNF agents act by suppressing downstream pathways mediated by TNF including angiogenesis, increase in T-helper cell 1 (Th1) cytokine production (interleukin-12 and interferon-γ), death of intestinal epithelial cells and T-cell resistance to apoptosis[5].

Anti-TNF medications are able to achieve and maintain MH, with growing evidence of a change in the natural history of the disease. Importantly, as opposed to a few years ago when clinical response and remission were the main goals in treating patients with IBD, MH has recently been emphasized as a stronger therapeutic goal, as it predicts sustained clinical remission. Therefore, a new concept of "deep remission" has been coined, including MH alongside clinical and/or biochemical remission[18]. Also thiopurines and EEN with polymeric diet have been previously reported to achieve MH, albeit less rapidly and to a lower degree than biologics[18]. According to the studies performed on adult populations, scheduled maintenance therapy with IFX maintains MH in up to 68% of patients, and the subgroup of patients achieving MH show decreased rate of surgeries and hospitalizations[18].

IFX

IFX is a chimeric monoclonal antibody and was the first biologic approved for the treatment of moderate to severe paediatric CD[34]. The advent of biological therapies has drastically modified the treatment strategies and disease course of IBD in children and the role of IFX and ADA in the management of paediatric IBD was recently updated in the Consensus guidelines of ECCO/ESPGHAN[6]. In CD, anti-TNF therapies are currently well established in moderate to severe disease with lack of response to conventional therapy including corticosteroids and immunomodulators, or with contraindications or intolerance to it[34]. Anti-TNF agents are also used as a primary induction option for children with active perianal fistulising disease, in combination with targeted surgical intervention, as well as in children at risk of poor outcomes (top-down treatment)[3,20]. One year response and remission rates for IFX in luminal disease are reported as up to 90% and 55%-60% respectively[35,36]. Repeated administration of IFX can lead to immunogenicity in some patients, with possible loss of efficacy and delayed-type hypersensitivity[34]. A low proportion of children with CD (10%-25%) are primary anti-TNF non-responders, *i.e.*, they fail to respond after the 6 wk induction course. More commonly, however, the formation of antibody against the drug over time can result in secondary loss of response. Concomitant treatment with either thiopurines or MTX has been shown to contain this process[3]. A key step in managing IFX therapy over the more recent years is the increasing availability of therapeutic drug monitoring (TDM), that has improved response rates and has become a most effective tool for the management of secondary failure to IFX[37].

Increasing evidence has shown that trough IFX concentrations < 3 mg/mL during maintenance therapy are associated with treatment failure. Also, children with lower albumin levels have higher IFX clearance and lower drug exposures[38]. Therefore, standard IFX maintenance dosing of 5 mg/kg every 8 wk may not be adequate for all children with CD to achieve sufficient concentration level and thus minimise loss of response (Table 1). Unfortunately, patients who don't respond to one anti-TNF are more likely to also fail a second agent[39]. Researchers hypothesized that a combination therapy of an anti-TNF antibody and another immunomodulator (*i.e.*, thiopurines or MTX) will increase the efficacy and reduce the risk of loss of response[40].

There are several adult trials showing higher treatment efficacy (especially for induction of remission) in patients receiving combination therapy. In particular, concomitant immunomodulators increase IFX levels and reduce immunogenicity[40]. On the other hand, combination therapy in adults exposes patients to the

individual toxicity of both drugs and also seems to increase the risk of malignancy[40]. In paediatric IBD, the safety of combined treatment has been questioned after several cases of hepatosplenic T-cell lymphoma (HSTCL) in young patients with IBD so treated were reported.

Nevertheless, a review by Cozijnsen *et al*[40] points out that almost all studies in paediatric patients with IBD have failed to prove increased benefit from combination therapy compared to monotherapy. Given the controversial aspects above, the Authors suggest to target the use of combination therapy to children with a high risk of serious disease-related complications, such as growth delay, stricturing or fistulising CD phenotype, or panenteric CD[40].

In order to assess the risk of malignancies associated to immunosuppressive treatments in IBD, a retrospective multinational survey of malignancy and mortality in paediatric IBD was conducted over a 6 years period (2006-2011) by the Porto Pediatric IBD working group of ESPGHAN[41]. The most common malignancies identified were hematopoietic tumors (n = 11), of which 3 were HSTCL and 3 Ebstein-Barr virus-associated lymphomas[41]. These 6 patients had all been treated with thiopurines until diagnosis of cancer and only 1 patient had also received 3 IFX infusions, 5 years before the diagnosis of cancer[41]. All 3 patients who developed HSTCL were males and had exposure to thiopurines ranging from 32 to 108 mo; none of them received a biologic[41].

ADA

ADA is a fully human IgG1κ monoclonal antibody which is similar to IFX in the mode of action, but it differs from it as the mouse-derived sequence is removed, in order to reduce the immunogenic reactions induced by chimeric antibodies[23,34]. ADA is therefore to consider as an alternative treatment option in patients who have lost response or are intolerant to IFX, or in some primary non-responders to IFX[34].

ADA was recently approved in Europe and the United States for the treatment of paediatric patients with CD, based on the results from the IMAgINE-1 study[7,42,43].

IMAgINE-1 study is a phase-3, randomized, double-blind study conducted by Sharma *et al*[7] aimed to analyse the PK of ADA in a paediatric CD population (n = 192), and to evaluate the effect of various factors, including demographics (body weight, sex), laboratory measurements (CRP, albumin), previous IFX use, concomitant immunomodulators, and baseline PCDAI, on ADA PK in paediatric patients with moderate-to-severe CD (Table 1). Furthermore, the relationship between serum ADA concentration and remission/response was explored[24].

Trough serum ADA (measured at 5 time points from baseline up to 52 wk) and serial anti-ADA antibody measurements were performed. The study confirmed a strong positive association between serum ADA concentration and clinical remission/response to treatment[24]. Higher body weight, baseline CRP, and lower baseline albumin levels were associated with greater clearance of ADA (lower trough levels)[7]. Previous treatment with other anti-TNF therapy, presence of antibodies to previous IFX therapy, and absence of concomitant use of immunomodulators were also associated with increased clearance of ADA[7]. According to the published experiences from tertiary centres, in anti-TNF antibody naiive children the 1 year remission rate for ADA is 45%[42], and its efficacy has been documented in nearly two-thirds of patients who failed IFX[33]. A retrospective study was conducted by Fumery *et al*[33] who used the population-based EPIMAD registry to evaluate the effectiveness and safety of ADA in children with CD experiencing IFX failure (Table 1).

Twenty-seven children with CD who received ADA before 18 years because of IFX failure or intolerance were included. Clinical response measured by the physician global assessment score after a median follow-up of 16 (8-26) mo was observed in 19 patients (70%). Cumulative probability of failure to ADA treatment at 6 mo and 1 year was 38% and 55%, respectively. Overall, the results from this population-based cohort of paediatric-onset CD with IFX failure show that treatment with ADA was safe and effective in two-thirds of patients. More specifically, ADA was effective in 100% of children intolerant to IFX, 68% of children with secondary failure to IFX, and only 25% of children with primary failure to IFX[33]. A systematic review on the same topic was performed by Dziechciarz *et al*[34]. Who assessed the published evidence on the efficacy and safety of ADA for CD in children (Table 1).

Randomised controlled trials and observational studies (cohort studies, case series of more than 5 patients) were included. A total of 14 studies (1 randomised controlled trial, 13 case series), altogether including 664 patients (age range 1.9-21 years) were available for analysis. The pooled remission rates were: 30% at 4 wk, 42% at 6 mo and 44% at 12 mo. Of the total patients, 6% were primary non-responders and 12% had severe adverse events reported. However, studies differed with respect to patients' characteristics, including percentage of IFX-naïve patients, disease duration, disease localisation, ADA doses, treatment duration, and follow-up period[34].

The Authors' conclusion, though limited by the low-quality evidence based mainly on case series, is that approximately half of the children with CD on ADA therapy achieve remission during the first year of treatment with reasonable safety profile[34].

Vedolizumab

Vedolizumab is a recent biologic treatment, approved for adult patients with IBD in 2014. It is an anti-integrin therapy that blocks the a4b7 integrin receptor molecule

present on the surface of lymphocytes, and thus inhibits the migration of intestinal T-lymphocytes into the tissue[39,44,45]. As this mechanism of action is restricted to the gastrointestinal tract, the risk of systemic immunosuppression (*i.e.*, infections and malignancies) seen with other IBD therapies is mitigated[39].

Its predecessor, natalizumab, acts with a non-specific binding to the a4 chain which causes interference with the lymphocyte trafficking in the central nervous system and led to the concern for reactivation of John Cunningham (JC) virus and subsequent development of progressive multifocal leukoencephalopathy (PML)[45]. Vedolizumab, being gut specific, does not interfere with immune surveillance in the central nervous system, therefore there is no risk of PML as assessed by the placebo-controlled GEMINI studies[44]. Anti-adhesion therapy appears to have a favourable safety profile, though the experience in children is still extremely limited[17]. Due to its mechanism of action of targeting gut-specific T-cell interactions, it is thought that Vedolizumab may not sufficiently treat the extra-intestinal manifestations of IBD. A dual therapy with therapeutic doses of immune-suppressants may therefore be needed to treat extra-intestinal manifestations[39]. So far, Vedolizumab has been particularly effective amongst UC patients, with a clinical response rate of 50% during induction[39]. Whilst the use of Vedolizumab has been approved for the treatment of CD and UC in adults, there is increasing off-label use in paediatric IBD[44].

Singh *et al*[44] conducted a retrospective review to describe the experience with Vedolizumab in 52 children with IBD (58% CD and 42% UC) at 3 tertiary IBD centres and to examine predictors of remission. Ninety percent of the patients had failed at least one anti-TNF agent. Week 14 remission rates for UC and CD were 76% and 42%, respectively ($P < 0.05$). At week 4, eighty percent of anti-TNF-naive patients were in remission. At week 22, anti-TNF-naive patients had higher remission rates than those previously exposed to anti-TNF (100% *vs* 45%, $P = 0.04$). There were no safety concerns.

These results support Vedolizumab as an effective and safe treatment in children with IBD, with UC patients experiencing earlier and higher rates of remission than children with CD. Also, the data reviewed shows that anti-TNF-naive patients had higher remission rates compared to those with previous anti-TNF exposure[44].

Conrad *et al*[39] conducted an observational single-centre prospective cohort study aimed to determine the impact of Vedolizumab on clinical response and on achieving steroid-free remission over 22 wk of therapy. They recruited 21 children with refractory IBD (16 with CD), who had previously failed anti-TNF therapy.

Clinical response was observed in 31.6% and in 57.9% by week 6 and by week 22, respectively. Steroid-free remission was seen in 1 patient at week 6 and in 4 (20%) at week 22. No infusion reactions were observed. Vedolizumab was discontinued in 2 patients because of severe colitis, requiring surgical intervention[39]. These results, though limited by the small sample size, describe a number of children with severe disease who achieve clinical response in the first 6 wk and a further increase in remission rate by week 22[39]. Overall, the data currently available on Vedolizumab from adult and paediatric studies suggests its use as an option to achieve clinical improvement in the most severe paediatric IBD patients (both CD and UC).

Biosimilars

Biosimilars are defined as biological agents that are highly similar to another reference drug already authorized for use[37,46]. This definition also implies that the quality, safety and efficacy of the biosimilar should not be affected by any molecular and/or structural dissimilarities or any potential differences in the underlying mechanisms[37].

Despite keeping the same aminoacid sequence as their reference drug, biosimilars end up being a different final product due to manufacturing process (including cell line, growth condition and purification processes), storage and transport, and subsequent various post-translational modifications (*e.g.*, glycosylation, phosphorylation, sulfation)[37]. Therefore, some uncertainty still exists regarding the exact drug efficacy, immunogenicity and pharmacology of biosimilars in IBD.

In 2013, the EMA authorized two IFX biosimilars, based on two randomized trials on CT-P13 (clinical development name for the biosimilar of Remicade): Remsima (Celltrion Inc., Incheon, South Korea) and Inflectra (Celltrion Inc., Hospira UK Ltd). Because both trials showed equivalent efficacy, tolerance and safety, EMA extended the approval to all indications for which the reference product is labelled, including both adult and paediatric CD and UC[37,46]. At present, a number of IFX biosimilars are licensed for treatment of CD and UC also in the paediatric population.Cost containment remains one of the predominant reasons for development of biosimilars, with a reduction in costs of anti-TNF therapy for IBD by up to 70%[37].

Sieczkowska *et al*[46] conducted a prospective study on 32 children diagnosed with CD and 7 children with UC at 3 academic hospitals in Poland; these patients were switched from IFX originator to its biosimilar (Remsima) (Table 1). Analysis of biosimilar efficacy revealed rates of clinical remission of 88 and 57% for CD and UC patients, respectively, so, in conclusion, switching from IFX originator to its biosimilar was a safe option in this cohort and after the switch, the biosimilar was just as effective as the originator[46].

To date, preliminary results on CT-P13 in IBD are only available from small post-marketing registries and case series with a relatively short-term follow-up period. Although this data suggests comparable efficacy and safety to IFX, more robust post-marketing

studies and pharmacovigilance are warranted to evaluate the bioequivalence of CT-P13 in the coming years[37]. In Europe, at present, in order to switch patients with IBD from IFX originator to its biosimilar, the supervision of the treating physician and the patient's consent are both required[46].

THALIDOMIDE

Thalidomide is an immunosuppressant drug used rarely in the treatment of refractory CD and UC[47]. Its mechanism of action includes several pathways such as inhibition of TNF, IFN-γ and IL-12, stimulation of IL-4 and IL-5 production and, more broadly, a shift in the pattern of lymphocyte cytokine from a Th1 (IFN-γ, IL-12) to Th2 (IL-4, IL-5) type[5]. Thalidomide also interferes with integrin expression, decreases circulating helper T-cells and inhibits angiogenesis[5].

After its suspension due to major teratogenic effects, thalidomide has been more recently re-introduced under FDA approval as an effective treatment for multiple myeloma and severe erythema nodosum leprosum. It is also extensively used off-label for immune-mediated and neoplastic conditions like discoid lupus erythematosus, erythema nodosum leprosum, Behcet's syndrome, aphthous stomatitis, juvenile idiopathic arthritis, brain tumors, graft-*vs*-host disease and IBD[5,18,48].

Thalidomide is used infrequently in the management of paediatric CD, nevertheless it represents a helpful option in treating children who lose response to one or more conventional agents such as thiopurines, MTX, and anti-TNF[48].

Thalidomide (administered from 50 to 400 mg/d in adults and 1.5 to 2.5 mg/kg per day in children[47]) has been shown to induce clinical remission and possibly MH[48]. A systematic review by Yang *et al*[5] selected twelve studies (2 RCTs and 10 case series) where thalidomide was used to induce remission in 248 patients with IBD of all age groups (10 with UC, 238 with CD), 92 of whom were children. Remission rate was 49% and 25%, in adult luminal and perianal CD respectively. In adults with UC, 50% achieved remission and 10% had a partial response. One case series reported 21 patients (17 CD, 4 UC) who maintained remission for 6 mo[5]. Amongst the adverse effects associated with thalidomide and reported in this review, the most common was sedation, in 32.3% of all patients, followed by peripheral neuropathy in 19.8% which was also the main cause of discontinuation[5]. Amongst the studies in this review, one high quality RCT showed that thalidomide is effective in inducing remission in paediatric CD[49]. Based on the evidence reviewed and given the limited data available, the Authors support the use of Thalidomide in the most severe cases of IBD for induction or maintenance of remission[5].

Lazzerini *et al*[49,50] conducted randomized placebo-controlled trials of thalidomide in both paediatric CD and UC (Table 1). In their CD trial, they randomized 52 children to receive thalidomide or placebo; almost all patients had not responded to thiopurines, and about 35% had also not responded to biologics. The majority of children had luminal disease and few had perianal disease. Although no significant response was noted at 4 wk, by 8 wk 46% of children treated with thalidomide had a reduction in their PCDAI greater than 75%, compared with 12% amongst patients treated with placebo[49].

Their UC trial enrolled 26 children with active UC who were randomized to receive thalidomide or placebo. All patients had active disease despite thiopurines, and about 35% had received previous IFX treatment. The UC children treated with thalidomide achieved higher remission rates at 8 wk (83% *vs* 19% for placebo) than those in the CD trial[50].

Both trials showed that thalidomide does not work quickly, as there were no significant differences between placebo and thalidomide at 4 wk, whereas major differences were seen by 8 wk[49,50]. These trials also support the use of Thalidomide as a maintenance agent in cases of refractory CD or UC, for example patients with secondary loss of response to biologics[49,50]. Another more recent systematic review conducted by Bramuzzo *et al*[47] analysed 722 papers, including two randomized controlled trials and 29 uncontrolled studies for a total of 489 patients, 135 (28.4%) of whom were children.

Overall, thalidomide appeared to be a promising therapy for IBD: induction of clinical remission was achieved in 51.4% of cases, and in 69.3% a clinical response was observed in the first months of treatment. In almost 50% of the cases in which endoscopy was performed, complete MH was observed and a further 15% of patients showed an improvement in their endoscopy score[47]. IBD remission was maintained in 72.2% after 12 mo and in 54.5% after 2 years[47].

Adverse events leading to drug suspension had a cumulative incidence of 19.7/1000 patients-month, with neurological symptoms being the main cause[48]. This review highlights that thalidomide is an effective alternative in patients who fail biologic treatment, which is most likely due to the different mechanism of action of Thalidomide compared to anti-TNF agents[47]. Careful precautions must be taken to avoid its use in pregnant women. No case of teratogenicity has been observed in 124000 patients enrolled in the thalidomide distribution risk management program for more than 6 years[49,50]. Other reported side effects of thalidomide include peripheral neuropathy (clinical or subclinical, primarily with axonal damage) followed by sedation, constipation, mood disturbances, skin rash, pedal oedema, neutropenia and deep vein thrombosis[5,48].

STUDIES ON NEW TREATMENTS

New biologics and other agents are being tested

in phase Ⅱ and Ⅲ trials on adult patients with IBD and are therefore on the horizon within the field of paediatric gastroenterology as well. Examples are the IL-23 inhibitor risankizumab and the IL 12- IL 23 inhibitor ustekinumab. Drug therapies that interfere selectively with lymphocyte trafficking are also emerging treatment options for UC[11,51]. Etrolizumab is a humanized monoclonal antibody against the b7 integrin subunit that acts by reducing the homing of leukocytes to the gut mucosa and the retention of lymphocytes in the epithelium[11]. It has recently been tested in a phase 2 study showing efficacy in patients with moderate to severe UC, compared to placebo[11]. Levels of granzyme A (GZMA) and integrin aE (ITGAE) mRNAs in colon tissues can identify patients with UC who are most likely to benefit from etrolizumab[11] (Table 1).

Another agent recently developed is Ozanimod (RPC1063), an oral agonist of the sphingosine-1-phosphate receptor subtypes 1 and 5 that induces sequestration of peripheral lymphocytes, and as a consequence a decrease in the number of activated lymphocytes circulating to the gastrointestinal tract[51]. Its agonists induce internalization and degradation of the S1P1 receptor, which makes B and T lymphocytes incapable of migrating from secondary lymphoid organs, with subsequent reduction in circulating lymphocytes[51]. Being an oral formulation, Ozanimod represents an alternative to infusions of monoclonal antibodies for the treatment of UC, with no risk of sensitization and formation of antidrug antibodies. On the other hand, this product can be less selective than monoclonal antibodies, which may expose to adverse effects[51].

Sandborn *et al*[51] performed a double-blind, placebo-controlled phase 2 trial of Ozanimod in 197 adults with moderate-to-severe UC. Clinical remission at 8 wk was observed in 16% of the patients who received 1 mg of Ozanimod and in 14% of those who received 0.5 mg, as compared with 6% of those who received placebo (P = 0.048, P = 0.14, respectively) (Table 1).

At week 32, the rate of clinical remission was 21% in the group that received 1 mg of Ozanimod, 26% in the group that received 0.5 mg of Ozanimod, and 6% in the group that received placebo; the rate of clinical response was 51%, 35%, and 20%, respectively[51].

At week 8, absolute lymphocyte counts dropped by 49% from baseline in the group that received 1 mg of Ozanimod and by 32% from baseline in the group that received 0.5 mg[51]. The most common adverse events overall were anemia and headache[52].

From this preliminary trial, the Authors conclude that Ozanimod at a daily dose of 1 mg is more effective than placebo in inducing clinical remission of UC. However, complete assessment of clinical efficacy and safety could not be achieved by this trial due to limitations in size and duration[51]. Another monoclonal antibody recently investigated is the anti-natural killer group 2 member D (NKG2D), which acts by antagonising the human immunoglobulin G4 that binds to NKG2D receptors.

The interaction between intestinal epithelial cells and T-cells in the gut mucosa has a key role in T-cell regulation. NKG2D receptors are expressed by T cells and innate lymphoid cells, and exhibit pro-inflammatory properties. Upregulated NKG2D ligands on epithelial cells in the inflamed tissue of patients with IBD may activate the proliferation of several subsets of effector T-cells, leading to increased production of pro-inflammatory cytokines and enhanced cytotoxicity[52]. Previous trials have demonstrated an increase in effector T cells as well as in the expression of NK receptors on T cells in patients with CD[52]. Also, neutralising anti-NKG2D antibodies have been shown to reduce inflammatory-induced colitis in murine models[52].

Allez *et al*[52] performed a randomised, double-blind, parallel group trial of a single subcutaneous dose of 2 mg/kg anti-NKG2D or placebo in 78 adult patients with active CD (Table 1).

Change in CDAI from baseline to week 4 was the primary end-point, and was not found to differ significantly between anti-NKG2D and placebo; however, a significant difference was observed by week 12 ($P \leqslant 0.10$)[52]. The group of patients who hadn't previously failed biologics and were treated with anti-NKG2D (n = 28) showed the most significant improvement from week 1 onward. Most adverse events were mild (49%) or moderate (43%). No antidrug antibodies were detected[52].

Based on the results of this trials, the Authors conclude that a single s.c. dose of 2 mg/kg anti-NKG2D did not reduce disease activity at week 4, but it showed significant response rate at week 12. Therefore, there is evidence to consider further investment in anti-NKG2D in IBD[52].

DISCUSSION

Though major progress has been achieved in treating IBD patients of all ages, there are still significant limitations in what is currently available to manage this condition. The advent of new biologics and other medications targeting pathways previously unexplored (*e.g.*, leukocyte trafficking through the gut mucosa) has provided clinicians with more hope for patients who fail to respond to current treatments. Nevertheless, whilst the causative mechanisms underlying IBD are not yet fully understood, treatment options can only target downstream components of this inflammatory chain.

IBD, and CD in particular, are difficult to categorise as distinct disease entities, as the spectrum of its clinical phenotype is very broad and variable, with mild disease responding to standard treatments, and severe disease often developing to structuring or penetrating

Table 2 Summary and take home messages

1. The pathogenesis of IBD is not completely understood yet, and all therapies currently available are aimed at downstream steps of the complex inflammatory process. Specific targets when treating children with IBD are achieving satisfactory growth and nutritional status.
2. Paediatric pharmacometric approaches are increasingly applied to drugs already in use but that remain unlicensed and off-label in children due to missing information on age appropriate dosing, efficacy and safety.
3. Corticosteroids can be used to induce remission in CD (when exclusive enteral nutrition is not possible) and are first-line therapy for induction of remission in UC, particularly in case of non-response to 5-ASA or with severe presentation.
4. One of the targets of current research is to customise therapy to a patient's predictive biomarker profile in order to personalise treatments and to maximise response.
5. 5-ASA are used in induction and maintenance of remission in UC. They are not recommended in CD except from post-operative maintenance of remission.
6. Thiopurines include AZA and 6-MP and are steroid sparing agents. They are effective in maintaining disease remission in patients with CD and UC as well as post-surgical remission in CD. The use of TPMT activity and 6-TGN level measurements helps avoiding nearly a quarter of episodes of myelosuppression as well as to monitor non-compliance, under-dosing, drug-resistance or refractory state.
7. An increase in mean 6-TGN blood level has been reported in patients on 6-MP or AZA co-treated with 5-ASA, with a higher rate of myelotoxicity in respect to patients treated with the thiopurine alone.
8. MTX is effective in 50%-80% of the children who fail to respond or are intolerant to thiopurines. It is particularly suitable to patients who have coexistent inflammatory arthritis.
9. In CD, anti-TNF agents are used to treat moderate to severe disease with inadequate response, or contraindication to, or intolerance to, conventional therapy including corticosteroids and immunomodulators. They are also indicated in children with active perianal fistulising disease. Therapeutic drug monitoring of IFX has improved response rates and is increasingly used in clinical practice as a tool for the management of secondary failure to IFX.
10. ADA is a fully human IgG1k monoclonal antibody, which represents a treatment option in patients who have lost response or are intolerant to IFX. ADA achieves remission rates of 45% at 1 yr in anti-TNF naïve children and is effective in nearly 2/3 of patients with IFX failure.
11. Vedolizumab is an anti-integrin therapy which inhibits the migration of intestinal T lymphocytes. The mechanism of action of Vedolizumab is restricted to the GI tract, mitigating the risks of systemic immunosuppression such as infections and malignancies. The clinical response rate for induction with vedolizumab is 50% in UC patients. Vedolizumab is approved for treatment of CD and UC in adults and there is increasing off-label use in children.
12. Thalidomide is an immunosuppressant drug used infrequently off-label in the treatment of refractory CD and UC. Induction of remission is achieved in aroud 50% cases and clinical response in 70%.
13. Drug therapies that interfere selectively with lymphocyte trafficking (*e.g.*, etrolizumab, ozanimod) are emerging treatment options for UC.

UC: Ulcerative colitis; IBD: Inflammatory bowel disease; ADA: Adalimumab; IFX: Infliximab; TPMT: Thiopurine methyl transferase; 5-ASA: Aminosalicylates; CD: Crohn's disease; 6-MP: 6-mercaptopurine; AZA: Azathioprine; MTX: Methotrexate; GI: Gastrointestinal.

phenotypes that require surgery, despite the use of multiple treatment escalations[53]. Once significant chronic bowel damage occurs in IBD, the chances of recovery with medical treatments alone are limited. Therefore, the ideal treatment should be offered before complications develop[53]. Step-up and top-down approaches have been debated for different risk groups of children with IBD. The management of paediatric IBD has evolved significantly over recent years with evidence-based guidelines in place to provide uniform and solid guidance in clinical practice. Nevertheless, a long-term response is only observed in less than half of the patients with CD[3,52]. Although new biologics are continuously being developed, primarily monoclonal antibodies targeting the trafficking of immune cells, we certainly are in need of more therapies with novel mechanisms of action[52]. More significant advances have been achieved in monitoring drug administration and the response to medications, in particular the clinical availability of AZA metabolites, IFX and ADA trough levels and anti-IFX antibody measurements in clinical practice (*i.e.*, TDM). This has allowed a major step forward in monitoring and targeting patients' treatments with a more personalised approach.

Despite routine use of solid clinical scores (*e.g.*, PCDAI, PUCAI) and biochemical parameters (blood-based and stool-based), we are currently still depending on invasive reassessments (*i.e.*, endoscopic procedures) for an adequate monitoring of the disease course. One next goal on the horizon is therefore the development of reliable biomarkers to be used for prediction of prognostic outcomes in IBD. The ability to stratify individual patients' risk would allow clinicians to personalise treatment from disease presentation, tailoring more potent drugs (possibly in combination) to patients with a high risk of severe disease, using more standard options for patients who are destined for a milder disease course[53]. This individualised approach requires reliable prognostic biomarkers and hence major efforts are being made in the development of such markers. Risk stratification models would allow clinicians to treat patients effectively before complications arise, and to optimise majorly the management of patients with IBD as improve the cost effectiveness of their care[53].

CONCLUSION

Our narrative review summarises some of the recent advances in treating children with IBD (Table 2). Whilst the mechanisms underlying this condition are yet to be fully understood, both old and new generation treatments can still only target known pathways of what is a very complex pathogenesis. A significant proportion of children with IBD does not respond to currently available treatments, either at diagnosis

or during disease course, therefore new treatment options are urgently needed. Major advances have been achieved in monitoring the individual metabolism, toxicity and response to treatments in IBD. Amongst the priorities in current research is the development of reliable prognostic biomarkers, an essential step towards the personalised treatment of patients with IBD.

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P- Reviewer: Matowicka-Karna J, Tambuwala M, Zhang MZ
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ISSN 1007-9327