World Journal of Gastroenterology

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World J Gastroenterol 2024 June 14; 30(22): 2902-2919

DOI: 10.3748/wjg.v30.i22.2902

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

SYSTEMATIC REVIEWS

Approach to loss of response to advanced therapies in inflammatory bowel disease

Nikil Vootukuru, Abhinav Vasudevan

Specialty type: Gastroenterology and hepatology

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's classification

Scientific Quality: Grade B, Grade C

Novelty: Grade B, Grade C

Creativity or Innovation: Grade B, Grade C

Scientific Significance: Grade B, Grade C

P-Reviewer: Li G, China; Zheng L, China

Received: February 27, 2024

Revised: May 6, 2024

Accepted: May 28, 2024

Published online: June 14, 2024

Nikil Vootukuru, Abhinav Vasudevan, Department of Gastroenterology and Hepatology, Eastern Health, Victoria, Box Hill 3128, Australia

Nikil Vootukuru, Abhinav Vasudevan, Eastern Health Clinical School, Monash University, Victoria, Box Hill 3128, Australia

Corresponding author: Abhinav Vasudevan, BMed, FRACP, Doctor, Department of Gastroenterology and Hepatology, Eastern Health, 8 Arnold St, Victoria, Box Hill 3128, Australia. abhinav.vasudevan@monash.edu

Abstract

BACKGROUND

Remarkable progress over the last decade has equipped clinicians with many options in the treatment of inflammatory bowel disease. Clinicians now have the unique opportunity to provide individualized treatment that can achieve and sustain remission in many patients. However, issues of primary non-response (PNR) and secondary loss of response (SLOR) to non-tumour necrosis factor inhibitor (TNFi) therapies remains a common problem. Specific issues include the choice of optimization of therapy, identifying when dose optimization will recapture response, establishing optimal dose for escalation and when to switch therapy.

AIM

To explores the issues of PNR and SLOR to non-TNFi therapies.

METHODS

This review explores the current evidence and literature to elucidate management options in cases of PNR/SLOR. It will also explore potential predictors for response following SLOR/PNR to therapies including the role of therapeutic drug monitoring (TDM).

RESULTS

In the setting of PNR and loss of response to alpha-beta7-integrin inhibitors and interleukin (IL)-12 and IL-23 inhibitors dose optimization is a reasonable option to capture response. For Janus kinase inhibitors dose optimization can be utilized to recapture response with loss of response.

CONCLUSION

The role of TDM in the setting of advanced non-TNFi therapies to identify

patients who require dose optimization and as a predictor for clinical remission is not yet established and this remains an area that should be addressed in the future.

Key Words: Inflammatory bowel disease; Ulcerative colitis; Crohn; Biologics; Interleukin-12 and interleukin-23 inhibitors; Alpha-beta7-integrin inhibitors; Janus kinase inhibitors; Sphingosine-1-phosphate receptor modulators

Core Tip: In the setting of primary non-response (PNR) and loss of response (LOR) to alpha-beta7-integrin inhibitors and interleukin (IL)-12 and IL-23 inhibitors dose optimization is a reasonable option to capture response. For Janus kinase inhibitors dose optimization can be utilized to recapture response with LOR is less successful in the setting of PNR. The role of therapeutic drug monitoring in the setting of non-tumour necrosis factor inhibitor therapies to identify patients who require dose optimization and as a predictor for clinical remission is not yet established and this remains an area that should be addressed in the future research.

Citation: Vootukuru N, Vasudevan A. Approach to loss of response to advanced therapies in inflammatory bowel disease. *World J Gastroenterol* 2024; 30(22): 2902-2919
URL: https://www.wjgnet.com/1007-9327/full/v30/i22/2902.htm
DOI: https://dx.doi.org/10.3748/wjg.v30.i22.2902

INTRODUCTION

It has been over two decades since tumor necrosis factor antagonists revolutionized the management of inflammatory bowel disease (IBD) and allowed for the achievement of sustained disease remission with relatively few side effects from treatment including in people who were previously refractory to medical therapy[1]. Many advanced therapies have subsequently been approved for use in IBD with varying mechanisms of action, including alpha-beta7-integrin inhibitors, interleukin (IL)-12 and IL-23 inhibitors, Sphingosine-1-phosphate (S1P) receptor modulators and Janus kinase (JAK) inhibitors[2]. With the shift in the treatment paradigm favoring earlier utilization of advanced therapies, there is added complexity in determining the best methods for optimizing, switching, and escalating medical therapy to achieve the best outcomes. With the growing therapeutic armamentarium, it is important that the choice of therapy is individualized and both patient and disease related factors are considered to improve the likelihood of achieving disease remission while being tolerable for the patient. Yet, there is complexity in identifying the most appropriate individualized treatment for patients, with no single factor being able to identify which agent is most suitable. Similarly, identifying patients who are not responding to a treatment early, and deciding the best course of action can also be challenging. Determining why a particular therapy was not effective can be useful in deciding the best approach to a patient with an inadequate response to treatment and what further measures should be taken. Treatment non-response can be classified into two broad categories-primary non-response (PNR) which refers to a lack of clinical response during initial treatment or secondary non-response which refers to an initial response to therapy follow by a loss of response (LOR) over time[1]. This review will focus on the management options before class switching for clinicians faced with PNR and secondary LOR of non-tumour necrosis factor inhibitor (TNFi) based advanced therapy.

MATERIALS AND METHODS

This review aims to explore the efficacy of dose intensification and in-class switching in cases of PNR and LOR with non-TNFi advanced therapy. A literature search was performed in PubMed and Ovid Medline up to November 2023 for original articles and reviews under the subject headings "inflammatory bowel disease," "Crohn's disease," "CD," "ulcerative colitis," "JAK Inhibitors," "Tofacitinib," "Upadacitinib," "Ustekinumab," "anti- IL- 12/23p40," "alpha-beta7-integrin inhibitors," "Vedolizumab," "Sphingosine-1-phosphate," "ozanimod," "dose escalation," "dose intensification," "re-induction," "drug levels," "TDM," and their synonyms .In addition, the reference lists from the selected articles were reviewed to identify additional studies of potential interest. Only studies conducted in adults were included.

RESULTS

What is treatment failure?

There is no clear consensus on the definition of PNR but in general PNR refers to a failure to display improvement in clinical signs or symptoms during the induction phase[3-5] with significant variability in time to clinical response noted

between therapeutics[6,7]. The time of expected response varies with different therapies, but it is usually considered PNR if there is a lack of response to induction treatment or within 14 weeks of commencing therapy[6,7]. Our understanding of the mechanism of PNR comes from experiences with anti-tumour necrosis factors (TNFs). The two major recognised mechanisms of PNR to anti-TNFs are pharmacokinetic (due to rapid drug clearance resulting in low trough levels) and pharmacodynamic (mechanistic) failure[8], which refers to failure due to inflammation mediated by alternative pathways to the mechanism targeted by the allocated therapy[9]. Secondary non-response or LOR describes the clinical phenomenon whereby patients who initially respond to advanced therapy then subsequently lose response[10]. As with PNR, our understanding of the mechanisms leading to LOR are primarily derived from experiences with anti-TNFs. The main causes of LOR with anti-TNFs are suboptimal drug concentrations due to low trough level drug concentrations and/or anti-drug antibodies or mechanistic failure due to disease transitioning to another pathway of inflammation[11,12].

Predictors for failure of advanced therapies in IBD

Predictive factors for PNR and LOR appear to be similar with different agents and seem to relate to the underlying inflammatory burden. For vedolizumab the GEMINI trials demonstrated that less severe disease activity at baseline was associated with higher likelihood of remission in IBD[13,14] which has since been reflected in real word studies[15-23]. Furthermore, an association of elevated inflammatory markers with lower rates of clinical response and remission has also been described[13-15,24-26]. A post-hoc analysis of the GEMINI trials reported higher rates of rates of induction and maintenance of clinical remission among TNF antagonist naïve patients[27,28] which has been confirmed by real world trials[17,21,23,26,29-32]. Patients who achieve early response to vedolizumab also appear to be more likely to have a long-term response[15,16,30,33,34]. Similar to vedolizumab, a higher rate of clinical response and remission is expected with ustekinumab in both Crohn's and ulcerative colitis (UC) among patients with less severe disease activity at baseline[35-44] with an elevated C-reactive protein (CRP) associated with lower rates of clinical remission[45,46]. With ustekinumab therapy, failure of both TNF and vedolizumab was associated with lower rates of clinical remission[38,47,48]. As with other advanced therapy, patients lower baseline disease activity were more likely to achieve remission with tofacitinib[49-51] whereas higher CRP levels[50,52] and prior TNF[50,53] or biologic therapy[51,54] was associated with lower rates of clinical response. Interestingly, younger patients were less likely to demonstrate clinical response or remission[50,52] with tofacitinib. For ozanimod, a similar rate of clinical remission of UC is seen among patients with prior biologic use with a slower rate of onset[55,56] whereas lower rates of clinical remission are seen with etrasimod among patients with prior biologic or JAK-inhibitor exposure[57].

Approach to PNR to therapies?

The approach to patients with suspicion for PNR or LOR requires detailed assessment to determine if worsening symptoms are caused by increased IBD activity and then to determine the possible causes of PNR or LOR[10,58]. Disease activity is assessed through assessing clinical symptoms aided by evaluation with a combination of objective measures such as laboratory testing, endoscopy, and cross-sectional imaging[10,58]. It is essential at this stage that alternative causes for presumed PNR and LOR are excluded such as co-infection[59], poor adherence[60], improper drug storage [61], irritable bowel disease, bacterial overgrowth and bile acid malabsorption[58]. There is a consensus in guidelines for reactive therapeutic drug monitoring (TDM) in patients who fail to respond to anti-TNF therapy[11,62] however the role of TDM with other advanced therapies is less clearly defined. Thereafter the clinician is faced by three main methods of recapturing response-treatment escalation, addition of immunomodulator therapy, switching to a different therapy with a similar mechanism (in class switch) or switching to a therapy with a different mechanism (out of class switch).

Vedolizumab-management options for PNR/LOR

Vedolizumab is a full human IgG1 monoclonal antibody which targets α4β7 integrin, modulating lymphocyte trafficking in the gut[63]. Vedolizumab is administered intravenously (at a dose of 300 mg) with induction does at week 0 and 2 and maintenance doses thereafter at an interval of 4, 6 or 8 weekly[13,14]. The seminal GEMINI trials established the role of vedolizumab in IBD with clinical response rates of 47.1% and 25.7% in the treatment of UC and Crohn's disease (CD) respectively[13,14]. Despite the recognised efficacy of vedolizumab, eventual LOR to treatment is common, with rates reported to be 47.9 per 100 person-years in Crohn's and 39.8 per 100 person-years in UC[64]. Where mechanistic failure is thought to be unlikely clinicians will most often dose escalate from 300 mg every 8 weeks to every 4 week and less commonly every 6 weeks to attempt to induce or recapture remission[65]. Yet it is unclear if vedolizumab levels can be utilised to identify patients who will not respond to dose escalation and hence require therapy class-switching (Table 1).

Dose escalation: Observational data suggest that dose escalation of vedolizumab is effective in overcoming PNR and secondary LOR. The GEMINI long-term safety trials confirmed that vedolizumab 300mg dose escalation to 4 weekly restored clinical remission following LOR in UC and Crohn's[66,67] in a clinical trial setting. A retrospective study of 192 IBD patients among whom 58 patients were dose escalated (largely to 4 weekly vedolizumab) for secondary LOR or subclinical disease reported a clinical response rate of 62%[68]. Another observational study of 23 IBD patients who underwent dose optimisation of vedolizumab for primary or secondary LOR showed that increased vedolizumab dosing frequency resulted in a treatment response in more than half of IBD[69]. Similar findings establishing the efficacy of vedolizumab dose intensification were described in further recent retrospective and prospective studies[23,68-76]. This has been confirmed in a systematic review by Peyrin-Biroulet *et al*[64] which reports that dose intensification of vedolizumab following secondary LOR restores clinical response in more than half of IBD patients on maintenance vedolizumab therapy.

Table 1 Dose optimisation approaches for advanced therapies in inflammatory bowel disease

Ref.	Number	Disease	PNR and/or SLOR	Study design	Intervention	Follow-up	Outcome	Result
Trials: Vedolizumab dose escalation								
Loftus *et al* [66]	32	UC	LOR	Single-arm open label-multicentre	4 weekly 300 mg	28 weeks	Clinical response/clinical remission	53.1% (19% with response prior to escalation)/25.0% (6% in remission prior)
Vermeire *et al* [67]	57	Crohn's	LOR	Single-arm open label-multicentre	4 weekly 300 mg	28 weeks	Clinical Response/Clinical Remission	54.4% (39% with response prior to escalation)/22.8% (4% in remission prior)
Vaughn *et al* [68]	58	Crohn's or UC	LOR	Retrospective cohort study-multicentre	4-7 weekly 300 mg	15 weeks	Clinical Response	62.0%
Gouynou *et al*[69]	23	Crohn's or UC	PNR/LOR	Retrospective cohort study-single centre	NS-increased frequency	9 months	Clinical response	52.2%
Outtier *et al* [70]	59	Crohn's or UC	LOR	Prospective observational study-multicentre	4 weekly 300 mg	8 weeks	Clinical response	54.2%
Kolehmainen *et al*[71]	36	Crohn's or UC	PNR/LOR	Retrospective cohort study-single centre	NS-increased frequency	12 months	Clinical response	33.3%
Perry *et al*[23]	24	UC	PNR/Partial Responder	Retrospective cohort study-single centre	4 weekly 300 mg	51 weeks	Clinical response/corticosteroid free remission	41.7%/41.7%
Christensen *et al*[72]	43	Crohn's or UC	NS	Prospective cohort study-single centre	4 or 6 weekly 300 mg	26 weeks	Clinical response/clinical remission	58.1%/55.8%
Dreesen *et al* [74]	16	Crohn's or UC	NS	Retrospective cohort study-single centre	4 weekly 300 mg	14 weeks (UC), 22 weeks (Crohn's)	Clinical response	56.3%
Kopylov *et al* [73]	48	Crohn's or UC	NS	Retrospective cohort study-multicentre	4 weekly 300 mg	52 weeks	Clinical response	62.5%
Williet *et al* [75]	15	Crohn's or UC	PNR	Prospective cohort study-single centre	4 weekly 300 mg	36 weeks	Clinical response	53.8%
Attauabi *et al* [76]	37	Crohn's or UC	LOR	Retrospective cohort study-2 centre	4-7 weekly 300 mg	< 70 weeks	Clinical remission	62.2%
Jairath *et al* [77]	55	UC	PNR	Open label multicentre RCT	4 weekly 300mg or 600 mg	30 weeks	Clinical response/clinical remission	30.9/9.1%
Trials: Ustekinumab frequency								
Dalal *et al*[41]	75	Crohn's	LOR	Retrospective cohort study-single centre	4 or 6 weekly 90 mg	12 months	Corticosteroid free clinical remission	54.7%
Derikx *et al* [48]	47	Crohn's	NS	Retrospective cohort study-single centre	4 or 6 weekly 90 mg	8.9 months	Corticosteroid free remission	29.6%
Bundschuh *et al*[98]	27	Crohn's	LOR	Retrospective cohort study	4 or 6 weekly 90 mg	NS	Clinical response	54.5%
Haider *et al* [100]	15	Crohn's	PNR	Retrospective cohort study-single centre	4 weekly 90 mg	78 weeks	Clinical response/clinical remission	46.6%/33.3%

Fumery *et al* [101]	100	Crohn's	Partial Response/LOR	Retrospective cohort study-single centre	4 weekly 90 mg	2.4 months	Clinical response/clinical remission	61%/31%
Ollech *et al* [102]	51	Crohn's	NS	Retrospective cohort study-single centre	4 weekly 90 mg	5.9 months	Clinical remission	27.5%
Dalal *et al*[96]	157 (Crohn's: 117, UC: 40)	Crohn's or UC	Partial Response/LOR	Retrospective cohort study-single centre	4 or 6 weekly 90 mg	12 months	Steroid free clinical remission	Crohn's 57.3%/UC 52.5%
Rowbotham *et al*[107]	24	UC	NS	Randomised-withdrawal maintenance study	8 weekly 90 mg	16 weeks	Clinical remission	58.3%
Trials: Ustekinumab reinduction								
Sedano *et al* [109]	15	Crohn's	Partial Response/LOR	Retrospective cohort study-single centre	IV reinduction	14.9 weeks	Clinical response/clinical remission	66.7%/53.3%
Heron *et al* [110]	65	Crohn's	Partial Response/LOR	Retrospective cohort study - multicentre	IV reinduction	14 weeks	Clinical Remission with either biochemical and endoscopic response or remission	31.0%
Bermejo *et al* [111]	43	Crohn's	LOR	Retrospective cohort study-multicentre	IV re-induction	16 weeks	Clinical response/clinical remission	52.8%/43.3%
Ten Bokkel *et al*[112]	29	Crohn's	LOR	Prospective cohort study-multicentre	IV re-induction	52 weeks	Clinical remission	44.8%
Trials: Ustekinumab increased frequency and/or reinduction								
Cohen *et al* [99]	68	Crohn's	PNR/Partial Response	Retrospective cohort study-single centre	IV induction + 4 or 6 weekly 90 mg	3-6 months	Clinical response/clinical remission	79.4%/30.9%
Yao *et al*[114]	128	Crohn's	Partial Response/LOR	Retrospective cohort study-single centre	4 weekly 90 mg +/- IV Re-induction	3 months	Clinical remission	62.9% Shortening/69.6% re-induction
Hudson *et al* [113]	18	Crohn's	SLOR	Retrospective case series-single centre	IV re-induction +/- 4 or 6 weekly 90 mg	4-8 weeks	Clinical remission or response	83.3%
Ramaswamy *et al*[106]	31	Crohn's	Partial response/LOR	Retrospective cohort study-single centre	4 weekly 90 mg +/- IV re-induction	12 weeks	Clinical response	64.5%
Chaparro *et al*[40]	60	Crohn's	PNR/LOR	Retrospective cohort study-multicentre	4 weekly 90 mg /IV re-induction	NS	Clinical remission	78.3%
Ma *et al*[115]	24	Crohn's	LOR	Retrospective cohort study-multicentre	4 or 6 weekly 90 mg +/- IV reinduction	NS	Clinical response	54.2%
Young *et al* [97]	21	Crohn's	PNR/LOR/partial response	Retrospective cohort study-single centre	4 or 6 weekly 90 mg +/- IV induction	177 days	Clinical response	52.4%
Johnson *et al* [103]	229	Crohn's	PNR/LOR	Retrospective cohort study-multicentre	4 or 6 weekly 90 mg + IV reinduction/IV reinduction	NS	Clinical response	45.9%
Olmedo *et al* [104]	91	Crohn's	PNR/LOR	Retrospective cohort study-multicentre	4 or 6 weekly 90 mg + IV reinduction	16 weeks	Steroid free clinical response/Steroid free clinical remission	62.6%/25.3%
Kopylov *et al* [105]	142	Crohn's	NS	Retrospective cohort study-multicentre	4 or 6 weekly 90 mg +/- IV induction	16 weeks	Clinical response/clinical remission	51.4%/38.7%
Trials: Tofacitinib dose escalation								
Ma *et al*[51]	71	UC	LOR	Prospective	10 mg BD	NS	Clinical response	54.9%

				cohort study-multicentre				
Honap *et al* [52]	19	UC	LOR	Retrospective cohort study-multicentre	10 mg BD	NS	Clinical response	47.4%
Sandborn *et al*[150]	57	UC	LOR	Prospective cohort study-multicentre	10 mg BD	12 months	Clinical response/clinical remission	64.9%/49.1%
Trials: Upadacitinib dose escalation								
Sandborn *et al*[151]	60	Crohn's	NS (inadequate response)	Phase II placebo controlled RCT	12 mg BD/24 mg BD IR	52 weeks	Clinical remissions	15% 12 mg BD/24 mg BD 39%
Panaccione *et al*[153]	190	UC	LOR/inadequate response	Prospective cohort study	30 mg ER daily	48 weeks	Clinical remission	27.9%

PNR: Primary non-response; LOR: Loss of response; BD: Twice a day; UC: Ulcerative colitis; ER: Extended release; IR: Immediate release; SLOR: Secondary loss of response.

However, a recent randomized control trial (RCT) including 278 UC patients reported that among patients with early nonresponse to vedolizumab (at week 6) and high drug clearance, vedolizumab dose escalation ranging from 300 mg to 600 mg every 4 to 6 weeks did not lead to higher rates of clinical remission and response. In fact, Jairath *et al* reported that approximately 10% of patients with early non-response achieved clinical remission at week 30 irrespective of the dose received[77]. The findings of this RCT may explain the heterogeneity of data regarding the correlation of vedolizumab trough levels with remission and support the fact that time on therapy with careful monitoring may be sufficient to ensure adequate response is eventually achieved rather than switching therapies.

Role of TDM: In 2017, post-hoc analysis of the GEMINI trial reported that higher vedolizumab serum concentrations were associated with higher remission rates after induction therapy in patients with moderately to severely active UC or CD[32]. These finding were confirmed in a prospective trial of 51 IBD patients which showed that vedolizumab trough levels were higher at weeks 6 and 22 in patients with combined clinical and endoscopic remission[78]. The correlation between vedolizumab levels and response has subsequently been described in further studies including an association with endoscopic response and histological healing[74,79-81]. Furthermore, observational studies describe the role of early vedolizumab trough level as a predictor for clinical[78,82-84] and histological remission[85] and the need for dose intensification within 6 months[75]. Interestingly a multicentre retrospective study of 58 patients with IBD with secondary LOR to vedolizumab reports reported an odds ratio of 3.7 for clinical response to dose escalation with vedolizumab concentration < 7.4 μg/mL compared to a vedolizumab concentration ≥ 7.4 μg/mL[68] and a small retrospective study of 23 patients showed that early changes in the pharmacokinetic profile of vedolizumab may predict recapture of response after dose optimization[69]. A prospective study of 47 primary non-responders to vedolizumab with IBD who were dose-escalated reported that all patients with vedolizumab trough levels < 19.0 mg/mL at week 6 required dose escalation and achieved clinical response 4 weeks later[75]. Furthermore, Singh *et al*[86] undertook a meta-analysis in UC patients which reported vedolizumab trough concentration ≥ 18.5-20.8 μg/mL at week 6, and ≥ 9.0-12.6 μg/mL during maintenance may be associated with clinical remission at week 14 and clinical/endoscopic/biochemical response or remission with maintenance therapy respectively. A systematic review by Cao *et al*[87] suggested a blood concentration of vedolizumab surpassing 25.0 μg/mL indicated mucosal healing in UC patients under maintenance therapy but was unable to provide a clear predictive cut-off value of blood concentration on mucosal healing or endoscopic remission under induction therapy in IBD reporting a range between 8.0 and 28.9 μg/mL.

Given these findings, it would appear TDM may have a role in monitoring response to treatment in vedolizumab and in determining mechanistic failure. However, more recent observational data has not found an association with trough vedolizumab levels and clinical remission[88,89]. A prospective study of 159 patients with IBD did not find a correlation between trough vedolizumab concentration and clinical remission among patients on maintenance therapy[89]. Furthermore, the utility of vedolizumab trough levels to guide dose escalation was explored by a multicentre retrospective study which found no difference in vedolizumab trough levels prior to optimisation among those reaching clinical remission compared with those with active disease after dose escalation[81]. Similar findings were reported in a prospective study that found baseline trough levels of vedolizumab were not predictive of clinical and biological response at weeks 4 and 8 to dose escalation[70].

Predictors of failure to respond to dose escalation: With this apparent equipoise, the role of vedolizumab drug monitoring to guide management and identify patients with mechanistic failure in IBD is unclear. Currently, there is also insufficient data to establish predictive factors for response to dose intensification. A prospective study of maintenance vedolizumab in UC reported that clinical improvement was similar magnitude following an increase in dosing frequency among TNF antagonist-naïve and TNF antagonist-failure subgroups, although the absolute rates of response were higher in the former group[66]. While a retrospective study of vedolizumab maintenance in IBD found that concurrent steroid use was associated with lower rates of clinical remission following dose escalation[68].

Further RCTs are required to clearly delineate the optimal frequency and dose for optimisation of vedolizumab therapy. With regards to TDM, further research is required to establish if TDM could aid in management of patients on vedolizumab and identify potential predictors for response to dose escalation. Currently, it appears that a strategy of persisting with therapy and possible dose escalation in patients with early nonresponse to therapy or following secondary LOR to treatment can overcome LOR to therapy.

Ustekinumab-management options for PNR/LOR

Ustekinumab is a humanised monoclonal antibody targeting the p40 subunit of IL-12 and IL-23[90]. The landmark UNITI trials established the utility of Ustekinumab in Crohn's disease and UC[90,91]. LOR also occurs with ustekinumab therapy[92,93] and is estimated to occur in 21% per person-year on standard dosing and 25% per person- year for dose interval shortened therapy[94]. Approximately 20% of patients will require dose-interval shortening during the maintenance therapy[95]. The optimal management of primary nonresponse and secondary LOR to standard ustekinumab dosing remains unclear[96]. Potential approaches include empiric dose intensification through reduction of dose interval, re-induction to recapture clinical response in both CD and UC or use of TDM as outlined below[41] (Table 1).

Dose-escalation: Treatment intensification with 4 weekly or 6 weekly ustekinumab to capture response in Crohn's disease is an established management strategy for LOR to therapy[41,48,97-106]. A multicentre study of 100 patients with active CD showed clinical remission at a median follow-up of 2.4 months in approximately 30% of patients following treatment intensification with ustekinumab 90 mg every 4 weeks for LOR or incomplete response[101]. Similar findings were also described in a recent retrospective study of 110 patients with CD which reported that shortening ustekinumab 90 mg dose interval to 4 weekly among 55 patients with PNR or LOR achieved clinical remission in 28% and endoscopic remission in 36% of patients at a median follow-up of 5.9 months[102]. Furthermore, Dalal *et al* reported in a retrospective study of 123 patients with Crohn's disease that dose intensification to both 4 weekly and 6 weekly is clinically effective with 50% of patients in both groups achieving corticosteroid-free clinical remission within 12 months[41]. The efficacy of treatment intensification of ustekinumab was further demonstrated in a recent large retrospective multicentre study including 1113 CD patients treated with ustekinumab which reported among 77 patients who experienced loss of remission and underwent dose optimisation 57% achieved clinical response and among 152 patients who were dose-optimized because of primary nonresponse or incomplete response to ustekinumab approximately 40% achieved clinical response[103].

While there is less evidence for dose intensification in UC, it still appears robust with a single retrospective cohort study including 123 patients with CD and 40 patients with UC which described corticosteroid free clinical remission rates > 50% among all CD and UC patients at 12 months after ustekinumab dose intensification and ≥ 40% at 24 months[96]. Rowbotham *et al*[107] report 58% rate of clinical remission at week 16 in UC patients with increase in frequency of ustekinumab to 8 weekly from 12 weekly.

Re-induction: Re-induction following LOR to ustekinumab in Crohn's is another strategy that can be used and is supported by several observational studies[105,108-113]. A retrospective study of 65 patients with Crohn's reported that clinical remission was achieved at week 14 in approximately 30% of patients even among those already on escalated maintenance dosing of ustekinumabevery 4 weeks[110]. A recent retrospective observational study of 128 patients with Crohn's which compared dose optimisation of ustekinumab by shortening interval or through intravenous reinduction reported greater increases in ustekinumab trough level and higher rates of clinical and endoscopic remission at 3 months with intravenous reinduction compared with shortening of drug intervals[114]. Similar findings were described in a retrospective observational study which reported that among patients with severe CD optimization of ustekinumab with 2 initial intravenous inductions was more effective than standard with clinical response and clinical remission rates of 92% and 88% respectively[115]. The findings suggest that even a temporary increase in the dose of ustekinumab therapy may be sufficient to recapture response to ustekinumab treatment so should be considered for patients losing response to therapy.

While more data is needed to delineate efficacy of dose optimisation of ustekinumab with reinduction as opposed to interval shortening and the role of dose optimisation, the findings of meta-analyses by Meserve *et al*[116] and Yang *et al* [94] provide strong evidence for a benefit to recapture clinical response with dose escalation in Crohn's disease following LOR or inadequate response.

Switch from subcutaneous to intravenous therapy or risankizumab: Switching from subcutaneous to intravenous ustekinumab or to therapies with a similar mechanism is an evolving area of practice with potential to overcome LOR to ustekinumab[117]. Argüelles-Arias *et al*[117] describe a clinical remission rate of approximately 43% with the use of intravenous ustekinumab maintenance following LOR to subcutaneous dosing. This is not unexpected given the established role of re-induction of ustekinumab[105,108-112] however further data is needed to support this switch from subcutaneous to intravenous ustekinumab. A switch from ustekinumab to risankizumab which isa selective inhibitor of the p40 subunit of IL-23 has shown potential in inducing early response in cases of treatment failure with ustekinumab as reported in recent case report[118].

Role of TDM: Despite some contrary findings regarding the association between trough levels and Crohn's disease response (clinical or biochemical)[119-123], there is robust evidence to suggest that ustekinumab trough levels correlate with clinical, biomarker and/or endoscopic response in Crohn's[124-139]. This was confirmed in meta-analysis which showed higher median ustekinumab trough concentrations occur in individuals who achieve clinical remission compared with those who do not achieve remission[140].

In UC, a single prospective study by Adedokun *et al*[129] evaluates ustekinumab levels in UC describing dose-proportional serum concentrations of ustekinumab and association of serum concentrations with clinical and histologic response as well as normalization of inflammation markers.

However, despite these findings the role of TDM to guide ustekinumab therapy is limited. The significant variations between studies in reported ustekinumab levels to achieve response in conjunction with the heterogeneity in methods of reporting ustekinumab levels do not currently permit a clear cutoff value for defining a response to therapy[140]. Furthermore, there is only sparse data evaluating ustekinumab levels following dose escalation[110,123,133,141] and endoscopic remission was associated with an increase in ustekinumab levels in only one of these observational studies [133]. Interestingly, Hanžel *et al*[133] reported that patients with ustekinumab concentrations < 3.5 mg/L following dose optimisation were unlikely to achieve endoscopic or biochemical remission. There is currently a lack of data regarding optimal drug levels and drug level response to dose escalation with ustekinumab and further clinical studies are required in order to guide treatment.

Predictors for failure to respond to dose escalation: Given the current lack of sufficient data to utilise ustekinumab levels to guide therapy, factors including patient and disease characteristics may potentially be used to identify patients at risk of mechanistic failure. Dalal *et al*[41] reported that perianal disease, pre-intensification Harvey-Bradshaw Index, current opioid use, and current corticosteroid use were associated with ustekinumab failure after dose intensification in Crohn's disease. Heron *et al*[110] did not identify any predictors of clinical response or remission to ustekinumab reinduction and Cohen *et al*[99] described response to initial ustekinumab induction therapy as the only independent predictor of response to ustekinumab dose escalation. Therefore, while factor such as perianal disease and disease severity should be considered when considering dose-escalation of ustekinumab for LOR, there is insufficient evidence for these predictors to identify patients unlikely to respond to dose optimisation. Further research is required to establish predictors of response to ustekinumab dose escalation or reinduction as well as identifying a drug level that can reliably delineate patients with clinical remission. As a result, dose escalation or reinduction in patients with early nonresponse to ustekinumab therapy or following secondary LOR is a viable management option.

JAK-inhibitors-management options for PNR/LOR

In recent times the JAK inhibitors have emerged as efficacious therapy in IBD[142-144]. Tofacitinib is an oral, small molecule JAK inhibitor which inhibits all JAKs but preferentially inhibits JAK1 and JAK3[145] and upadacitinib is an oral selective reversible inhibitor of JAK1[146]. The landmark OCTAVE and U-ACHIEVE/U-ACCOMPLISH trials established the efficacy of tofacitinib and upadacitinib respectively in induction and maintenance of remission in UC[142,143] and Loftus *et al*[144] established the efficacy of upadacitinib in induction and maintenance therapy in Crohn's disease. Yet despite their efficacy, a significant portion of patients experience primary or secondary LOR with JAK Inhibitor therapy. There is a reported PNR rate of approximately 20% and LOR rate of 39% per person year in UC patients treated with tofacitinib[142,147]. With upadacitinib treatment there is a PNR rate of approximately 50% in Crohn's and 65%-75% in UC[143,144] (Table 1).

Dose escalation of tofacitinib: Higher numerical rates of remission (total mayo score ≤ 2) in UC have been noted at 40.6% with 10 mg twice daily dosing of tofacitinib compared to 34.3% with 5 mg twice daily tofacitinib during maintenance therapy[142]. Furthermore, dose-escalation of tofacitinib from 5 mg twice daily to 10 mg twice daily whilst on maintenance therapy can be effective in recapturing response to tofacitinib in patients with UC[51-53,148,149]. In fact, the OCTAVE long-term extension study reported that dose escalation to 10 mg bowel disease (BD) following treatment failure with 5 mg BD tofacitinib recaptured clinical response in approximately 65% of patients and clinical remission in approximately 50% at 12 months of escalated therapy[148]. Similarly in a retrospective study of patients with UC, Honap *et al*[52] and Ma *et al*[51] described recapture of response with dose-escalation of tofacitinib to 10mg BD in approximately half of patients who had lost response. However, in a post hoc analysis which evaluated tofacitinib treatment persistence in this same group described discontinuation among the dose escalation group of approximately 49% with a median time to discontinuation of 4.4 years[53]. In the setting of PNR, extended induction therapy from 8 weeks to 16 weeks of tofacitinib 10 mg BD is able to capture clinical response in 52.2% of patients at week 16[150].

Dose escalation of upadacitinib: The U-ACHIEVE and U-ENDURE trials both reported higher rates of remission with 30 mg upadacitinib compared to 15 mg upadacitinib[143,144]. Furthermore, early data from the phase 2 CELEST study in Crohn's disease reported that patients with inadequate response obtained clinical remission and endoscopic response with upadacitinib dose escalation[151]. Reassuringly, the long-term extension study of CELESTE described clinical remission at 30 months in 55% of patients dose escalated from 15 mg to 30 mg maintenance[152]. Panacionne *et al* also noted the efficacy of dosing escalation of upadacitinib to 30 mg daily for LOR or inadequate response with clinical remission following escalation in 30% of UC patients at 48 weeks[153]. Extended induction therapy for PNR from 8 weeks to 16 weeks of upadacitinib 45 mg daily is able to capture clinical response in 46.6% of patients at week 16[154].

Switch between JAK inhibitors: Furthermore, the addition of upadacitinib as a treatment option for UC permits within drug class switching following treatment failure of tofacitinib with PNR or LOR. Two small case series have reported clinical remission with upadacitinib in UC patients with PNR or LOR to tofacitinib[155,156]. Furthermore a prospective study of 26 patients with IBD reported that upadacitinib was effective in inducing clinical and biochemical remission following primary or secondary nonresponse to tofacitinib[157]. There are currently no published studies assessing the efficacy of switching from upadacitinib to tofacitinib following PNR or LOR.

Role of TDM: Given the recent integration of the JAK Inhibitors in IBD therapeutic armamentarium the role of drug monitoring with JAK-Inhibitors is unclear[158]. Early pharmacokinetic studies of tofacitinib in UC reported that while plasma tofacitinib concentrations increased proportionately with dose there was no difference in tofacitinib concentrations at baseline versus at the end of induction at week 8 and that tofacitinib concentrations did not differ with clinical remission at specific doses[159].

Further studies are needed to elucidate the role of TDM and the association between drug levels and clinical remission. Additional clinical research will also be essential to establish predictors for mechanistic failure with JAK-inhibitors to guide treatment decisions. However currently dose escalation of both tofacitinib and upadacitinib or in-class switching both represent potential methods of recapturing response.

Ozanimod/S1P receptor modulators-management options for PNR/LOR

Ozanimod and etrasimod are selective S1P receptor modulators of S1P1 and S1P5[160] and S1P1, S1P4 and S1P5[57] respectively. S1P receptor modulators have recently emerged as therapeutic options for induction and maintenance of remission in UC[57,161]. There are no studies evaluating management of LOR and secondary nonresponse with S1P receptor modulators.

DISCUSSION

As with TNF-inhibitor therapy, patients with suspected PNR and LOR to non-TNFi advanced therapy require detailed assessment to exclude other causes of symptoms and to assess disease activity[10,58].

In PNR and LOR to vedolizumab therapy, it appears reasonable to increase frequency of vedolizumab dosing[23,68-77]. While increasing the frequency of vedolizumab 300 mg to 6 weekly and 4 weekly may both be effective strategies[68,72,76], we favour an increase to 4 weekly dosing, if available, in order to maximise likelihood of capturing response and minimise risk of prolonging futile therapy. The role for TDM prior to vedolizumab dose optimisation is not yet established but may be used depending on availability. There is significant heterogeneity in reported drug levels which correlate with clinical remission[75,86,87] and conflicting data regarding the utility of drug levels to predict clinical remission[88,89] and response to dose escalation[70,81]. We propose assessing for response to vedolizumab at approximately 12-24 weeks to allow adequate time for effect of vedolizumab dose escalation[68,70,72,74]. If clinical response is not captured by 24 weeks, we suggest switching therapy (Figure 1).

Once PNR/LOR is confirmed with ustekinumab therapy, options to capture response include increasing dose frequency, intravenous reinduction or a combination of both. While increasing the frequency of ustekinumab 90 mg to 4 weekly or 6 weekly is an effective method of capturing response in the setting of PNR/LOR[41,48,96,98,100-102,107], we favour an increase to 4 weekly dosing, if available, in order to maximise likelihood of capturing response with a view to consider reducing dose at a later stage if remission is achieved and sustained. Intravenous reinduction of ustekinumab is effective for recapturing response in LOR but not PNR[109-112] and consequently in the setting of PNR intravenous reinduction should be combined with increased frequency of ustekinumab[97,99,103-106,113,114]. While ustekinumab levels appear to be positively correlated with response[124-139] there are significant variations in the reporting of levels to achieve clinical remission, which make it more difficult to use levels to guide therapy[140]. Response to ustekinumab should be assessed at approximately 12-24 weeks to allow adequate time for the effect of dose escalation to be assessed [97,99,104-107,109-111,114]. If clinical response is not captured at 24 weeks, we suggest confirming LOR with objective measures and consideration for switching to an alternate therapy (Figure 2).

In the setting of PNR to tofacitinib extended induction to 16 weeks from 8 weeks may be an effective means of inducing clinical response[150]. Where patients have LOR with tofacitinib, dose optimisation to 10 mg BD is an effective means of recapturing response[51,52,148]. We suggest assessing for response can be performed as early as 8 weeks after treatment adjustment given the rapid onset of action of tofacitinib, although some people may take many months to respond as response rates continue to increase up until 12 months after dose escalation of tofacitinib[142,148]. If clinical response is captured at reassessment, we suggest continuing tofacitinib therapy otherwise we suggest utilisation of an alternate therapy.

In the setting of PNR to upadacitinib extended induction to 16 weeks from 8 weeks may be an effective means of inducing clinical response[154]. Following LOR with upadacitinib, dose optimisation to 30 mg daily effectively recaptures response in about[152,153]. An assessment for response can occur as early as 8 weeks, although some patients may take longer to respond and response rates continue to increase to 52 weeks of additional treatment at 30 mg daily, so consideration in the clinical context of whether a patient should continue treatment would be on a case by case basis[144]. We suggest continuing upadacitinib therapy if response is captured at the time of reassessment, otherwise an alternate therapy should be considered.

CONCLUSION

With significant shifts in the treatment paradigm of IBD over the last decade, there remains many unanswered questions regarding the optimal treatment algorithm with non-TNF-i advanced therapy. In this review we propose practical algorithms for the management of PNR and secondary LOR to non-TNF-i advanced therapy. Further clinical research and real-world experience is required to optimise these treatment pathways and to establish the role of TDM to better identify

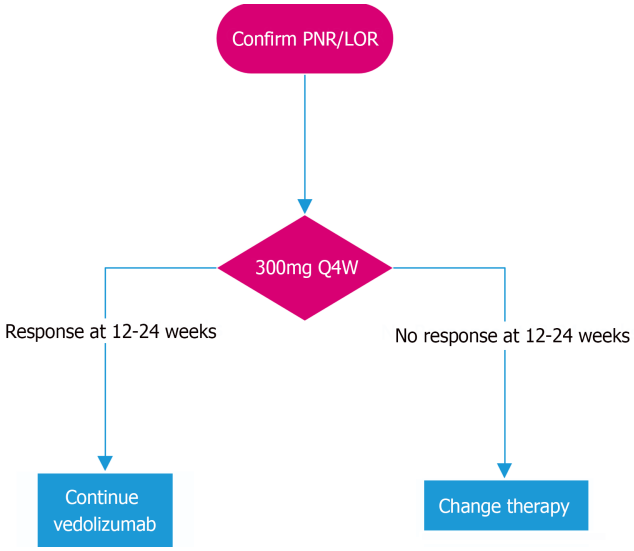

Figure 1 Management of loss of response to vedolizumab. PNR: Primary non-response; LOR: Loss of response.

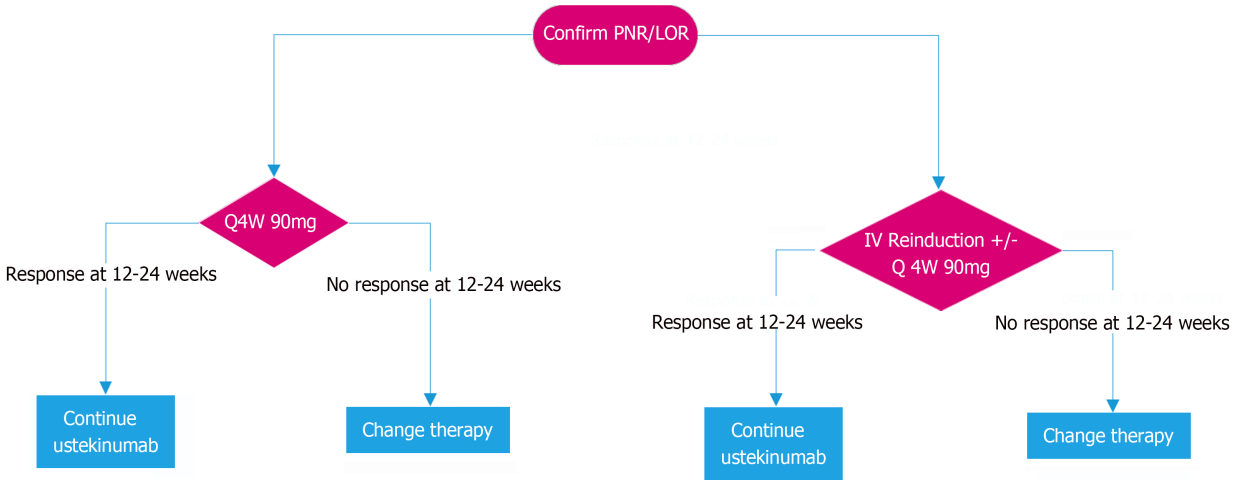

Figure 2 Management of loss of response to ustekinumab. PNR: Primary non-response; LOR: Loss of response.

patients who will not respond to dose optimisation. This knowledge will help minimise risk of prolonging futile therapy with dose escalation while also ensuring advanced therapies are not prematurely discarded in the absence of evidence of irrecoverable non-response.

FOOTNOTES

Author contributions: Vasudevan A and Vootukuru N were involved in the conception and design of the manuscript, writing and editing of the manuscript and final approval of the version to be submitted.

Conflict-of-interest statement: All the authors report no relevant conflicts of interest for this article.

PRISMA 2009 Checklist statement: The authors have read the PRISMA 2009 Checklist, and the manuscript was prepared and revised according to the PRISMA 2009 Checklist.

Country of origin: Australia

ORCID number: Abhinav Vasudevan 0000-0001-5026-9014.

S-Editor: Qu XL
L-Editor: A
P-Editor: Cai YX

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