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Therapeutic drug monitoring in IBD: for every patient and every drug?

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Abstract

Purpose of review—This review provides an updated overview on the role of therapeutic drug monitoring (TDM) of biological therapies in IBD. We examine the data behind TDM for the anti-tumor necrosis factor (anti-TNF) agents, vedolizumab and ustekinumab, in patients with inflammatory bowel disease (IBD). In addition, we discuss reactive vs. proactive TDM.

Recent findings—There is a positive correlation between biologic drug concentrations and favorable therapeutic outcomes in IBD, although the majority of data refer to anti-TNF therapy. Reactive TDM has rationalized the management of patients with IBD with loss of response to biological therapy. Moreover, reactive TDM of infliximab has been proven to be more cost-effective when compared to empiric dose optimization. Preliminary data suggest that proactive TDM of infliximab and adalimumab applied in patients with clinical response/remission is associated with better therapeutic outcomes compared to standard of care (empiric treatment and/or reactive TDM).

Summary—For all biologics in IBD, there is a positive correlation between drug concentrations and favorable therapeutic outcomes. Reactive TDM is the new standard of care for optimizing biologic therapies in IBD, while recent data suggest an important role of proactive TDM for optimizing anti-TNF therapy in IBD.

Keywords

Crohn’s disease; ulcerative colitis; immunogenicity; biologics; infliximab

INTRODUCTION

Biologic agents, such as infliximab, adalimumab, certolizumab pegol and golimumab [anti-tumor necrosis factor (TNF) therapy], vedolizumab ($\alpha_4\beta_7$ integrin inhibitor) and ustekinumab (interleukin 12/23 inhibitor) have revolutionized the treatment of patients with inflammatory bowel disease (IBD) [1]. Nevertheless, up to 30% of patients with Crohn’s disease (CD) and ulcerative colitis (UC) are primary non-responders and have no clinical benefit following induction therapy. Moreover, up to half of the patients with an initial

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clinical benefit have a secondary loss of response (SLR) and need to intensify or even discontinue therapy. Both primary non-response (PNR) and SLR can be explained by pharmacokinetic (PK) problems, characterized by undetectable or subtherapeutic drug concentrations with or without the development of anti-drug antibodies (ADA), or a mechanistic failure [2–5].

Numerous studies suggest that higher serum drug concentrations are associated with a higher rate of favorable therapeutic outcomes including clinical, biochemical [normalization of C-reactive protein (CRP) or fecal calprotectin (FC)], endoscopic, histologic or composite remission [6–48]. Based on these studies, therapeutic drug concentration thresholds to target have been proposed, although clinically relevant cut-offs can vary depending on IBD phenotype, therapeutic outcome and the TDM assay used (Table 1). For example, to achieve more stringent outcomes, such as mucosal healing, higher drug concentrations are needed compared to clinical response/remission (Table 1). On the other hand, ADA and undetectable or low drug concentrations have been associated with treatment failure and drug discontinuation [49–57].

Reactive therapeutic drug monitoring (TDM) of biologics applied in patients with a disease flare or an infusion reaction has rationalized the management of SLR [58–63]. Moreover, reactive TDM and has been proven to be more cost-effective when compared to empiric infliximab dose optimization [64–67]. Additionally, recently published data demonstrate that proactive TDM performed with the goal of attaining adequate drug concentration thresholds can effectively optimize anti-TNF therapy leading to better therapeutic outcomes when compared to standard of care (empiric dose escalation and/or reactive TDM) [68**–71]. Although many IBD specialists are already utilizing this therapeutic strategy in clinical practice TDM, proactive TDM is not yet considered standard of care [72–77].

This review will describe the role of TDM in optimizing biologic therapies in IBD and will focus on recent data regarding both reactive and proactive TDM as well as exposure-outcome relationship studies.

Therapeutic drug monitoring for every drug?

Numerous exposure-therapeutic outcomes studies highlight the importance of TDM for optimizing biological therapy in IBD. These studies emphasize that higher concentrations are needed during the induction phase, and higher concentrations are associated with better outcomes.

Infliximab

Several studies have shown that higher infliximab concentrations during both induction and maintenance therapy are associated with favorable therapeutic outcomes in both CD and UC (Table 1) [6–23]. The optimal drug therapeutic threshold to target during induction has not been clearly defined, although higher concentrations than during maintenance treatment are typically required. A post-hoc analysis of the TAILORIX (Drug-concentration versus Symptom-driven Dose Adaptation of Infliximab in patients with active Crohn's disease) randomized controlled trial (RCT) showed that higher infliximab concentrations at week 2 (≥23.1 μg/mL) and 6 (≥10 μg/mL) are associated with early endoscopic remission at week

12 [9]. A single-center retrospective study of patients with UC identified infliximab concentration thresholds of 28.3 μg/ml and 15 μg/ml at week 2 and 6 to be associated with short-term mucosal healing [11]. On the other hand, a recent retrospective observational case-control study found that infliximab concentrations <6.8 μg/mL and antibodies to infliximab (ATI) >4.3 μg/mL-eq before the second infusion are associated with PNR, especially among patients with CD [54].

Regarding maintenance therapy, current data suggest that infliximab trough concentrations >3 μg/ml are associated with clinical response/remission, although for more rigorous therapeutic outcomes (endoscopic, histologic, and fistula healing), higher drug concentration are needed (Table 1). For example, a recent single-center retrospective study of patients with CD showed that infliximab concentrations >9.7 and >9.8 μg/mL were associated with endoscopic and histologic remission, respectively [10]. Another study in UC identified infliximab trough concentrations >7.5 to be associated with endoscopic healing and concentrations >10.5 μg/mL to be associated with histologic healing [12]. Moreover, a multi-center inception pediatric cohort study identified a post-induction (week 14) drug concentration threshold of 12.7 ug/mL to best predict healing of fistulizing perianal CD at week 24 [18]. Another single-center cross-sectional study found that infliximab concentrations ≥10.1 μg/mL were associated with fistula healing in patients with perianal CD [16].

Adalimumab

Several studies have shown that higher adalimumab concentrations during both post-induction (week 4) and maintenance therapy are associated with improved therapeutic outcomes in both CD and UC (Table 1) [21–30]. These studies suggest an optimal therapeutic trough concentration threshold to target during maintenance therapy of >5 μg/ml for clinical response/remission, but for more rigorous therapeutic outcomes, higher drug concentrations are needed. For example, one recent retrospective multi-center study identified adalimumab concentration cut-offs of 11.8, 12, and 12.2 μg/mL in CD and 10.5, 16.2, and 16.2 μg/mL in UC to stratify those with or without biochemical, endoscopic, or histologic remission, respectively. [24]. On the other hand, patients with low drug concentrations at week 4 (<8.3 μg/mL) were found to be at significantly higher risk of having ADA by week 12 (46.7% vs. 13%, p=0.009). These patients also had a significantly higher need of dose escalation (p<0.001) and less frequently experienced sustained clinical benefit due to PNR or SLR (p=0.02) [55*]. Furthermore, a recent prospective study or 98 CD patients treated with adalimumab showed that ADA are strongly associated with PNR [odds ratio (OR) = 5.4, 95% confidence interval (CI): 1.6–17.8, p = 0.005]. In this study, 32% of patients developed ADA as early as week 2 and 55% of patients developed ADA as early as week 14 [53*]. These studies highlight the potential importance of early (proactive) TDM of adalimumab to guide dose optimization for preventing immunogenicity and attaining better long-term outcomes in IBD.

Certolizumab pegol

Although there are only limited data, current evidence from exposure-response relationship studies show that higher certolizumab pegol concentrations are associated with better therapeutic outcomes in CD (**Table 1)** [31, 32].

Golimumab

Although there are only limited data, current evidence from exposure-response relationship studies demonstrate that higher golimumab concentrations are associated with better therapeutic outcomes in UC (Table 1) [33, 34].

Vedolizumab

Several studies have shown that higher vedolizumab concentrations during both induction and maintenance therapy are associated with improved therapeutic outcomes in both CD and UC (Table 1) [35–45]. A post hoc analysis of the GEMINI 1 (Vedolizumab in Patients with Moderate to Severe Ulcerative Colitis), GEMINI 2 (Vedolizumab in Patients with Moderate to Severe Crohn's Disease) and GEMINI 3 (Vedolizumab in Patients with Moderate to Severe Crohn's Disease) RCTs demonstrated that higher vedolizumab serum concentrations at week 6 were associated with higher clinical remission rates after induction therapy (at week 14) in patients with moderately to severely active IBD. Trough concentration increases from Quartile (Q)1 (≤17.1 μg/ml) to Q4 (>35.7–140 μg/ml) in UC and from Q1 (≤16.0 μg/ml) to Q4 (> 33.7–177 μg/ml) in CD resulted in an absolute increase in remission rate of approximately 31% and 14%, respectively [38]. A post hoc analysis of the GEMINI 1 RCT demonstrated that UC patients in the higher steady-state vedolizumab trough concentration quartiles had greater deep remission rates at week 52 compared to those in the lowest quartile (Q1<9.26 μg/mL to Q4 >41 μg/mL) or those who received placebo [44]. A propensity-score-based case-matching analysis using data from GEMINI 1 identified vedolizumab concentrations thresholds of 37.1 (week 6), 18.4 (week 14) and 12.7 μg/mL (steady state) to be associated with clinical remission at week 52 [45].

Ustekinumab—Although there are only limited data, current evidence from exposure-response relationship studies show that higher ustekinumab concentrations are associated with better therapeutic outcomes (Table 1) [46–48]. A recent prospective, open-label cohort study showed that ustekinumab concentrations ≥4.2μg/mL at week 8 were associated with a 50% decrease in FC. Week 16 ustekinumab concentrations ≥2.3μg/mL and week 24 concentrations ≥1.9μg/mL were associated with endoscopic response at week 24 [48].

Therapeutic drug monitoring for every patient?

TDM is efficacious for optimizing anti-TNF therapy in IBD. The data is stronger for reactive than proactive TDM, and data for other biologics is lacking. Two large retrospective single-center studies did show that the lack of any TDM was associated with infliximab discontinuation [60, 63] and frequent intestinal surgeries [63].

Reactive therapeutic drug monitoring—Reactive TDM can better explain and therefore manage SLR to anti-TNF therapy in IBD [58, 60–62]. It can identify patients who

will respond to more drug (dose escalation) and those that would benefit from another strategy. Yanai et al. showed that at the time of SLR, infliximab concentrations >3.8 μg/mL and adalimumab concentrations >4.5 μg/mL identified patients who appeared to have a mechanistic failure and benefited more from a switch to a non-anti-TNF than dose escalation or switching to another anti-TNF [58]. Similarly, Roblin et al. demonstrated that at the time of SLR, adalimumab concentrations < 4.9 μg/mL without ADA strongly predicted response to dose intensification, whereas patients with antibodies did better when switched to another anti-TNF. Adalimumab concentrations >4.9 μg/mL were associated with failure of a second anti-TNF agent, identifying a group of patients mechanistically failing adalimumab who would require a non-anti-TNF agent [61]. In addition to better directing care, reactive TDM is also more cost-effective when compared to empiric infliximab dose optimization [58–67]. An observational cohort study showed that reactive TDM was associated with higher endoscopic remission and clinical response when compared to empiric infliximab optimization [59]. The same study showed that post-adjustment infliximab concentrations >4.5 μg/mL and ATI <3.3 U/mL were associated with endoscopic remission [59]. A suggested treatment algorithm for using reactive testing to infliximab is shown in Figure 1.

Proactive therapeutic drug monitoring—Proactive TDM is the measurement of trough concentrations and antibody levels with the goal of optimizing drug concentrations to achieve a threshold drug concentration. The aim of proactive TDM is to improve response rates and prevent secondary loss of response by targeting drug concentrations which are considered to be in the optimal therapeutic range. There is recent data that suggests that proactive TDM of anti-TNF therapy is associated with better therapeutic outcomes when compared to empiric dose escalation or reactive TDM (currently the standard of care). The landmark TAXIT (Trough Level Adapted Infliximab Treatment) RCT, although it failed to meet its primary outcome due to some methodological issues, demonstrated that proactive TDM of infliximab was associated with a lower frequency of undetectable drug concentrations and a lower risk of relapse compared to clinically-based dosing. Additionally, in patients with CD and low infliximab concentrations, a one-time dose optimization improved clinical remission rates and CRP [68**]. More recently, proactive compared to reactive TDM of infliximab was associated with less treatment failure, need for IBD-related surgery or hospitalization, risk of ATI and serious infusion reactions [71]. Additionally, another study demonstrated that in patients who underwent reactive TDM, subsequent proactive TDM of infliximab was associated with greater drug persistence and fewer IBD-related hospitalizations than reactive TDM alone [69]. Recently, a multi-center retrospective study showed that at least one proactive TDM of adalimumab was independently associated with a reduced risk for treatment failure when compared to standard of care [hazard ratio (HR): 0.4; 95%CI: 0.2–0.9; p=0.022) [70*].

Another potential benefit of proactive TDM is that de-escalation could be cost savings, although data are still sparse [68, 78]. This strategy is also safe as an observational single-center study including IBD patients in clinical and biological remission with infliximab concentrations >7 mg/L who de-escalated therapy showed that concentration-based de-escalation was associated with a decreased risk of relapse (HR: 0.45, p=0.024) [79]. However, as there are only limited data on what is the therapeutic window of infliximab and

current data in IBD do not demonstrate that higher anti-TNF therapy concentrations associated with increased toxicity, it may be reasonable to continue current dosing, especially in patients who had been very ill, despite high drug concentrations [80]. Nevertheless, physicians must follow the patients closely as a study in spondyloarthritis showed that the risk of an infection episode was significantly increased in the highest quartile of the mean of the last 3 trough infliximab concentrations (>20.3 μg/mL) (HR: 2.65, 95%CI: 1.14–6.14, p=0.023) [81]. In our practice, we typically dose de-escalate for infliximab concentrations that are consistently greater than 15 mg/L.

Furthermore, a recent retrospective cohort study of 83 IBD patients showed that drug durability did not differ between patients on infliximab monotherapy dosed based on proactive TDM and patients receiving combination therapy with an immunomodulator [82]. This concept of ‘optimized monotherapy’, or proactive TDM with a biologic alone, is further supported by a recent post-hoc analysis of the SONIC (Study of Biologic and Immunomodulator Naive Patients in Crohn Disease) RCT. This study stratified patients by infliximab concentration quartiles and demonstrated that patients had similar outcomes irrespective of concomitant azathioprine [83**]. A treatment algorithm for using proactive testing for infliximab is shown in Figure 2.

Though most of the data for proactive TDM is during the maintenance phase, it is probably most important during the induction phase when the disease is active and drug clearance is greatest. As noted above, drug concentrations need to be higher during induction and adequate drug concentrations during induction are associated with better short and long-term outcomes. The recent TAILORIX trial attempted to look at symptom-driven dose adaptation of infliximab vs. symptoms plus biomarkers, and infliximab drug concentrations in CD. Unfortunately, due to the design, little can be said about the role of TDM aside from higher infliximab concentrations during induction therapy at week 2 and 6 are associated with early endoscopic remission at week 12. The primary endpoint, sustained clinical remission with no endoscopic ulceration, was not different between the groups. However, two of the groups were only able to dose escalate based on clinical symptoms and biomarker elevation or trough concentrations whereas the control group was able to dose-escalate based only on clinical symptoms. In fact, in control group, 60% (9/15) of dose escalations based on only on symptoms had normal biomarkers, whereas, 53% (23) of possible dose escalations based on symptoms in interventional arms were avoided as biomarkers were not elevated. Furthermore, only 25–30% of patients were dose escalated based on trough concentrations, less than 50% of the “optimized” groups even attained a sustained infliximab concentration >3μg/ml (less than control group, 60%). Another major drawback was that one had to wait 8 weeks until the next dose to make a change. In the end, trough concentrations were similar in all 3 groups which likely accounts for the similar efficacy outcomes [84].

Therapeutic drug monitoring can also be applied in patients who resume anti-TNF therapy after a prolonged drug holiday (> 6 months) due to relapse. A single-center retrospective study showed that checking infliximab concentrations and ATI after the first dose following a drug holiday was related with improved outcomes. In this setting the absence of ATI was associated with fewer infusion reactions and detectable infliximab trough concentrations were associated with greater long-term response [85].

Conclusion

Numerous studies have demonstrated that higher biologic drug concentrations are associated with higher rates of favorable therapeutic outcomes in IBD, whereas low drug concentrations and anti-drug antibodies lead to primary non-response and secondary loss of response. Reactive TDM has emerged as the new standard of care in IBD, while there is cumulative evidence for the benefits of proactive dose optimization of anti-TNF therapy. While proactive TDM requires more studies, many clinicians caring for IBD patients feel that those patients at highest risk for relapse and surgery should have a post induction TDM, especially with infliximab and adalimumab. Specifically, patients with more severe UC and those with perianal fistulizing CD probably benefit most from TDM during or right after induction in order to optimize maintenance dosing. Although there is recent data that suggests that proactive TDM of anti-TNF therapy is associated with better therapeutic outcomes when compared to empiric dose escalation or reactive TDM, before individualized TDM algorithms can be fully applied in real-life clinical practice several barriers need to be addressed. These barriers include the optimal concentration therapeutic window to target, when (peak, intermediate, trough) and how (type of assay) to measure drug concentrations, and out-of-pocket cost of the assays. Future perspectives for maximizing the efficacy of TDM include the development of rapid assays and software decisions support tools incorporating predictive PK models to allow a faster and more accurate drug dose optimization.

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KEY POINTS

- Association studies have shown that higher biologic concentrations have been associated with favorable objective therapeutic outcomes in inflammatory bowel disease.
- Reactive TDM has rationalized the management of patients with loss of response to biologics and has been proven to be more cost-effective compared to empiric infliximab dose optimization.
- Preliminary data suggest that proactive TDM of anti-TNF therapy is associated with better therapeutic outcomes when compared to empiric treatment and/or reactive TDM (standard of care).
- As there are limited data, more studies are needed to clarify the role of proactive TDM and TDM for biologics other than anti-TNFs in IBD.

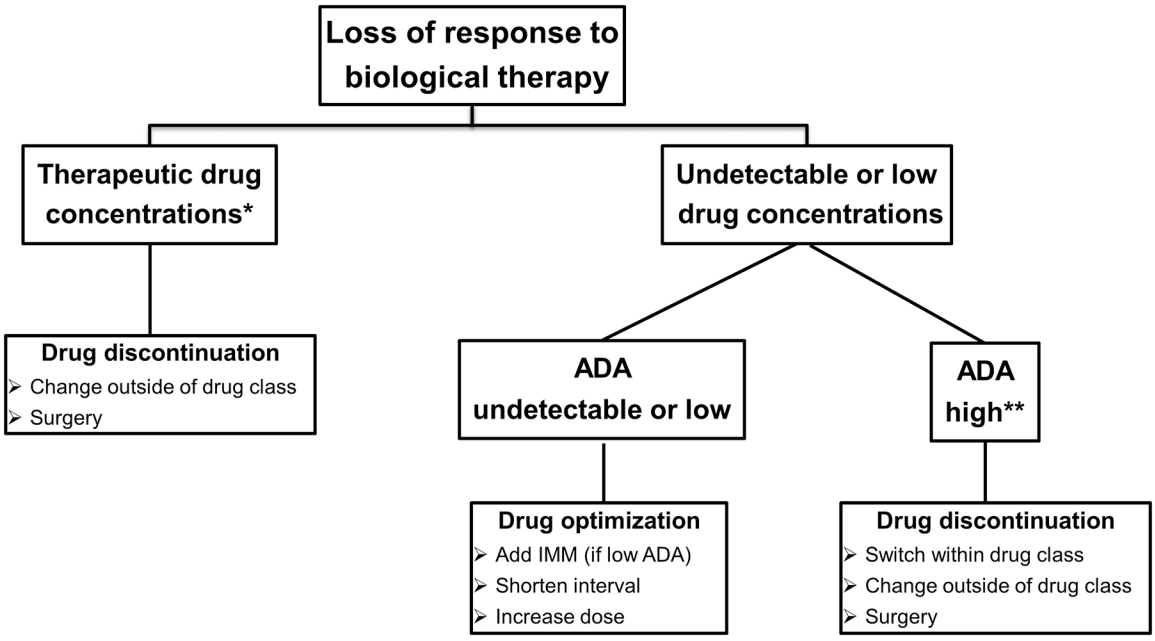

Figure 1. Reactive TDM algorithm of IBD patients on biological therapy.

*For relative values refer to Tables 1; **ATI >8 μg/mL-eq for ELISA and >10 U/ml for HMSA.

ADA: anti-drug antibody; IMM: immunomodulators; ELISA: enzyme-linked immunosorbent assay; ATI: anti-infliximab antibodies; HMSA: homogeneous mobility shift assay; TDM: therapeutic drug monitoring; IBD: inflammatory bowel disease.

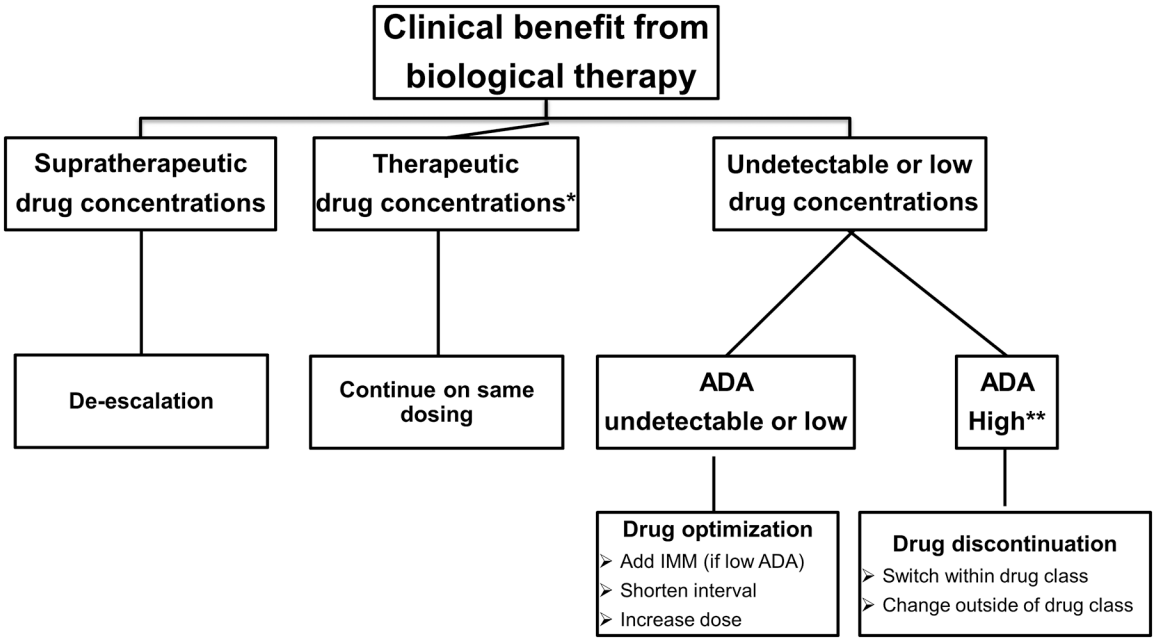

Figure 2. Proactive TDM algorithm of IBD patients on biological therapy.

*For relative values refer to Tables 1; **ATI >8 μg/mL-eq for ELISA and >10 U/ml for HMSA.

ADA: anti-drug antibody; IMM: immunomodulators; ATI: anti-infliximab antibodies; ELISA: enzyme-linked immunosorbent assay; HMSA: homogeneous mobility shift assay; TDM: therapeutic drug monitoring; IBD: inflammatory bowel disease.

Table 1.

Biological drug concentration thresholds to target associated with favorable therapeutic outcomes in inflammatory bowel disease.

Biological drug	Treatment time point	Suggested drug concentration threshold for clinical response/ remission (μg/ml)	Suggested drug concentration threshold for mucosal healing (μg/ml)
Infliximab	Induction (week 2)	≥20	≥25
	Induction (week 6)	≥10	N/A
	Post-induction (week 14)	≥3	≥7
	Maintenance	≥3	≥7
Adalimumab	Post-induction (week 14)	≥5	≥7
	Maintenance	≥3	≥8
Certolizumab pegol	Post-induction (week 6)	≥32	N/A
	Maintenance	≥15	N/A
Golimumab	Post-induction (week 6)	≥2.5	N/A
	Maintenance	≥1	N/A
Vedolizumab	Induction (week 2)	≥28	N/A
	Induction (week 6)	≥24	N/A
	Post-induction (week 14)	≥15	≥17
	Maintenance	≥12	≥14
Ustekinumab	Post-induction (week 8)	≥3.5	N/A
	Maintenance	≥1	≥4.5

N/A: not applicable, due to paucity of data.