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Precision medicine for pediatric inflammatory bowel disease: a perspective

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ABSTRACT

There has been a growing need to utilize the concept of "precision medicine" in the treatment of inflammatory bowel disease (IBD). In practice, precision medicine for IBD comprises prediction and personalizing therapies. Prediction is divided into two subcategories: pre-treatment investigation and monitoring response to therapy. Pre-treatment prediction includes clinical outcome assessment, investigation of factors for poor outcome, magnetic resonance enterography, and measurement of TPMT, NUDT15, and other biologic markers. Mucosal healing or transmural healing is considered the "treat-to-target" approach in IBD. To achieve "treat-to-target," the "top-down strategy" is recommended in patients with pediatric Crohn's disease, because the therapeutic window of opportunity may be shorter than that generally believed. We are unable to state that we are truly utilizing biologics in a perfect manner until both "treat-to-target" and "top-down strategy" are supported by "therapeutic drug monitoring (TDM)," a key component of personalizing therapy for IBD. Proactive TDM, or more precisely, model-based proactive dosing with point-of-care assay will soon emerge as the new standard for IBD treatment. It is speculated that "treat-to-target," "top-down strategy," and "TDM" may aid personalized therapy to achieve outstanding improvement in patients with pediatric IBD.

Keywords: Biologic products; Drug monitoring; Humans; Inflammatory bowel disease; Precision medicine

INTRODUCTION

A new era of precision medicine has arrived [1]. Everyone working in the medical field is trying to adopt new initiatives in precision medicine. Precision medicine refers to the "tailoring of medical treatment to the individual characteristics of each patient [2]." Crohn's disease (CD) and ulcerative colitis (UC) have complex pathophysiology including genomes and immune responses, variable clinical manifestations and disease courses, stepwise treatment options, many clinical parameters for monitoring, and unpredictable complications. Therefore, there has been a growing need to utilize the "precision medicine" concept in the treatment of inflammatory bowel disease (IBD).

For optimal "precision medicine" in IBD, precise analysis of the pathophysiology on a case

by case basis should take precedence. However, the exact pathogenesis of IBD remains unknown. Genetic investigations such as genome-wide association studies reveal only about 25% of IBD heritability [3]. Even though a recent study on multi-omics of the gut microbiome in IBD provided the most comprehensive descriptions of host and microbial activities in 132 subjects for 1 year, it is still unknown whether dysbiosis is the cause or result of IBD [4]. A study that immunological dysregulation within the gut leading to imbalances in pro- and anti-inflammatory pathways is involved in innate and adaptive immunity showed the possible development and persistence of inflammation in IBD [5]. Approximately 25% of patients with CD develop symptoms during childhood or adolescence, and pediatric CD is more progressive and extensive than adult-onset CD [6]. Moreover, linear growth impairment is a unique feature of pediatric CD [7]. For the pediatric gastroenterologist, the issue of timing of initiating early biologic treatment is of common interest and one that should be clarified in patients with pediatric IBD [8].

Because of complex disease susceptibility and clinical phenotype, the real-world concept of precision medicine to improve the outcome of patients with pediatric IBD needs to be narrowed down to personalizing therapies by clinicians who attend to these patients. Practical precision medicine in IBD consists of two key areas; one is prediction and the other, personalizing therapies. Prediction is divided into two subcategories: pre-treatment investigation and monitoring response to therapy.

In this article, I focus on the real-world practice of precision medicine in pediatric IBD.

PREDICTION I: PRE-TREATMENT

Clinical outcome assessment

In order to select the optimal treatment and predict short- and long-term prognosis, clinicians should be aware of the current status of the patient, based on the objective criteria. Until recently, clinical outcomes have been assessed using the Pediatric Crohn's Disease Activity Index (PCDAI), which is very simple and useful to define severity grading, remission, loss of response, and relapse [9]. It has also been modified as the abbreviated, short, modified, and weighted PCDAI to address various limitations [10]. Because colonoscopic assessment is less acceptable in children, the noninvasive Pediatric Ulcerative Colitis Activity Index (PUCAI) was developed [11]. However, consensus on the definition of successful treatment outcome (clinical response and/or remission) and collaboration in the development of well-defined and reliable measures of signs and symptoms for use in conjunction with endoscopic parameters of mucosal healing has become necessary to facilitate pediatric IBD drug development [12]. Endoscopy in pediatric IBD provides a more definitive diagnosis and disease extent evaluation, assesses therapeutic efficacy, and leads to a targeted therapy [13]. The reference standard score to evaluate mucosal healing can be measured using the Crohn's Disease Endoscopic Index of Severity (CDEIS), Simple Endoscopic Score for Crohn's Disease (SES-CD), and the Rutgeerts score (for assessing after ileocecal resection) in CD, and the Mayo score, Ulcerative Colitis Endoscopic Index of Severity (UCEIS), and Ulcerative Colitis Colonoscopic Index of Severity (UCCIS) in UC. As a noninvasive surrogate biomarker, fecal calprotectin is available to reveal the current mucosal inflammation and is used in an algorithm for monitoring pediatric UC during the maintenance phase [14].

After clinical outcome assessment, clinicians classify the patients into subgroups. In 2010, pediatric modification and modernization of the Montreal Classification for IBD by the international group of pediatric IBD experts led to the Paris Classification [15]. The Paris Classification includes age at diagnosis, location, behavior, and growth for CD, and extent and severity for UC.

Factors for poor outcome

According to the consensus guidelines of the European Crohn's and Colitis Organization (ECCO)/European Society of Pediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN), deep colonic ulceration, persistent severe disease despite adequate induction therapy, extensive (pan-enteric) disease, marked growth retardation, severe osteoporosis, structuring and penetration disease at onset, and severe perianal disease are considered as potentially predictive for poor outcome. These factors may lead to anti-tumor necrosis factor (TNF) therapy as the first-line treatment on an individual basis [16].

TPMT and 6-thioguanine nucleotide

Thiopurines are recommended as an option for maintenance of steroid-free remission in children at risk for poor disease outcome, and for reducing the formation of antibodies to biologics [16,17]. Azathioprine (AZA) is converted to the inactive metabolite 6-methylmercaptopurine by thiopurine S-methyltransferase (TPMT), and patients with inherited TPMT deficiency present with higher 6-thioguanine nucleotide (6-TGN) level and have an increased risk of myelotoxicity [18]. Myelosuppression in patients with IBD treated with thiopurine is re-

ported more frequently in Korea (31.0% to 56.4%) than in Western countries (2.0% to 16.7%) [18]. According to a Korean report, 137 patients with IBD treated with AZA showed a wild type (**1/*1*) in 130 (94.9%) patients and variant genotypes in seven patients (**1/*3C* in four, **1/*6* in one, **1/*16* in one, and **3C/*3C* in one) [19]. They also reported that the AZA dosing guidelines for Asian patients with IBD (median AZA dose, 1.01 mg/kg/day in this study) may be lower than those of universal guidelines (2 to 3 mg/kg/day in the Clinical Pharmacogenetics Implementation Consortium guidelines [20] and 1.5 to 2.5 mg/kg/day in the ECCO guidelines [21]).

NUDT15

In addition to TPMT gene polymorphism, a recent genome-wide association study reported nudix hydrolase 15 (NUDT15) as a novel thiopurine-metabolizing enzyme, a missense variant of which is strongly associated with thiopurine-induced leukopenia, especially in Asians [22]. Previous studies have reported no difference in 6-TGN levels among the NUDT15 genotypes, which implies that NUDT15 variants are independent of 6-TGN levels [23,24]. Recently, we conducted a study on NUDT15 polymorphisms in 167 Korean patients who were treated with AZA (unpublished data). Leukopenia was observed in 16% (19/119), 44% (20/45), and 100% (3/3) of the NUDT15 normal (**1/*1*), intermediate (**1/*2, *1/*3, *1/*5*, and **1/*6*), and poor (**3/*3*) metabolizer groups, respectively. NUDT15 polymorphism was the only factor associated with time-to-leukopenia (hazard ratio [HR], 4.64; 95% confidence interval [CI], 2.28 to 9.45; $P<0.001$). Additional analysis revealed that the 6-TGN levels were significantly higher in patients with leukopenia than those without leukopenia among the 'NUDT15 intermediate+TPMT normal' metabolizer subgroup (median 361.3 vs. 263.8 pmol/8 $\times 10^8$ RBC, $P=0.013$), indicating that a lower 6-TGN cut-off level is required to avoid leukopenia in this subgroup during AZA treatment. We found that the NUDT15 variant is the most potent factor associated with thiopurine-induced leukopenia and time-to-leukopenia in patients with pediatric IBD during AZA treatment regularly adjusted by thiopurine metabolite monitoring. Therefore, pre-treatment determination of the NUDT15 genotype represents a helpful and effective method for avoiding this life-threatening adverse effect of thiopurines, especially in East Asian pediatric patients.

Anti-*Saccharomyces cerevisiae* antibodies

Anti-*Saccharomyces cerevisiae* antibodies (ASCA) are a useful tool for distinguishing CD from UC [25], and its value as a prognostic marker has been gradually recognized [26]. ASCA is known to be common in younger age groups and those with ileal involvement, fibrostenosis, and more aggressive disease behavior [27]. Several studies have examined whether ASCA titers changed with disease activity, and successful treatment has shown that its titers were stable or decreased [28,29]. Recently, our team evaluated the role of ASCA as a predictor of clinical remission and mucosal healing in 61 patients with pediatric IBD (unpublished data). Their ASCA titers maintained similar levels for up to 7 years, and repeated measurements of ASCA after diagnosis are considered unnecessary. In patients who have not achieved mucosal healing, ASCA is closely related with mucosal damage and clinical remission. Therefore, monitoring seems necessary when the titer is initially high. Unlike in Western studies, ASCA immunoglobulin G (IgG) is more helpful than IgA in predicting prognosis in Korean patients. However, it is speculated that ASCA alone is not enough to be used as an indicator predicting the relapse.

Magnetic resonance enterography

Recently, magnetic resonance enterography (MRE) and computer tomography enterography have emerged as useful tools for determining small bowel involvement and perianal lesions in CD [30]. The main advantage of MRE over computer tomography enterography is its lack of ionizing radiation, which is of particular importance when considering small bowel imaging studies in children [31]. The magnetic resonance index of activity (MaRIA) score, a quantitative assessment index based on MRE, was developed and validated for use in the detection of mucosal ulcers and the evaluation of mucosal healing in active CD in adults [32,33]. Our team conducted a study to evaluate 1-year treatment responses to combined immunosuppression using MaRIA with the SES-CD as the reference standard in children and adolescents [34]. Therapeutic response assessed by MRE correlated with ileocolonoscopic findings. It was concluded that the baseline wall thickness was lower in mucosa-healed segments 1 year after anti-TNF treatment.

Transmural healing is emerging as a new optimal treatment goal, and we also investigated transmural healing and its relationship with mucosal healing in 72 patients with pediatric CD under maintenance treatment with biologics (unpublished data). Transmural healing was defined as wall thickness ≤ 3 mm with the absence of ulcers, edema, enhancement, and complications on all ileocolonic segments evaluated by MRE. At 1-year, mucosal healing and transmural healing were achieved in 59.7% and 22.3% of the subjects,

respectively. At 2-year, they were achieved in 66.7% and 17.2%, respectively. The efforts to achieve transmural healing may alter the natural course of CD in the era of treat-to-target.

REAL WORLD TREATMENT

Treat-to-target

The "treat-to-target" approach started from the concept based on the selection of appropriate treatment targets and subsequent adjustment of treatment [35]. In many chronic diseases, reaching an objective target improves long-term outcomes such as low blood pressure in hypertension or low hemoglobin A1c in diabetes. After risk stratification, we specify a target and continue therapy with target surveillance [36]. In IBD, we use this strategy to avoid long-term bowel damage. According to data from large-scale cohort studies and randomized controlled trials, mucosal healing or transmural healing is considered to be the potential treatment target in CD [37-40].

Initiating biologics in pediatric IBD

The rationale to target early CD, especially in children, lies in the fact that they are in the stage of inflammation. They do not yet have fistula, abscess, or stricture. Biologic antibodies to TNF are the strongest anti-inflammatory agents to heal the mucosa. When CD progresses to the fibrostenosing stage, it is more difficult to reverse the bowel damage even with biologics. A recent prospective inception cohort study showed that patients who received early anti-TNF therapy were less likely to have penetrating complications, supporting the usefulness of risk stratification of patients with pediatric CD at diagnosis, and selection of biologics [41].

Preference for the top-down strategy

There are some reasons why I recommend the top-down strategy in pediatric CD. First, it helps better and faster mucosal healing. Kang et al. [42] investigated mucosal healing in patients receiving combo treatment and compared the outcomes between escalation and early treatment. Seventy-eight patients were divided into two groups: the step-up and top-down groups. At 1-year, mucosal healing was better in the top-down group than that in the step-up group. When we investigated the factors associated with mucosal healing at 1 year using multivariate analysis with stepwise selection, the top-down group and mucosal healing at 14 weeks were positively associated with 1-year mucosal healing. Second,

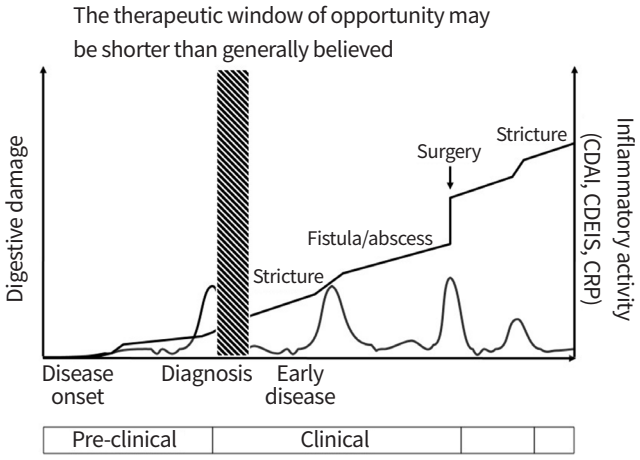

Fig. 1. **Progression of digestive damage and inflammatory activity in a theoretical patient with Crohn's disease (CD). The reason "top-down" strategy is recommended in pediatric CD is because the therapeutic window of opportunity may be shorter than generally believed. Adapted from Pariente et al. [45]. CDAI, Crohn's Disease Activity Index; CDEIS, Crohn's Disease Endoscopic Index of Severity; CRP, C-reactive protein.**

our team compared long-term remission between the top-down and step-up treatments. The top-down strategy had a longer remission period than that of the step-up strategy in pediatric Crohn disease during the study period of 3 years based on the relapse-free rate and remission period rate [43]. Third, because data comparing the efficacy of the two approaches on growth of children are limited, we investigated the effect of early combined immunosuppression on linear growth in patients with pediatric CD who had sustained remission for 3 years in comparison with those treated by the step-up strategy. The top-down group displayed superior linear growth 3 years after diagnosis ($P=0.026$). Moreover, a significant difference was also observed in the linear growth of a subgroup at Tanner stages 1–2 ($P=0.016$). It was late when the treatment started at Tanner stages 4–5 [44]. Based on the above lines of evidence, I would recommend the top-down strategy, especially in pediatric CD, because the therapeutic window of opportunity may be shorter than generally believed (Fig. 1) [45].

PREDICTION II: THERAPEUTIC DRUG MONITORING, A RESPONSE MONITORING DURING MAINTENANCE

Clinical significance of therapeutic drug monitoring

Assuming that we start treating patients with IBD with biologic antibodies, what would be the issues of most concern?

The answer must be how to optimize treatment and how to prevent adverse events. For optimal and safe treatment, therapeutic drug monitoring (TDM) is mandatory. TDM provides us not only the important information regarding prediction of patient's response to biologics and/or immunomodulators such as primary non-response, secondary loss of response, remission, relapse, and adverse events during the maintenance of treatment, but also the algorithmic approach in treatment on an individual basis. TDM comprises trough level (TL) and anti-drug antibody measurement. The representative clinical significance of TDM is that high anti-TNF TLs and low anti-drug antibodies are associated with superior clinical and endoscopic outcomes. It is well known that patients who have poor responses and subtherapeutic infliximab (IFX) TLs have an improved response to dose intensification [46]. However, TDM is not yet widely used over the world. CALM study showed that timely escalation with an anti-TNF therapy on the basis of clinical symptoms combined with biomarkers (fecal calprotectin and C-reactive protein) resulted in better clinical and endoscopic outcomes [47].

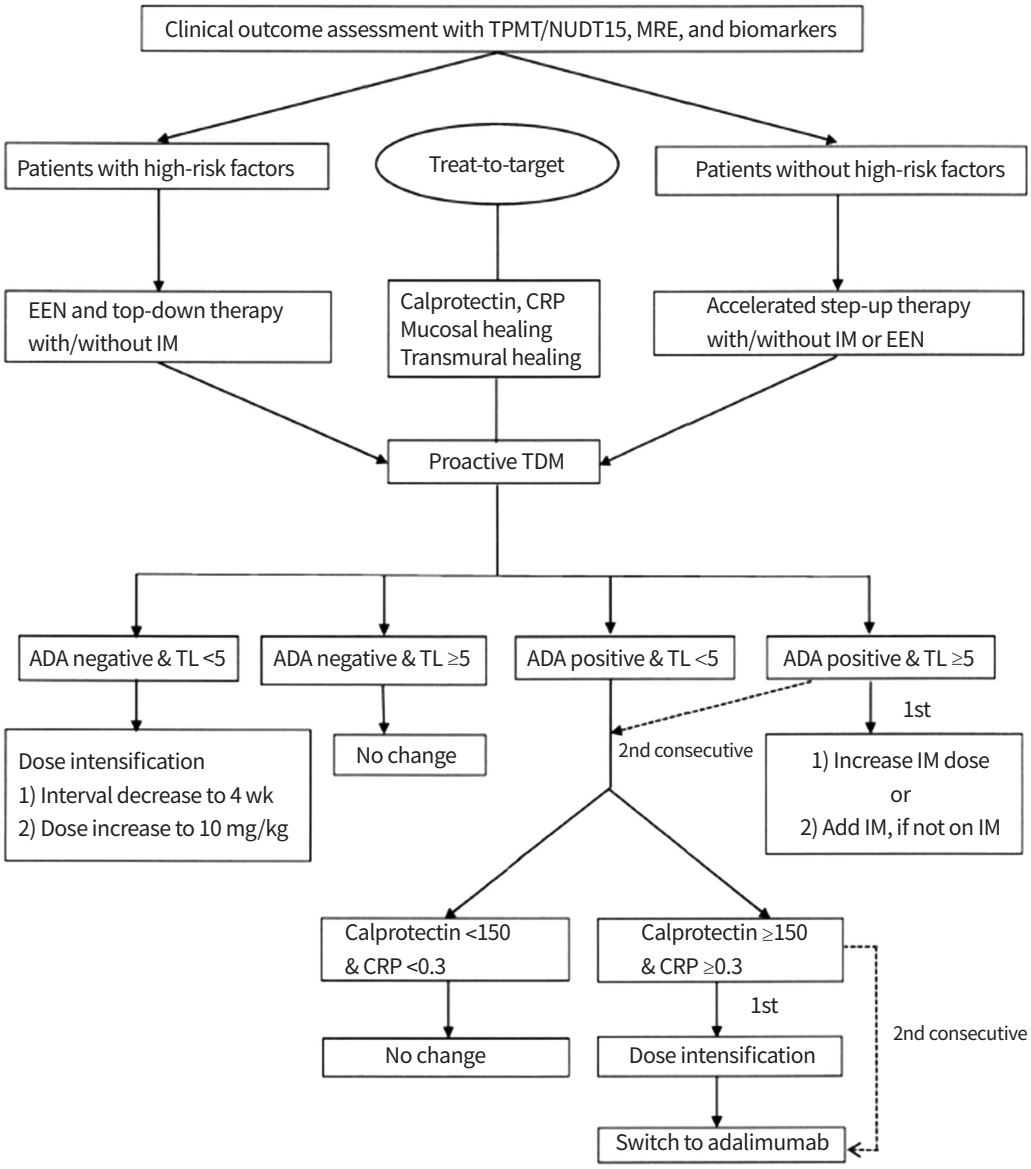

Fig. 2. The Samsung Medical Center protocol of personalizing therapy with infliximab for patients with pediatric Crohn's disease. Measurement units: trough level (TL), μg/mL; anti-drug antibody (ADA), AU/mL; calprotectin, μg/g; C-reactive protein (CRP), mg/dL. High-risk factors: deep colonic ulcerations, extensive disease, marked growth retardation, severe osteoporosis, B2 and/or B3 behavior, severe perianal disease. Adapted from Ruemmele et al. [16]. TPMT, thiopurine S-methyltransferase; NUDT15, nudix hydrolase 15; MRE, magnetic resonance enterography; EEN, exclusive enteral nutrition; IM, immunomodulator; TDM, therapeutic drug monitoring.

Reactive vs. proactive TDM

Reactive TDM is widely accepted in practice at the time of loss of response, especially for anti-TNF antibodies. Besides reactive testing, there is a movement toward proactively adjusting biologic dosing to prevent loss of response, in keeping with the tight control philosophy of IBD care [48]. Although the American Gastroenterological Association advocates reactive TDM in adults with active IBD failing response to anti-TNF therapy in a recent guideline regarding TDM, Papamichael et al. [49] contradict this statement. They mention that it is more rational to proactively optimize anti-TNF therapy before immunogenicity and/or loss of response, because proactive TDM is a standard of care for many medical therapies such as anticoagulants, antibiotics, and transplantation [50]. Our team at the Samsung Medical Center is also using the proactive TDM protocol in pediatric patients with moderate-to severe CD (Fig. 2). As worldwide data accumulate, it is expected that proactive TDM will emerge as the standard IBD treatment.

De-escalation

There are currently insufficient data to recommend when and in whom discontinuing anti-TNF treatment is suitable among patients with CD, and in clinical practice, the decision of whether to continue biologics is typically based on weighing the risks and benefits for each patient on an individual basis [51]. According to clinicians who treat patients with IBD, we are concerned regarding loss of response or relapse during maintenance; therefore, doctors prefer the long-term use of current biologics. However, if I were a patient or a parent of the patient who is in the quiescent phase, I would consider cessation of the biologic antibodies and/or immunomodulators because of the possible adverse events after long-term use. According to a STORI trial, an IFX TL of $\geq$2 μg/mL was associated with relapse after IFX cessation (HR, 2.5; 95% CI, 1.1 to 5.4; P=0.02) [52]. Meanwhile, Papamichael et al. [53] reported that an IFX TL of <6 μg/mL was associated with sustained clinical remission after IFX cessation. We also conducted a study on subtherapeutic IFX TLs and complete mucosal healing associated with sustained clinical remission after IFX cessation in patients with pediatric CD. Patients were followed for up to 7 years after IFX cessation and the sustained clinical remission rate was high when IFX was stopped at TL under 2.5 μg/mL and complete mucosal healing was achieved [51]. It is speculated that there may be a subgroup of patients who are good candidates for IFX withdrawal, even though IFX cessation in patients with pediatric CD remains inadvisable at present.

Point-of-care assay

Point-of-care (POC) assays are analytical devices that can be performed on-site for TDM by clinical staff without laboratory training and ideally without the need for sample transportation and preparation, thereby decreasing the turnaround time. POC assay is quite promising in optimizing the drug dosage based on real-time pharmacokinetic information without a delay in information by weeks to months as previously [48]. If the whole blood can be applied technically for assay instead of the serum, on-site use of POC TDM will become widespread. While not currently available for all biologics, POC TDM is warranted in certain circumstances such as acute severe colitis and enables personalized, precision dosing [54].

NEW CONCEPT OF IBD TREATMENT

Optimized monotherapy

Although current data have suggested that combination therapy is superior to IFX monotherapy, a retrospective study showed that optimizing IFX to a TL of $\geq$5 μg/mL may provide an alternative treatment strategy to combination therapy, suggesting proactive TDM can potentially guide immunomodulatory withdrawal in patients on combination therapy [55]. A recent study further supported the concept of "optimized monotherapy" by showing that IFX durability did not differ between patients on IFX monotherapy doses based on proactive TDM and patients receiving combination therapy, if the first maintenance infusion is dosed based on week 10 proactive TDM [56].

Dual biologic treatment

Anti-TNF antibodies are widely used biologic agents for IBD treatment, and vedolizumab is a monoclonal antibody against a4b7, an integrin facilitating leucocyte migration to the gut via binding of MADCAM1 on the intestinal endothelium. A gut-specific anti-integrin therapy like vedolizumab has the benefit of being potentially safer than systemic therapies and could be the ideal drug for concomitant use with other target therapies [57]. Given its mechanism of action, it seems reasonable to postulate that vedolizumab could be safely combined with other biologics, without increasing the risk of serious infections [57]. Through a systematic review including seven studies with 18 patients who received dual biologics, Ribaldone et al. [57] reported that a clinical improvement was obtained in 100% of patients and an endoscopic improvement in 93% of patients. No serious adverse events

were reported. They concluded that the use of dual biological therapy is an attractive therapeutic option and may be an opportunity to better tailor and personalize the therapies for patients [57].

Model-informed precision dosing

Even though reactive or proactive TDM algorithms have proposed optimal dosing strategies to guide rational decision making, there are still numerous cases with unpredictable pharmacokinetic variability, which confuses clinical practitioners, thereby undermining the benefits of TDM. Model-informed precision dosing (MIPD) has emerged as a strategy to overcome this problem. A population pharmacokinetic model is the basis of MIPD and serves as a Bayesian prior [48]. Based on patient characteristics and drug concentration measurements, the individual pharmacokinetic parameters can be calculated (empiric Bayes estimates) and subsequently be used to predict the next dose that is required for that patient to achieve a predefined exposure target [48]. Strik et al. [58] conducted a study to compare the efficacy of model-based dose optimization of IFX TL 3.0 μg/mL with that of a control group that continued IFX dosing without dose adaptation in the PRECISION trial. They revealed that a higher proportion of patients significantly maintained clinical remission when on model-based TDM.

CONCLUSION

This review discusses the real-world practice of patients with pediatric IBD from pre-treatment prediction to maintenance therapy with TDM, and suggests future treatment strategy based on the current possible approach of precision medicine. The "treat-to-target" concept gave birth to the "top-down strategy," especially in pediatric IBD, even though each of these started from different branches of medicine. There has been a trend that both have converged during the past decade. We are unable to state that we are truly utilizing biologics in a perfect manner until both the "treat-to-target" and "top-down strategy" are supported by "TDM," a key component of personalizing therapy for IBD. Proactive TDM, more precisely, model-based proactive dosing with POC assay will soon emerge as the new standard for IBD treatment. In conclusion, it is speculated that "treat-to-target," "top-down strategy," and "TDM" are in the same context of personalizing therapy to achieve outstanding improvement in patients with IBD.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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AUTHOR CONTRIBUTIONS

Conception or design: YHC.
Acquisition, analysis, or interpretation of data: YHC.
Drafting the work or revising: YHC.
Final approval of the manuscript: YHC.

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