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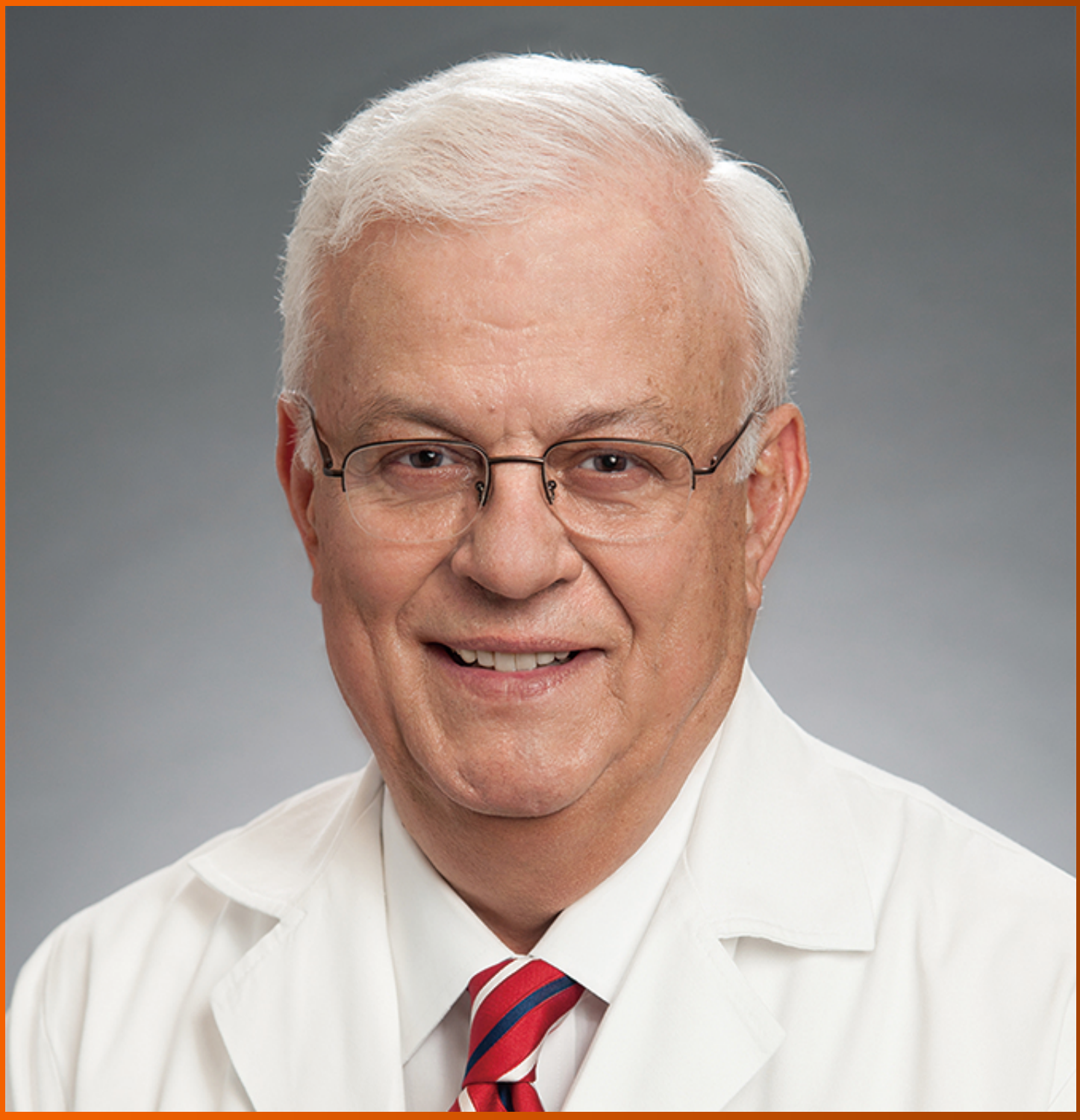

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REVIEW

Precision medicine in inflammatory bowel disease: Individualizing the use of biologics and small molecule therapies

Eric Cheah, James Guoxian Huang

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Eric Cheah, Department of Gastroenterology and Clinical Nutrition, The Royal Children's Hospital Melbourne, Parkville, VIC 3052, Australia

James Guoxian Huang, Department of Paediatrics, Khoo Teck Puat-National University Children's Medical Institute, National University Health System, Singapore 119228, Singapore

James Guoxian Huang, Department of Paediatrics, Yong Loo Lin School of Medicine, National University of Singapore, Singapore 119228, Singapore

Corresponding author: James Guoxian Huang, MBBS, Assistant Professor, Attending Doctor, Staff Physician, Department of Pediatrics, Khoo Teck Puat-National University Children's Medical Institute, National University Health System, NUHS Tower Block Level 12, 1E Kent Ridge Road, Singapore 119228, Singapore. james_huang@nuhs.edu.sg

Abstract

The advent of biologics and small molecules in inflammatory bowel disease (IBD) has marked a significant turning point in the prognosis of IBD, decreasing the rates of corticosteroid dependence, hospitalizations and improving overall quality of life. The introduction of biosimilars has also increased affordability and enhanced access to these otherwise costly targeted therapies. Biologics do not yet represent a complete panacea: A subset of patients do not respond to first-line anti-tumor necrosis factor (TNF)-alpha agents or may subsequently demonstrate a secondary loss of response. Patients who fail to respond to anti-TNF agents typically have a poorer response rate to second-line biologics. It is uncertain which patient would benefit from a different sequencing of biologics or even a combination of biologic agents. The introduction of newer classes of biologics and small molecules may provide alternative therapeutic targets for patients with refractory disease. This review examines the therapeutic ceiling in current treatment strategies of IBD and the potential paradigm shifts in the future.

Key Words: Precision medicine; Therapeutic ceiling; Inflammatory bowel disease; Biologics; Small molecules

Core Tip: Precision medicine and individualizing patient care has been the holy grail in the management of inflammatory bowel disease (IBD). A one-size-fits-all approach, utilizing the current armamentarium of biologics and small molecules, still yields less than ideal clinical outcomes, with significantly high non-response rates. Multiple challenges remain in breaking this therapeutic ceiling: Achieving an early diagnosis of IBD ideally even in the pre-clinical phase; accurately prognosticating the disease course; and tailoring an appropriately sequenced therapy regime to a patient's disease severity, pharmacokinetic and pharmacodynamic profile.

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INTRODUCTION

The incidence of inflammatory bowel disease (IBD) has seen a rise within Asia Pacific. Overall incidence and prevalence rates in Asia are lower than the West, but are on the rise[1,2]. Treatment of IBD has progressed rapidly over the past several decades. A new era in the treatment of IBD began with the development of the chimeric monoclonal anti-tumor necrosis factor (TNF)-alpha antibody cA2 in the early 1990's. cA2 was subsequently renamed infliximab, and was first licensed by the United States Food and Drug Administration (FDA) in August 1998 for the treatment of Crohn's disease (CD)[3]. Since the introduction of infliximab, there has been an advent of newer biologics and small molecule agents, along with paradigm shifts in the treatment goals of IBD. The agents currently FDA approved for use include the anti-integrin (vedolizumab), anti-interleukin (IL)-12/23 p40 (ustekinumab), anti-IL-23p19 (risankizumab), oral Janus kinase (JAK) inhibitors (tofacitinib, upadacitinib), and sphingosine-1-phosphate (S1P) receptor modulator (ozanimod). As of 2019, mesenchymal stem cell therapy (darvadstrocel) received a regenerative medicine advanced therapy designation for complex perianal fistulas in adult patients with CD. New targets and treatments being explored in Phase II/III trials include anti-integrin (etrolizumab, ontamalimab), IL-23p19 inhibitors (mirikizumab, brazikumab, guselkumab), oral JAK inhibitor (filgotinib), and S1P modulator (etrasimod)[4].

Current treatment goals in IBD aim to more than just achieve clinical remission. Deep remission, the combination of clinical remission and mucosal healing, represents an important therapeutic target that is now increasingly attainable with the timely use of biologics[5]. Expert consensus statements in the STRIDE[1]/STRIDE-II guidelines, with evidence from the CALM study, have helped us define treat-to-target strategies in adults and children utilizing clinical indices, biomarkers, and endoscopic parameters [6-8]. Aspirational targets include transmural healing in CD and histologic healing in ulcerative colitis (UC).

There is an increasing need to develop newer biologics and small molecules targeting novel cytokine pathways, as current therapeutic options are far from perfect in achieving the above-mentioned treatment targets. A meta-analysis of real-world deep remission rates with anti-TNF agents demonstrated that deep remission was only achieved in 48.6% of CD patients and 43.6% of UC patients at 1 year[9]. In a review by Papamichael *et al*[10], the rates of primary non-response and non-remission to anti-TNF agents in IBD were between 10%-40% and 50%-80%, respectively. A further 23%-46% of those initial responders or those who achieve remission have a secondary loss of response over time [11]. The clinical remission rates with second-line biologics are also poorer in patients, who have had a prior loss of response to anti-TNF agents, especially those who had a primary non-response[12-14]. Such data distinctly highlight the therapeutic ceiling in current IBD management: how can we optimize current therapies to go beyond this therapeutic ceiling?

BIOMARKERS IN IBD

Predictive and prognostic biomarkers, pharmacogenomics, and response to therapy

Precision and personalized medicine has long been a discussed topic in the management of IBD. It is an aspirational goal to accurately predict those with a complicated and aggressive clinical course, and to administer timely targeted therapy to the individual's molecular inflammatory profile[15]. Particularly for CD, the emphasis is for appropriately early management within the window of opportunity, before permanent digestive damage is done[16,17]. However, management decisions are still currently made using a one-size-fits-all approach. The conventional strategy is the step-up approach, which will inevitably undertreat patients who are destined to run a more aggressive disease course. With easier

access to biologics and small molecules, a top-down approach may be used, which has been shown to improve clinical outcomes in prognostically severe CD[18,19] but this may otherwise expose patients destined to have mild disease to unnecessary risks and overtreatment. This top-down strategy would also be unaffordable in financially constrained health-care settings particularly in the Asia-Pacific region, and may pose a challenge in health jurisdictions that limit the use of expensive novel therapies.

Furthermore, the heterogeneity and variability of the clinical course of IBD between different individuals would mean a suboptimal approach in a substantial group of patients. There is a general consensus that a tailored approach is required, with a need for accurate biomarkers that enable the right patient to be matched to the right treatment (Table 1).

Stratification of treatment approaches can help identify those of a more complicated course and hence tailoring treatment accordingly. Among prognostic biomarkers at diagnosis predicting a more complex CD phenotype and worse outcomes including stricturing phenotype and need for surgery, identified microbial predictors include circulating antibodies against bacterial antigens such as anti-outer membrane protein C, anti-*Saccharomyces cerevisiae* antibody, perinuclear anti-neutrophil cytoplasmic antibodies, and anti-CBir1 flagellin. However, it is unclear if these represent a cause or effect of severe disease[20-24].

A CD8+ T-cell clonal signature was identified to predict worse outcomes and relapse in IBD patients [25,26]. This genomic biomarker was subsequently validated in independent cohorts of newly diagnosed CD and UC patients in the United Kingdom[27]. There is now a trial in progress in the United Kingdom to assess this whole-blood biomarker to guide treatment for newly diagnosed CD patients[28]. It is currently available in clinical use: PredictSure IBD; PredictImmune, Cambridge, United Kingdom.

Other predictive tools include the use of fecal calprotectin as a predictor of endoscopic disease activity as well as histologic inflammation, and fecal calprotectin values have been shown to be predictive of relapse in asymptomatic patients with IBD[29-33]. In a biomarker discovery trial, the EMBARK study, serum matrix metalloproteinase 9 and serum IL-22 were found to be associated with inflammatory disease activity for patients with UC and CD respectively[34].

Pharmacogenomic testing has also become common place in IBD. A commonly used predictor of risk of adverse drug reactions and pharmacologic response is the utility of thiopurine methyltransferase (TPMT) genotyping and metabolite testing, as well as nudix hydrolase 15 (NUDT15) genotyping. Thiopurine use is associated with adverse effects (AEs) in up to 40% of patients[35]. TPMT genotype testing is cost effective, and heterozygous and homozygous TPMT genotypes correlate with AEs. Dose reduction in the TPMT variants significantly reduce adverse hematologic effects without reducing treatment efficacy[36]. NUDT15 variants, first elucidated in a Korean population, have also been more recently described as associated with thiopurine induced myelosuppression and is more predictive of myelosuppression in East Asians[37-39]. Furthermore, thiopurine metabolite testing can aid in dose optimization and compliance[40] and prevents hepatotoxicity by identifying a subgroup of thiopurine-'shunters' who preferentially produce the hepatotoxic metabolite 6-methylmercaptopurine.

Apart from this, several biomarkers as predictors of non-response to anti-TNF include higher oncostatin M expression[41,42] and low expression of triggering receptor expressed on myeloid cells 1 [43,44]; antibody formation to anti-TNF is associated with the HLA-DQA1*05 genotype[45]. Higher baseline concentrations of serum cytokine IL-22, whose expression is induced by IL-23, is associated with greater likelihood of response to brazikumab[46].

OPTIMIZING AND MAXIMIZING CURRENT BIOLOGIC AGENTS

Therapeutic drug monitoring and drug dosing strategies

Introduction of therapeutic drug monitoring (TDM) has guided our approach in going beyond the therapeutic ceiling. Multiple studies have demonstrated an association with serum drug concentration of biologics, mainly in anti-TNF agents, and outcomes of patients[47-55]. It has assisted us in guiding dose modification (dose escalation or reduction), and informed us of primary or secondary loss of response, thus avoiding persistence of potentially ineffective therapy[56]. The approach of proactive *vs* reactive therapeutic drug monitoring remains a hotly debated topic[57].

Dashboard systems are clinical decision support tools utilizing computer software modelling to predict ideal personalized medication dosing[58,59]. This 'model-based dosing' has long been used by pharmacists and pharmacologists, for example, to dose antibiotics such as aminoglycosides. For anti-TNF dosing, dashboard driven pharmacokinetic (PK) dose optimization considers individual patient covariates including C-reactive protein, albumin, body-weight, sex and also serum drug levels. The PRECISION trial demonstrated that dashboard driven personalized dosing resulted in a significantly higher proportion of patients maintaining clinical remission after 1 year of treatment compared with patients that continued treatment without proactive adjustments: 88% *vs* 64%, respectively[60]. Utilizing the same PK dashboard system during Infliximab induction, Dubinsky *et al*[61] recently showed improved infliximab durability; and at 52 wk, 119/123 patients remained on infliximab in steroid free remission. The OPTIMISE trial is underway to evaluate the safety and efficacy of proactive TDM

Table 1 Selected list of biomarkers in inflammatory bowel disease

Biomarker class	Biomarker	Clinical utility
Prognostic biomarkers	Anti-ompC, ASCA, ANCA, anti-CBir1, flagellin	Prediction of more severe CD phenotype- particularly stricturing and need for surgery
	CD 8+ T cell clonal signature	Prediction of more severe disease course and relapse in CD and UC
Surveillance of disease activity	Fecal calprotectin	Predictor of endoscopic disease activity as well as histologic inflammation, and relapse in asymptomatic patients with IBD
	MMP-9	Associated with disease activity in UC
	IL-22	Associated with disease activity in CD
Pharmacogenomics and prediction of safety	TPMT	Risk of thiopurine adverse reaction
	NUDT15	Risk of thiopurine adverse reaction, more common in East Asian/Asian populations
	Thiopurine metabolites (6TG, 6MMP)	Levels associated with adverse drug reaction: myelosuppression, hepatotoxicity. 6TG range also associated with therapy response
Prediction of response to therapy	Oncostatin M	Higher levels predictor of non-response to anti-TNF
	TREM-1	Low levels predictor of non-response to anti-TNF
	HLA-DQA1*05	Expression associated with risk of antibody formation to anti-TNF
	IL-22	Higher level associated with response to anti-IL23p19 (brazikumab)

ANCA: Anti-neutrophil cytoplasmic antibody; ASCA: Anti-Saccharomyces cerevisiae antibody; CD: Crohn's disease; IBD: Inflammatory bowel disease; IL: Interleukin; MMP: Matrix metalloproteinase; NUDT15: Nudix hydrolase 15; ompC: Outer membrane protein C; TG: Thioguanine; TNF: Tumor necrosis factor; TPMT: Thiopurine methyltransferase; TREM: Triggering receptor expressed on myeloid cells; UC: Ulcerative colitis.

combined PK dashboard-driven infliximab dosing compared with standard of care dosing in patients with CD[62].

"Supratherapeutic" anti-TNF dosing

Numerous exposure-response relationship studies including post-hoc analyses of randomized controlled trials show a positive correlation between biologic drug concentrations and favorable therapeutic outcomes in IBD and other immune-mediated inflammatory diseases; higher drug concentrations are typically associated with improved therapeutic outcomes[63]. Conversely, lower drug concentrations, with or without anti-drug antibodies, are associated with treatment failure and drug discontinuation[64,65].

Multiple clinical studies have provided various TDM targets, especially with the anti-TNF agents infliximab and adalimumab, at various time points that are associated with outcomes of clinical remission[51,66]. Several observational studies have suggested that higher median infliximab concentrations are associated with superior clinical and biochemical remission rates. Given the wide variation in observed concentrations among responders, one may even wonder if the "therapeutic threshold" is identical for all patients and for the different phases of the treatment (induction *vs* maintenance and active *vs* quiescent disease).

Yarur *et al*[67], found that that levels of infliximab ≥ 10 mcg/mL were best associated with fistula healing, though surprisingly, a small number of patients required levels of ≥ 20 mcg/mL to achieve fistula healing. Feng *et al*[68] demonstrated that on incremental gains analysis, mucosal healing rates gradually increased as infliximab levels went up and reached a brief plateau (> 85%) when the infliximab trough level was 10 μg/mL. However, there was still a small proportion that seemingly benefited from an anti-TNF levels > 12 mcg/mL to achieve mucosal healing. Ungar *et al*[69] similarly demonstrated in a retrospective study a significant association between serum levels of anti-TNF agents and level of mucosal healing. They went on to propose that serum levels of 6-10 μg/mL for infliximab and 8-12 μg/mL for adalimumab are required to achieve mucosal healing in 80%-90% of patients with IBD.

Several other studies demonstrated that higher trough levels of infliximab and adalimumab are associated with those achieving mucosal healing in CD[68-79]. In a substudy of the TAILORIX trial, Bossuyt *et al*[71] found that infliximab trough level of 7.8 μg/mL at the end of induction (week 14) was associated with both radiologic response and remission. Continuously high infliximab exposure (infliximab > 5 μg/mL at all time points) was associated with radiologic response.

Low infliximab trough concentrations and the presence of antibodies to infliximab are associated with worse outcomes. Trough concentrations of > 3 μg/mL during maintenance is associated with sustained clinical outcomes[54,70,80,81]. Vande Casteele *et al*[82] concluded that an appropriate infliximab therapeutic window is between 3 and 7 μg/mL for IBD responders during maintenance therapy based on previous studies, and prospectively validated it in a randomized controlled trial (TAXIT).

The optimal "therapeutic window" for biologics remains to be elucidated, and the upper limit is unclear. While the abovementioned studies observed an association between certain trough concentration ranges and a corresponding degree of disease remission, the 'ideal' trough concentration to induce remission may vary between individuals. This may be due to a variety of factors such as an individual's disease burden and therefore mucosal TNF burden, early *vs* advanced disease, and an individual's unique pharmacodynamic makeup. There may be a subset of patients who might benefit from dose escalation to 'supratherapeutic' trough concentrations and reassuringly, there is little evidence to indicate greater toxicity with higher infliximab levels.

Sequencing of biologics

While it remains a conventional strategy to offer an anti-TNF agent as the first-line biologic, it has been well established from network meta-analyses that anti-TNF non-responders do not have an optimal response after switching to second-line biologics[12-14]. It thereby raises the question whether certain individuals would benefit from receiving these traditionally second-line biologics as first-line therapy options, and highlights the importance of optimal biologic sequencing.

There are limited head to head trials between biologic agents: In the VARSITY trial (adalimumab *vs* vedolizumab) for moderate to severe UC, vedolizumab demonstrated superiority in clinical and endoscopic remission but not corticosteroid free clinical remission[83]. In the SEAVUE study (adalimumab *vs* ustekinumab) for moderate to severe Crohn's, ustekinumab failed to demonstrate superiority over adalimumab[84].

In the Galaxi-1 study involving participants with moderately to severely active CD, guselkumab was compared to placebo and ustekinumab. It was a phase 2, dose-ranging study[85], not powered to evaluate potential differences in efficacy and safety between guselkumab and ustekinumab.

From the HIBISCUS and GARDENIA trials[86,87] Etrolizumab *vs* adalimumab or infliximab in moderate to severe UC- failed to demonstrate superiority.

While offering novel alternate pathway biologics as first-line therapy may gain traction in the near future, this approach is often limited by government access in many jurisdictions. Access to newer therapies for adult patients is already limited by licensing authorities, but the pathways remain even more restricted for pediatric patients. Access to biologics in pediatric patients is often on compassionate grounds, due to a significant lag in clinical trials and therefore delaying official approval from medical licensing authorities such as the European Medicines Agency and United States FDA. There is a need for this cohort of patients to have better access to new/emerging therapies through more advanced pharmacogenomic, pharmacokinetic and pharmacodynamic modelling. This is to allow earlier initiation of trials or better ways to "extrapolate" adult data for presentation to licensing authorities to allow for use in children.

Dual biologics and combinations of newer advanced therapies

Combinations of biologic agents and recently combinations of biologics with newer small molecule agents have been attempted to go beyond our current therapeutic ceiling. This concept is not new, however, and was first attempted by Sands *et al*[88] as a randomized controlled trial comparing the safety and tolerability of patients on infliximab not in remission and adding natalizumab *vs* a placebo arm. Although the main trial ran for 10 wk and was not powered to assess for differences in efficacy between the groups, there was a higher proportion of patients achieving a clinical response at each time point and this proportion continues to increase over time in the combination biologic group, compared to response rates for the monotherapy arm which remained unchanged.

Since then, there has been much in the literature of dual biologics or with newer small molecule therapies, but as case reports or case series and observational cohort studies (Table 2). The data is largely heterogenous but reassuringly has demonstrated acceptable safety for patients with refractory IBD with no new concerning signals[89,90].

In the pipeline, there are several randomized controlled trials evaluating the efficacy of combination biologics. The EXPLORER trial (ClinicalTrials.gov Identifier: NCT02764762) in high-risk CD patients involved triple combination therapy with vedolizumab, adalimumab and methotrexate which has completed but not yet reported.

The phase 2a VEGA study evaluated the safety and efficacy of combination induction therapy with guselkumab plus golimumab (GOL) *vs* monotherapy with guselkumab or GOL in adults with moderately to severely active UC through to week 12, most recently presented at the European Crohn's and Colitis Organization 2022 congress[91,92]. A greater proportion of patients who received combination therapy achieved clinical response as judged by Mayo score at week 12 (83.1%) *vs* guselkumab (74.6%) or GOL (61.1%). Similarly, the proportion of patients who achieved clinical remission in the combination group (36.6%) was greater than that in the monotherapy group (21.1% and 22.2%, respectively). The DUET UC (ClinicalTrials.gov Identifier: NCT05242484) is a phase 2b study of

Table 2 Publications of dual biologics

Ref.	Type	Number of participants/IBD type	Biologic combinations	Therapy duration or follow up (mo)	Outcomes
Buer *et al* [97], 2018	Case series, prospectively followed	Adult: 10 (4 CD, 6 UC)	Anti-TNF, adding on vedolizumab. Combination was intended as a bridging therapy	12-20	Clinical: HBI, PMS, 100 % CRem, 50% endoscopic remission. No serious AE (3 minor infections)
Olbjørn *et al*[98], 2020	Case series	Pediatric: 13 (9 CD, 4 UC)	Anti-TNF + vedolizumab (8), anti-TNF + ustekinumab (5), (for anti-TNF side effects)	N/A	3/8 (37.5%) Clinical and biochemical remission
Kwapisz *et al*[99], 2021	Case series	Adult: 15 (14 CD, 1 UC)	8 vedolizumab + anti-TNF, 2 ustekinumab + anti-TNF, 5 vedolizumab + ustekinumab	24	73% CRes, 44% ERes, 27% SE, 20% surgery
Yang *et al* [100], 2020	Retrospective cohort	Adult: 22 (CD)	24 combinations: 13 vedolizumab + anti-TNF, 8 vedolizumab + ustekinumab, 3 ustekinumab + anti-TNF	1	Endoscopic, PRO2 response/remission, CRP, 50% CRes, 36% SF CRem, 43% ERes, 4% SE (1 SLE-1 cancer), 33% surgery
Glassner *et al*[101], 2020	Retrospective cohort	50	53 combinations: 25 vedolizumab + ustekinumab, multiple other combinations	5.5-13	50% CRem, 34% ERem, 16% SE, 12% surgery
Privitera *et al*[102], 2020	Case series, indication active IBD and active EIM	Adult: 16 (11 CD, 4 UC)	Variety of combinations. Most frequent: 3 vedolizumab + adalimumab, 3 vedolizumab + ustekinumab	0.5	At 6 mo: Response IBD/EIM: 42.8%, 11%; Remission IBD/EIM: 14.2%, 55.5%, AE: 3/16 (18.8%)
Dolinger *et al*[103], 2021	Case series	Pediatric: 16: (CD 7, UC 8, IBD-U 1)	Vedolizumab + ustekinumab, vedolizumab + tofacitinib, ustekinumab + tofacitinib	6	SF remission at 6 mo 12/16 (75%)
Goessens *et al*[104], 2021	Retrospective cohort, hetero-genous, active IBD and/or EIM	Adult: 98 (CD 58, UC 40)	Anti-TNF + vedolizumab, anti-TNF + anti-IL, anti-IL + vedolizumab, tofacitinib + anti-TNF, tofacitinib + vedolizumab, anti-IL + anti-IL, others	5-16	PGA: Complete or partial improvement was observed in 21/80 (26%) and 35/80 (44%); Mean clinical disease activity for IBD: Significantly higher prior to combination than during combination (2.2 +/- 0.7 *vs* 1.2 +/- 1.1; $P < 0.0001$). Simple clinical activity scores (quiescent scores 0, mild scores 1, moderate scores 2 and severe scores 3

AE: Adverse events; CD: Crohn's disease; CRes: Clinical response; CRem: Clinical remission; EIM: Extraintestinal manifestations; ERem: Endoscopic remission; ERes: Endoscopic response; HBI: Harvey Bradshaw index; IBD: Inflammatory bowel disease; IL: Interleukin; N/A: Not applicable; PGA: Physician global assessment; PMS: Partial Mayo score; PRO2: Patient reported outcome scores; SE: Serious infection; SF: Steroid free; TNF: Tumor necrosis factor; UC: Ulcerative colitis.

combination therapy with guselkumab and GOL (JNJ-78934804) in participants with moderately to severely active UC that is planned; the DUET CD (ClinicalTrials.gov Identifier: NCT05242471) is a phase 2b study of the same biologic combination in individuals with moderately to severely active CD, and is currently recruiting trial participants.

The other considerations to overcome current therapeutic plateaus with biologic agents include added adjunctive therapies such as vitamin D, curcumin, microbiome alteration *via* dietary modification, exclusive enteral nutrition and probiotics[93].

CONCLUSION

Ongoing efforts in adding to and optimizing IBD treatments must be commended. However, remission rates are still far from optimal with current treatment approaches. The urgent need to develop new therapeutics also brings us to the challenge that we must meet: Improving the design and delivery of clinical trials, allowing generalizability, be of clinical equipoise and to factor in biomarker discovery. Advances in basic science, translational and clinical aspects of drug development is essential to achieve breakthroughs in IBD therapeutics that meet the needs of patients, physicians and health regulators[94-96]. In conclusion, in addition to the strategies as aforementioned, to go beyond our current therapeutic

ceiling requires not only early diagnosis or early stratification but early treatment. This entails incorporating a multiomics approach to better personalize treatment, sequence or combine our therapies, and incorporate the ever-advancing artificial intelligence technology, rather than a one-size-fits all approach[95]. These goals remain attainable and we continue to have a sense of optimism.

FOOTNOTES

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Country/Territory of origin: Australia

ORCID number: Eric Cheah 0000-0002-9444-1119; James Guoxian Huang 0000-0002-5869-4194.

Corresponding Author's Membership in Professional Societies: Gastroenterological Society of Singapore.

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