Advances in Therapeutic Drug Monitoring in Biologic Therapies for Pediatric Inflammatory Bowel Disease

Akshay Kapoor and Eileen Crowley*

Division of Pediatric Gastroenterology, Hepatology, and Nutrition, London Health Sciences Centre, Children’s Hospital Western Ontario, Western University, London, ON, Canada

In the current era of treat-to-target strategies, therapeutic drug monitoring (TDM) has emerged as a potential tool in optimizing the efficacy of biologics for children diagnosed with inflammatory bowel disease (IBD). The incorporation of TDM into treatment algorithms, however, has proven to be complex. “Proactive” TDM is emerging as a therapeutic strategy due to a recently published pediatric RCT showing a clear benefit of “proactive” TDM in anti-TNF therapy. However, target therapeutic values for different biologics for different disease states [ulcerative colitis (UC) vs. Crohn’s disease (CD)] and different periods of disease activity (induction vs. remission) require further definition. This is especially true in pediatrics where the therapeutic armamentarium is limited, and fixed weight-based dosing may predispose to increased clearance leading to decreased drug exposure and subsequent loss of response (pharmacokinetic and/or immunogenic).

Model-based dosing for biologics offers an exciting insight into dose individualization thereby minimizing the chances of losing response. Similarly, point-of-care testing promises real-time assessment of drug levels and individualized decision-making. In the current clinical realm, TDM is being used to prolong drug durability and efficacy and prevent loss of response. Ongoing innovations may transform it into a personalized tool to achieve optimal therapeutic endpoints.

Keywords: pediatric, inflammatory bowel disease, therapeutic drug monitoring, biologics, precision medicine

INTRODUCTION

Biologic agents have revolutionized the treatment paradigm of pediatric inflammatory bowel disease (pIBD). Initially utilized as a second-line therapy in case of treatment failure with conventional medication (step-up approach), they are now considered as a primary induction option for children with active perianal fistulizing disease, in combination with targeted surgical intervention, as well as in children at risk of poor outcomes (top-down approach) (1, 2).

Infliximab (IFX) was the first licensed anti-tumor necrosis factor (TNF) approved for pediatric use in 2006 for treating Crohn’s disease (CD) (3). It was approved for use in the pediatric population for ulcerative colitis in 2010 (4). Adalimumab, which is a fully humanized monoclonal antibody, was approved for pediatric CD in 2012 (5) and has been recently approved by the US FDA for moderate to severe pediatric UC based on the ENVISION I phase 3 study (6). With the advent of gut selective anti-integrin molecules like vedolizumab, which offers promising clinical response in
colonic IBD with negligible side effects, the choice of biologic agents is increasing (7). Recently, ustekinumab, which is a biologic targeting the IL-12/23 pathway, has been approved for use in adult IBD (CD and UC) (8, 9) and is being used off label on a compassionate basis in pediatric IBD centers (10).

Therapeutic drug monitoring (TDM) which involves measuring drug concentration and antibody levels to optimize biologic exposure, thereby increasing efficacy and decreasing possible toxicity, is an essential tool in the arsenal to treat pIBD (Figure 1). Despite its widespread use in clinical practice, there are subtle issues which need to be addressed before uniform guidelines can be formulated. Questions around timing of TDM (proactive vs. reactive), frequency (during induction, maintenance, or both), and drug thresholds (underdosage vs. futility level) need to be aligned with the current treat-to-target paradigms (clinical, endoscopic, and histologic remission).

**METHODOLOGY**

A review of the medical literature incorporating keywords was performed on databases (to include PubMed, Medline, Embase, Scopus, Web of Sciences). Attention was given to previous reviews and seminal articles and an attempt was made to include recent advances and developments in the field. All relevant articles up to December 2020 were included.

**Reactive vs. Proactive TDM**

Reactive testing is performed in the setting of active diseaseflare/intolerance to the drug. It helps in delineating the possible cause of loss of response (LOR) and in possibly formulating a strategy to counteract it (Figures 2, 3). Intuitively, higher trough levels (TL) of the drug equate to higher exposure and should theoretically result in better clinical outcomes. This has been shown with different anti-TNFs in seminal adult studies (11–13). However, most of these studies were retrospective post hoc analyses. Recently published prospective studies seem to have confirmed this trend (14, 15). Similarly, pediatric retrospective studies performed during the maintenance phase demonstrate an inverse association between trough level and antibody formation (16–18). Prospective pediatric studies have looked at infliximab (IFX) levels in the postinduction phase (Table 1). Adedokun et al. (19) in a phase 3 RCT concluded that higher IFX TL at week 8 correlated with better clinical and histological outcomes in children with moderate to severe UC. Singh et al. (20) highlighted the importance of a week 14 TL as an indicator for clinical and endoscopic remission at week 54. TLs performed during the induction phase have the added benefit of differentiating between a mechanistic failure (primary non-response to anti-TNF) vs. a pharmacokinetic failure due to inadequate dosing and/or increased clearance (21).

Proactive TDM is performed in patients with quiescent disease to decrease the risk of disease relapse, treatment failure, and drug immunogenicity. It also may help in optimizing monotherapy with the biologic agent without the need for an immunomodulator, thereby avoiding potential toxic therapy. This has been examined in adult studies carried out by Lega et al. (22) and post hoc analysis of the SONIC trial (23). Papamichael et al. (24) in a multicentric retrospective study showed benefit for the proactive TDM approach with regard to treatment failure, disease-related hospitalization, surgery, and infusion reactions. The results of the two randomized control trials completed in adults, comparing proactive TDM to empiric optimization, have been disappointing. The TAXIT study (25) randomized IBD (UC and CD) patients on stable maintenance therapy with IFX to receive further dosing based on proactive monitoring or clinical symptoms. Interestingly, all patients were dose optimized to a TL of 3–7 µg/ml prior to randomization. At the end of 12 months, there was no difference between the groups with regard to clinical/biochemical remission. There was also no differences noted with regard to surgery and corticosteroid-free remission between the groups. The TAILORIX trial (26) included biologic naive CD adult patients starting IFX therapy and randomized them to three arms based on clinical symptoms alone, clinical symptoms and biomarkers, and clinical symptoms, biomarker, and/or IFX trough levels. Dose escalation of IFX was based on predefined criteria in the first two groups. The primary endpoint of the study was corticosteroid-free clinical remission, fistulae, or need for surgery between weeks 22 and 54. There was no difference between the groups with regard to the primary or secondary endpoints. The PAILOT (27) study is the only pediatric RCT comparing proactive and reactive TDM using adalimumab as the biologic of choice. The proactive approach demonstrated a clear benefit with regard to corticosteroid-free clinical remission between weeks 8 and 72. A recent retrospective pediatric paper showed the benefit of a proactive anti-TNF TDM approach in improving outcomes related to steroid-free clinical remission (28).

The AGA guidelines issued in 2017 recommended the use of reactive TDM to guide treatment decisions based on a very low grade of evidence; however, it refrained from making any recommendations on proactive TDM (29). A second guideline issued as a result of a Delphi process among 25 international IBD experts recommended reactive TDM for both primary non-response (PNR) and LOR. However, it also recommended proactive TDM for patients in remission immediately post induction and those on stable maintenance, to save costs (30). Systematic reviews and meta-analysis performed to resolve this deadlock have consistently shown no clear benefit of any TDM strategy over empiric optimization. The reviews have shown a consistent cost benefit with a reactive TDM strategy vs. empiric escalation (31) and drug durability benefit with the proactive strategy (32, 33). This assumes greater importance in pediatrics as IBD specialists try to factor in insurance coverage and payor–payee concerns into pharmacotherapeutic decision-making (34).

**TDM and the Newer Biologics**

The α4β7 anti-integrin vedolizumab (VDZ) has been documented to have an exposure–response relationship similar to the anti-TNFs for both UC (GEMINI-1) (35) and CD (GEMINI-2) (36). Post hoc analysis of the GEMINI trials completed by Rosario showed that remission rates associated with TL <17 µg/ml for UC and <16 µg/ml for CD were similar to placebo (37). These findings were subsequently confirmed in two real-world cohort studies. In a Belgian study by Dreesen...
et al. (38), cutoff points for trough levels were calculated using AUROC during both induction and maintenance. Similarly, Ungaro et al. (39) confirmed that higher TLs of VDZ were associated with steroid-free clinical remission.

The GEMINI trials also showed the low immunogenic potential of VDZ with persistent anti-drug antibody rates <1% (31, 32). This has been confirmed in subsequent studies wherein adding an immunomodulator to VDZ therapy neither enhanced drug levels nor regained therapeutic response (40). Studies have shown near complete saturation of the $\alpha_4\beta_7$ at drug levels as low as 1 µg/ml; therefore, it is currently unclear as to how dose optimization may help in recapturing therapeutic response (41). A recent abstract presented at the Digestive Diseases Week (DDW) virtual meeting suggested that colonic tissue VDZ concentration varies inversely with the severity of inflammation. Thus, increasing the TL might enable more drug to penetrate the inflamed tissue and help with clinical remission/endoscopic healing (42). While evidence is emerging that TL for VDZ may be associated with clinical and endoscopic remission (43), there are no clinical guidelines regarding the levels that need to be targeted. The ECCO-ESGAR committee recommends TDM for VDZ whenever available (44). Studies on pediatric TDM with respect to VDZ are limited. A recent Dutch study highlighted the exposure–efficacy relationship of VDZ in a pediatric IBD population which had failed anti-TNF. The authors concluded that a lower TL of VDZ in Crohn’s disease patients vs. UC/IBD-U was due to the transmural nature of the disease and may benefit from proactive TDM and subsequent higher dosing (45).

Ustekinumab (UST) is an IL-12/23 inhibitor which works by blocking the common p40 subunit. The exposure–efficacy relationship for UST dosing was proven in the pivotal studies IM-UNITI and UNIFI in CD and UC, respectively (8, 9). A real-world study by Battat et al. (46) showed that a TL $>$ 4.5 µg/ml during maintenance was associated with a biomarker and endoscopic response. Of note, the majority of patients in this study had been dose optimized to receive UST every 4 weeks, against the conventional 8-week dosing. Adedokun et al. in their study with more conventional eight-weekly maintenance dosing in adult CD patients showed a TL $>$ 0.8 µg/ml to be associated with prolonged clinical and endoscopic remission (47). The immunogenic potential of UST, similar to VDZ, is also quite low; consequently, the addition of azathioprine/methotrexate is seldom required. There is still a lot of variability in the optimization protocols for UST. The seminal extension study (IM-UNITI) (48) suggested 12-weekly maintenance dosing in biologic naive patients and 8-weekly dosing in anti-TNF therapy-experienced patients. Other ongoing trials include STARDUST (treat-to-target vs. routine case management in
TABLE 1 | Summary of pediatric studies utilizing TDM for biologic efficacy.

| Study                        | Type                      | Year  | Drug | Age (years) Median (IQR) | N   | Type of IBD | Outcomes measured                                                                 | Results                                                                 | ADA       | Assay  |
|------------------------------|---------------------------|-------|------|--------------------------|-----|-------------|-----------------------------------------------------------------------------------|-------------------------------------------------------------------------|-----------|--------|
| Adedokun et al. (19)         | Prospective randomized open label | 2013  | IFX  | 14.5 (11.5–16)           | 60  | UC          | IFX TL in children through induction and maintenance                               | PUCAI, Mayo score IFXw8: >41.1 associated with CR and MH ∼ 93%          | 4/52 (8%) | ELISA  |
| Singh et al. (20)            | Prospective observational cohort | 2014  | IFX  | 11.4 (6.6–18.4)          | 46  | CD/UC       | Postinduction TL, clinical and endoscopic outcomes                                 | W14: 5.1 (3.1–7.5) W54: 5.2 (3.7–9.1) CR: 4.7 µg/ml vs. NR 2.6 µg/ml (p = 0.03) | W1/4: 10% | ELISA  |
| Hoekman et al. (77)          | Prospective cohort        | 2015  | IFX  | 15 (12.9–16.3)           | 39  | CD/UC       | Maintenance TL, clinical, and biomarker remission                                  | CR (median): 3.5 µg/ml vs. NR 2.3 µg/ml (p = 0.2) TL ∼ CRP (p < 0.01) TL ∼ fCal (p < 0.01) | 4/32 (12%)| ELISA  |
| Zitomersky et al. (78)       | Cross-sectional           | 2015  | IFX  | 17.3 ± 4.3               | 134 | CD/UC       | Impact of ADAs on trough levels and clinical parameters                            | ADA < 5 U/ml: 80% ADA > 5: 20% ADA > 10: 13% ADA > 12: 10% IFX TL + ADA > 5: 1 µg/ml (1–9.3) IFX TL + ADA < 5: 12.2 µg/ml (7.6–25) | 27/134 (20%)| HMSA   |
| Sharma et al. (79)           | Post hoc analysis of double-blind randomized study | 2015  | Ada  | 13.6 (6–17)              | 189 | CD/UC       | Relationship of induction and maintenance TL with remission                      | W4: CR (14.5 µg/ml) vs. NR (13.6 µg/ml), p = 0.28 W26: CR (11.3 µg/ml) vs. NR (10.5 µg/ml), p = 0.02 W52: CR (13.3 µg/ml) vs. NR (9.85 µg/ml), p = 0.11 | 6/182 (3.3%)| ELISA  |
| Minar et al. (80)            | Retrospective cohort      | 2016  | IFX  | 12 ± 4                   | 72  | CD          | TL for dose intensification                                                        | Undetectable TL: 24% TL < 3: 38% Dose intensification on basis of TL: 35% | 14/72 (19%)| ELISA  |
| Dubinsky et al. (81)         | Post hoc analysis of double-blind randomized study | 2016  | Ada  | 13.6 (range 6–17)        | 83  | CD          | Clinical outcomes with dose escalation based on TLs                              | CR before dose increase TL 9.8 µg/ml CR after dose increase TL: 21 µg/ml Cre before dose increase TL: 9.1 µg/ml Cre after dose increase TL: 19.1 µg/ml | 6/182 (3.3%)| ELISA  |
| Stein et al. (76)            | Prospective cohort        | 2016  | IFX  | 14.79 (12.2–16.8)        | 77  | CD          | Durability of biologic based on W10 TL                                            | W10 TL Off IFX at 12 months: 8.7 µg/ml On IFX at 12 months: 20.4 µg/ml | 18/77 (23%)| HMSA   |
| Choi et al. (16)             | Retrospective cohort      | 2017  | IFX  | 14.7 (9–18.8)            | 39  | CD/UC       | Maintenance TL and clinical remission                                            | CR (median): 3.99 µg/ml vs. NR (median): 0.88 µg/ml, p = 0.02 | 7/39 (18%)| ELISA  |
| Study                        | Type                          | Year | Drug | Age (years) Median (IQR) | N  | Type of IBD                  | Outcomes measured                                                                 | Results                                                                 | ADA       | Assay   |
|-----------------------------|-------------------------------|------|------|--------------------------|----|-----------------------------|---------------------------------------------------------------------------------|--------------------------------------------------------------------------|-----------|---------|
| Merras-Salmio et al. (17)   | Retrospective cohort          | 2017 | IFX  | 14.8 (12.5–16)           | 146| CD/UC                       | Maintenance TL and clinical remission                                          | CR (median): 3.7 µg/ml vs. NR (median): 1.2 µg/ml, p = 0.005               | 52/208 (25%) | ELISA   |
| Rolandsdotter et al. (18)   | Retrospective cohort          | 2017 | IFX  | 16 (7–18)                | 45 | CD/UC                       | Maintenance TL, clinical, and biomarker remission                              | CR (median): 7.2 µg/ml vs. NR (median): 1.2 µg/ml, p < 0.05 CR ~ CRP (p = 0.008) TL ~ CRP (p = 0.003) TL ~ ESR (p = 0.003) TL ~ albumin (p = 0.0005) | 8/45 (18%) | ELISA   |
| Chi et al. (82)             | Prospective observational study | 2018 | IFX  | 18.5 ± 4.4               | 223| CD/UC                       | Combination IM + IFX therapy and relation to TL and ADA                        | Combination TL: 17 ± 1.33 µg/ml vs. monotherapy TL: 13.18 ± 1.26 µg/ml (p < 0.01) | 9.5% for combination therapy vs. 20% on monotherapy | Not reported |         |
| van Hoeve et al. (83)       | Retrospective cohort study    | 2018 | IFX  | 12.2 (9.5–14.4)          | 52 | CD/UC                       | Maintenance TL, clinical, endoscopic, and biomarker remission                  | TL (remission vs. not) p < 0.01 for all CR: 5.4 vs. 4.2 µg/ml BR: 5.2 vs. 4.2 µg/ml CR+BR: 5.7 vs. 4.4 µg/ml ER: 6.5 vs. 3.2 µg/ml | Low TL were associated with high ADA (OR 0.027) 95% CI 0.009–0.077 | ELISA     |         |
| Ohem et al. (84)            | Prospective observational study | 2018 | IFX  | 12.6 (10.5–15.1)         | 65 | CD                          | TL and biomarker remission                                                   | CRP <5mg/l: >1.1 µg/ml fCal <100: 3.5 µg/ml                                  | Not reported |         |
| van Hoeve et al. (85)       | Retrospective cohort study    | 2019 | IFX  | 11.6 (8.8–13.9)          | 35 | CD                          | Postinduction TLs as predictors of clinical and biological remission at W52  | Postinduction TL (remission vs. not), p < 0.002 CR: 4.6 vs. 1.5 µg/ml BR: 4.6 vs. 2.6 µg/ml CR+BR: 6.0 vs. 2.6 µg/ml | Not reported |         |
| Assa et al. (27)            | Non-blinded randomized control trial | 2019 | Ada  | 14.3 ± 2.6               | 78 | CD                          | Reactive vs. proactive drug monitoring and relation with sustained corticosteroid-free CR | CFCR (8–72 weeks) 82% in the proactive group vs. 48% in the reactive group (p = 0.02) CFCR+BR: 42% in the proactive group and 12% in the reactive group (p = 0.03) | 8/78 (10.2%) | ELISA   |
| Choi et al. (86)            | Retrospective cohort study    | 2019 | IFX  | 14.5                      | 103| CD/UC                       | Correlation of IFX levels with hematological remission (CRP, ESR, albumin, and hematocrit) | Week 6 IFX level 9.82 µg/ml was required to maintain CRP <0.5 (AUC 0.88) Week 14 IFX level of 1.28 µg/ml was required to maintain CRP <0.5 (AUC 0.86) | Not reported | ELISA   |

(Continued)
### TABLE 1 | Continued

| Study           | Type                        | Year | Drug | Age (years) Median (IQR) | N  | Type of IBD | Outcomes measured                                                                 | Results                                                                 | ADA   | Assay |
|-----------------|-----------------------------|------|------|--------------------------|----|--------------|------------------------------------------------------------------------------------|-------------------------------------------------------------------------|-------|-------|
| Naviglio et al. (87) | Prospective observational study | 2019 | IFX  | 14.4 (11.6–16.2)         | 49 | CD/UC        | CR as defined by PUCAI/PCDAI                                                                 | CR week 14, 76.3% CR week 54, 73.9% IFX level at the end of induction week 14, >3.11 µg/ml was strongest predictor of CR at week 54 | 10/49 (20.4%) | ELISA |
| Clarkston et al. (88) | Prospective observational study | 2019 | IFX  | 14.4                     | 72 | CD           | CR: wPCDAI at the fourth infusion                                                                 | CR: 64% BR: 54% Maintenance IFX level > 5 µg/ml: 22% Infusion 2 level > 29 µg/ml and infusion 3 > 18 µg/ml strongly associated with improved early outcomes | Not reported | ELISA |
| Gofin et al. (89)    | Retrospective cohort study   | 2020 | IFX  | 12.6 (10.1–14.2)         | 197| CD           | Effect on disease outcomes with TDM vs. without Drug retention Hospitalization rate/year Treatment intensification Surgical resection | Longer retention time with TDM Lower hospitalization rate with TDM Higher drug intensification rate with TDM No difference in surgical outcomes | Not reported | ELISA |
| Choi et al. (90)     | Prospective cohort study     | 2020 | ADA  | 14.1 ± 2.0               | 17 | CD           | CR based on PCDAI at week 16 MH at week 16 HR at week 16                                                                 | Ada TL was higher in those with MH (13 ± 6.5 vs. 6.2 ± 2.6 µg/ml; p = 0.02) Ada TL was higher in those with HR (17.9 ± 5.3 vs. 6.8 ± 2.5 µg/ml; p = 0.02) Optimal TL for MH at week 16, 8.76 µg/ml | 0%    | ELISA |

PUCAI, Pediatric Ulcerative Colitis Activity Index; IFX, infliximab; Ada, adalimumab; ADA, anti-drug antibody; TL, trough level; CR, clinical remission; NR, non-remission; Cre, clinical response; BR, biomarker remission; ER, endoscopic remission; fCal, fecal calprotectin; CFCR, corticosteroid-free clinical remission; MH, mucosal healing; HR, histologic remission.
CD patients on UST), POWER (efficacy and safety of UST reinduction therapy in patients with moderate and severe CD), and RESCUE (loss of response to UST treated with dose escalation), which might help in guiding formulation of desired TLs for different therapeutic endpoints (49).

Although, pediatric data are scarce, Dayan et al. (10) in a real-world pediatric cohort had reported 50% steroid-free remission (for biologic exposed) and 90% steroid-free remission (biologic naive) at 1 year. There was no significant difference in the trough levels between the patients on or off steroids at 52 weeks.

NOVEL TDM CONCEPTS

Personalized Medicine—Model-Informed Precision Dosing

Currently, most of the biologic agents are administered on the basis of fixed dosing or weight-based dosing algorithms. Utilizing a TDM-based approach to look at pharmacokinetic profiles is helpful but not perfect as several factors (weight, disease load, disease stage, drug clearance) may influence the eventual TL for an individual. Adaptive dosing dashboards based on population pharmacokinetic models as a backbone are being increasingly used. The individual patient’s characteristics and drug level measurements can be added on to this base model, to predict subsequent dosing requirement and frequency. While retrospective studies (50, 51) have validated the proof of concept, the PRECISION trial by Strik et al. (52, 53) was the first to employ this approach prospectively to IFX dosing. In this study, model-based dosing was superior to conventional dosing in maintaining remission. Subsequent studies performed by Dubinsky et al. (54, 55) have employed precision dosing models (Bayesian population-based pharmacokinetic model with weight, albumin, CRP, previous drug, and antibody levels added) to aim at prespecified individual TLs. Drug dosage and interval to next infusion was thus individualized based on this adaptive Bayesian modeling.

The Bayesian modeling approach seems to be a very promising development. Precision dosing has been used previously by clinical pharmacists for antibiotic dosing especially vancomycin and piperacillin–tazobactum (56, 57). However, the modeling requirements for a chronic disease like IBD are different. The efficacy of the model depends on the number of variables incorporated, and it will require constant updating and streamlining. Also, the target TL which the model aims to achieve is a moving target which varies with the disease phenotype and the disease phase. Although, it has the potential to eventually decrease drug costs by permitting de-escalation, in the short term, it will require more manpower, training, and coordination between health care teams and the pharmaceutical industry. Finally, more RCTs are needed especially during the induction phase to prove that model-informed precision dosing will be beneficial when parameters like TL and ADA are not available.

Point-of-Care Testing

Drug levels are currently processed in labs and are usually processed in batches. This leads to an increased turnover time and is particularly challenging in certain disease states
associated with unpredictable pharmacokinetics (acute UC, fistulizing CD) or during induction of therapy, especially when suspecting non-response.

Point-of-care assays can help in decreasing the turnaround time and help in providing an accurate, clinically relevant, real-time value to aid in clinical decision-making. Point-of-care assays for detecting IFX levels, adalimumab levels, and anti-IFX antibodies are commercially available. However, they are limited by their ability to use serum instead of blood (58–60). As with other point-of-care tests, there are concerns around quality control, reliability, cost, and external validation. Some of these issues were addressed by a pilot project published as an abstract by Bossuyt et al. (61), wherein, they used an ultra-proactive point-of-care TDM approach to demonstrate applicability and effectiveness. Curci et al. (62) in a pediatric study validated two point-of-care IFX assays and compared them with previously validated ELISA assays for measuring trough levels. The group observed good intraclass as well as interclass correlation.

**Therapeutic Drug Monitoring in VEOIBD**

The proportion of children aged <6 years with a new diagnosis of IBD is increasing (63). The disease in younger children is more extensive, usually colonic and requires optimized treatment regimens, including the use of biologic drugs (64). It has been shown that standard IFX regimens and trough levels may not be applicable in this age group (65, 66) and may require more frequent escalation of therapy (67). This may be in part related to the size of the antigenic sink at the start of treatment or to the increased clearance related to the low body weight. Studies have also shown how weight-based dosing systematically underdoses children with low body weight (68). A recent case series by Assa et al. (69) showed how an accelerated induction protocol (increased dosing and interval shortening) helped to recapture response in a group of children with infantile IBD after they had experienced initial non-response/secondary LOR with IFX.

However, the overall clinical management of VEOIBD using biologics may be more complex than adjusting for age or weight. A recent study by Jongsmna et al. (70) showed suboptimal TL for patients <10 vs. >10 years at the beginning of maintenance therapy. The former group also had a significantly higher antibody titer contributing to immunogenicity and, consequently, a lower TL. Multivariate analysis did not reveal a direct influence of age on TL. Proactive TDM in the younger age group did not seem to affect clinical remission rates at 52 weeks when compared with children >10 years.
Genomic Variants Influencing Trough Levels

The PANTS consortium tried to look at genomic variants which could influence antibody formation and, consequently, lead to lower TL and loss of response for IFX and ADA. The group performed a GWAS to identify genomic variants that were associated with immunogenicity. They concluded that the HLA-DQA1*05 allele significantly increased immunogenicity with a HR 1.9 (1.6–2.25) (71).

Tissue Drug Levels in Pediatric IBD

The ATLAS study demonstrated that anti-TNF concentration in tissue correlates with the degree of endoscopic inflammation, except in tissue with severe inflammation in which anti-TNF levels were lower (72). Tissue drug levels have not as yet been evaluated in pediatric IBD and may offer further insight into the individual’s target trough level to achieve mucosal healing as a therapeutic endpoint.

DISCUSSION

The treat-to-target strategies recommended by the STRIDE (73) IOIBD working group aim at composite endpoints of both clinical/patient-reported remission as well as endoscopic and/or radiological healing. TDM may be intuitively linked to this goal but cannot be included in this approach due to failure of the seminal RCT studies TAXIT and TAILORIX to meet their primary endpoint/s. The lack of well-powered, prospective RCTs means that there is a knowledge gap which needs to be addressed. Meta-analysis and systematic reviews on the role of TDM are limited by the heterogeneity in study design, timing, and use of TDM, combination of different disease phenotypes, and endpoints of the different trials. Thus, many of the recommendations that emerge regarding the use of TDM for treat-to-target are based on low-grade evidence. Encouragingly, the recent PAILOT study has been helpful in proving that proactive TDM in biologic naive children on adalimumab did better than reactive TDM in the control group with regard to corticosteroid-free remission.

Trough levels in clinical practice are intended for guidance. They can vary depending on the preselected endpoint (clinical remission vs. healing based on endoscopy and histology), disease severity, size of antigenic sink, and phase of treatment (induction vs. maintenance). Higher TLs may be aimed for in children with VEOIBD (61), those with perianal fistulae (74), severe UC (75), and during induction (20, 76). LOR scenarios are taxing for both the patient and the IBD physician. While drug levels are standardized ELISA tests that can be compared between different assays, the antidrug antibody tests are not standardized and various assays differ in cutoffs for low, intermediate, and high titer antibodies. Combining the lack of clarity on TLs and the varied recommendations on reactive and proactive TDM, this is an area of research that will require further clarification in the future. Proactive TDM is emerging as a new therapeutic strategy in pediatric patients; however, prospective interventional clinical trials looking at early induction and maintenance levels for novel biologic agents with endoscopic outcomes and/or composite surrogate outcomes are needed to advance our knowledge in the pediatric population.

Interest has been growing in personalizing treatment strategies by using predictive pharmacogenomics and machine learning to propose individualized treatment protocols. Exciting developments especially related to adaptive dosing dashboards utilizing Bayesian models herald the future of personalized medicine in IBD. If successful, they have the capacity to eliminate dosing tables and target TL values and possible inherent treatment bias of the physician. Coupled with point-of-care TDM and biomarker testing, this has the potential to revolutionize how pediatric IBD will be treated in the coming years.

AUTHOR CONTRIBUTIONS

AK and EC contributed to the design and implementation of this review article, to the analysis of the published studies, and to the writing of the manuscript. Both authors contributed to the article and approved the submitted version.

REFERENCES

1. Berg DR, Colombel JF, Ungaro R. The role of early biologic therapy in inflammatory bowel disease. *Inflamm Bowel Dis.* (2019) 25:1896–905. doi: 10.1093/ibd/izzo059
2. van Rheenen PF, Aloj M, Assa A, Bronsky J, Escher JC, Fagerberg UL, et al. The medical management of paediatric Crohn’s disease: an ECCO-ESPGHAN guideline update. *J Crohns Colitis.* (2020). doi: 10.1093/jcc/jjaa161. [Epub ahead of print]
3. Laharie D, Salzmann M, Boubekeur H, Richy F, Amouretti M, Quinton A, et al. Predictors of response to infliximab in laminal Crohn’s disease. *Gastroenterol Clin Biol.* (2005) 29:145–9. doi: 10.1016/S0399-8320(05)80718-3
4. Hyams J, Damaraju L, Blank M, Johanns J, Guzzo C, Winter HS, et al. Induction and maintenance therapy with infliximab for children with moderate to severe ulcerative colitis. *Clin Gastroenterol Hepatol.* (2012) 10:391–9.e1. doi: 10.1016/j.cgh.2011.11.026
5. Hyams JS, Griffiths A, Markowitz J, Baldassano RN, Faubion WA Jr, Colletti RB, et al. Safety and efficacy of adalimumab for moderate to severe Crohn’s disease in children. *Gastroenterology.* (2012) 143:365–74.e2. doi: 10.1053/j.gastro.2012.04.046
6. Aloj M, Bramuzzo M, Arrigo S, Romano C, D’Arcangelo G, Lacorte D, et al. Efficacy and safety of adalimumab in pediatric ulcerative colitis: a real-life experience from the SGENP-IBD registry. *J Pediatr Gastroenterol Nutr.* (2018) 66:920–5. doi: 10.1097/MPG.0000000000001883
7. Schneider AM, Weghuber D, Hetzer B, Entemann A, Muller T, Zimmermann G, et al. Vedolizumab use after failure of TNF-alpha antagonists in children and adolescents with inflammatory bowel disease. *BMC Gastroenterol.* (2018) 18:140. doi: 10.1186/s12876-018-0868-x
8. Fegan BG, Sandborn WJ, Gasink C, Jacobstein D, Lang Y, Friedman JR, et al. Ustekinumab as induction and maintenance therapy for Crohn's disease. *N Engl J Med.* (2016) 375:1946–60. doi: 10.1056/NEJMoa1602773
9. Sands BE, Sandborn WJ, Panaccione R, O'Brien CD, Zhang H, Johanns J, et al. Ustekinumab as induction and maintenance therapy for ulcerative colitis. *N Engl J Med.* (2019) 381:1201–14. doi: 10.1056/NEJMoa1900750
10. Dayan JR, Dolinger M, Benkov K, Dunkin D, Jossen J, Lai J, et al. Real world experience with ustekinumab in children and young adults at a tertiary care
pediatric inflammatory bowel disease center. *J Pediatr Gastroenterol Nutr.* (2019) 69:61–7. doi: 10.1097/MPG.0000000000002362

11. Adedokun OJ, Sandborn WJ, Feagan BG, Rutgeerts P, Xu Z, Marano CW, et al. Association between serum concentration of infliximab and efficacy in adult patients with ulcerative colitis. *Gastroenterology.* (2014) 147:1296–307.e5. doi: 10.1053/j.gastro.2014.08.035

12. Adedokun OJ, Xu Z, Marano CW, Strauss R, Zhang H, Johanns J, et al. Pharmacokinetics and exposure-response relationship of golimumab in patients with moderately-to-severely active ulcerative colitis: results from phase 2/3 pursuit induction and maintenance studies. *J Crohns Colitis.* (2017) 11:35–46. doi: 10.1016/j.jcjj.2017.02.016

13. Vande Casteele N, Feagan BG, Veermie S, Yassine M, Coarse J, Kosutic G, et al. Improved long-term outcomes of patients with inflammatory bowel disease on maintenance treatment. *J Pediatr Gastroenterol Nutr.* (2018) 67:297–305. doi: 10.1097/MPG.0000000000002362

14. Kennedy NA, Heap GA, Green HD, Hamilton B, Bewshea C, Walker GI, et al. Predictors of anti-TNF treatment failure in anti-TNF-naive patients with active luminal Crohn’s disease: a prospective, multicentre, cohort study. *Lancet Gastroenterol Hepatol.* (2019) 4:343–51. doi: 10.1016/S2468-1253(19)30012-3

15. Ungar B, Engel T, Tabelevitch D, Lahat A, Lang A, Avidan B, et al. Prospective observational evaluation of time-dependency of adalimumab immunogenicity and drug concentrations: the POETIC study. *Am J Gastroenterol.* (2018) 113:890–8. doi: 10.1038/s41395-018-0073-0

16. Choi SY, Kang B, Lee JH, Choe VH. Clinical use of measuring trough levels and antibodies against infliximab in patients with pediatric Crohn’s disease. *J Gastroenterol.* (2017) 52:55–61. doi: 10.5009/gnl16041

17. Merras-Salmio L, Kolho KL. Clinical use of infliximab trough levels and antibodies to infliximab in pediatric patients with inflammatory bowel disease. *J Pediatr Gastroenterol Nutr.* (2017) 64:272–8. doi: 10.1097/MPG.0000000000001258

18. Rolandsdotter H, Marits P, Sundin U, Wikstrom AC, Fagerberg UL, Finkel Y, et al. Serum-Infliximab trough levels in 45 children with inflammatory bowel disease on maintenance treatment. *Int J Mol Sci.* (2017) 18:575. doi: 10.3390/ijms18030575

19. Adedokun OJ, Xu Z, Padgett L, Blank M, Johanns J, Grifiths A, et al. Pharmacokinetics of infliximab in children with moderate-to-severe ulcerative colitis: results from a randomized, multicenter, open-label, phase 3 study. *Inflamm Bowel Dis.* (2013) 19:2753–62. doi: 10.1097/MIB.0b013e3182a43548

20. Singh N, Rosenthal CJ, Melmed GY, Mirocha J, Farrior S, Callejas S, et al. Early infliximab trough levels are associated with persistent remission in pediatric patients with inflammatory bowel disease. *Inflamm Bowll Dis.* (2014) 20:1708–13. doi: 10.1097/MIB.00000000000000137

21. Papamichael K, Vande Casteele N, Farrante M, Gils A, Cheifetz AS. Therapeutic drug monitoring during induction of anti-tumor necrosis factor therapy in inflammatory bowel disease: defining a therapeutic drug window. *Inflamm Bowll Dis.* (2017) 23:1510–5. doi: 10.1007/s10068-017-01231-0

22. Lega S, Phan BL, Rosenthal CJ, Gordon J, Haddad N, Pittman N, et al. Proactively optimized infliximab monotherapy is as effective as combination therapy in IBD. *Inflamm Bowll Dis.* (2019) 25:134–41. doi: 10.1093/ibd/izy203

23. Colombel JF, Adedokun OJ, Gasink C, Gao LL, Cornillie FJ, D’Haens GR, et al. Combination therapy with infliximab and azathioprine improves infliximab pharmacokinetic features and efficacy: a post hoc analysis. *Clin Gastroenterol Hepatol.* (2019) 17:1525–32.e1. doi: 10.1016/j.cgh.2018.09.033

24. Papamichael K, Chachu KA, Vavrajescu RK, Vaughn BP, Ni J, Osterman MT, et al. Improved long-term outcomes of patients with inflammatory bowel disease receiving proactive compared with reactive monitoring of serum concentrations of infliximab. *Clin Gastroenterol Hepatol.* (2017) 15:1580–8.e3. doi: 10.1016/j.cgh.2017.03.031

25. Vande Casteele N, Ferrante M, Van Assche G, Ballet V, Compernolle G, Van Steen K, et al. Trough concentrations of infliximab guide dosing for patients with inflammatory bowel disease. *Gastroenterology.* (2015) 148:1320–9.e3. doi: 10.1053/j.gastro.2015.02.031

26. D’Haens G, Vermeire S, Lambrecht G, Baert F, Bossuyt P, Pariente B, et al. Increasing infliximab dose based on symptoms, biomarkers, and serum drug concentrations does not increase clinical, endoscopic, and corticosteroid-free remission in patients with active luminal Crohn’s disease. *Gastroenterology.* (2018) 154:1343–51.e1. doi: 10.1053/j.gastro.2018.01.004

27. Assa A, Matar M, Turner D, Broido E, Weiss B, Ledger O, et al. Proactive monitoring of adalimumab trough concentration associated with increased clinical remission in children with Crohn’s disease compared with reactive monitoring. *Gastroenterology.* (2019) 157:985–96.e2. doi: 10.1053/j.gastro.2019.06.003

28. Lyles JL, Mullgund A, Bauman LE, Su W, Fei L, Chona DL, et al. Effect of a practice-wide anti-TNF proactive therapeutic drug monitoring program on outcomes in pediatric patients with inflammatory bowel disease. *Inflamm Bowll Dis.* (2020) 27:482–92. doi: 10.1093/ibd/izia102

29. Feagan BG, Rutgeerts P, Sands BE, Hanauer S, Colombel JF, Sandborn WJ, et al. Vedolizumab as induction and maintenance therapy for ulcerative colitis. *N Engl J Med.* (2013) 369:699–710. doi: 10.1056/NEJMoa1215734

30. Sandborn WJ, Feagan BG, Rutgeerts P, Hanauer S, Colombel JF; Sandborn WJ, et al. Vedolizumab as induction and maintenance therapy for ulcerative colitis or Crohn’s disease. *N Engl J Med.* (2013) 369:711–21. doi: 10.1056/NEJMoa1215739

31. Rosario M, French JL, Dirks NL, Sankoh S, Parihk A, Yang H, et al. Exposure-reliability relationships for vedolizumab induction therapy in patients with ulcerative colitis or Crohn’s disease. *J Crohns Colitis.* (2017) 11:921–9. doi: 10.1093/jcjj/ jjx021

32. Dreessen E, Verstockt B, Bhan S, de Bruyn M, Compernolle G, Tops S, et al. Evidence to support monitoring of vedolizumab trough concentrations in patients with inflammatory bowel disease. *Cln Gastroenterol Hepatol.* (2018) 16:1937–46.e8. doi: 10.1016/j.cgh.2018.04.040

33. Ungaro RC, Yarur A, Jossen J, Phan BL, Cheifetz E, Sehgal P, et al. Higher trough vedolizumab concentrations during maintenance therapy are associated with corticosteroid-free remission in inflammatory bowel disease. *J Crohns Colitis.* (2019) 13:963–9. doi: 10.1093/jcjj/ jjx041

34. Yacoub W, Williet N, Pouillon L, Di-Bernardo T, De Carvalho Bittencourt M, Nancey S, et al. Early vedolizumab trough levels predict mucosal healing in inflammatory bowel disease: a multicentre prospective observational study. *Aliment Pharmacol Ther.* (2018) 47:906–12. doi: 10.1111/apt.14548

35. Peyrin-Biroulet L, Danese S, Argollo M, Pouillon L, Peppas S, Gonzalez-Lorenzo M, et al. Loss of response to vedolizumab and ability of dose intensification to restore response in patients with Crohn’s disease or ulcerative colitis: a systematic review and meta-analysis. *Clin Gastroenterol Hepatol.* (2019) 17:838–46.e2. doi: 10.1016/j.cgh.2018.06.026

36. Van den Berge N, Verstockt B, Gils A, Ferrante M, Vermeire S, Thomas D. 238 vedolizumab concentrations in colonic mucosal tissue of ulcerative colitis patients inversely correlate with the severity of inflammation. *Gastroenterology.* (2020) 158:S47. doi: 10.1056/S0016-5085(20)30799-X
response in pediatric Crohn’s disease. *Inflamm Bowel Dis.* (2016) 22:1370–7. doi: 10.1097/MIB.0000000000000769

77. Hoekman DR, Brandse JF, de Meij TG, Hummel TZ, Lowenberg M, Benninga MA, et al. The association of infliximab trough levels with disease activity in pediatric inflammatory bowel disease. *Scand J Gastroenterol.* (2015) 50:1110–7. doi: 10.3109/00365521.2015.1027264

78. Zitomersky NL, Atkinson BJ, Fournier K, Mitchell PD, Stern JB, Butler MC, et al. Antibodies to infliximab are associated with lower infliximab levels and increased likelihood of surgery in pediatric IBD. *Inflamm Bowel Dis.* (2015) 21:307–14. doi: 10.1097/MIB.0000000000000284

79. Sharma S, Eckert D, Hyams JS, Mensing S, Thakkar RB, Robinson AM, et al. Pharmacokinetics and exposure-efficacy relationship of adalimumab in pediatric patients with moderate to severe Crohn’s disease: results from a randomized, multicenter, phase-3 study. *Inflamm Bowel Dis.* (2015) 21:783–92. doi: 10.1097/MIB.0000000000000327

80. Minar P, Saeed SA, Afreen M, Kim MO, Denson LA. Practical use of infliximab concentration monitoring in pediatric Crohn’s disease. *J Pediatr Gastroenterol Nutr.* (2016) 62:715–22. doi: 10.1097/MPG.0000000000001029

81. Dubinsky MC, Rosh J, Faubion WA Jr, Kierkus J, Ruemmele F, Hyams JS, et al. Efficacy and safety of escalation of adalimumab therapy to weekly dosing in pediatric patients with Crohn’s disease. *Inflamm Bowel Dis.* (2016) 22:886–93. doi: 10.1097/MIB.0000000000000715

82. Chi LY, Zitomersky NL, Liu E, Tollefson S, Bender-Stern J, Naik S, et al. The impact of combination therapy on infliximab levels and antibodies in children and young adults with inflammatory bowel disease. *Inflamm Bowel Dis.* (2016) 22:1344–51. doi: 10.1093/ibd/izy010

83. van Hoeve K, Hoffmann I, Vermeire S. Therapeutic drug monitoring of anti-TNF therapy in children with inflammatory bowel disease. *Expert Opin Drug Saf.* (2018) 17:185–96. doi: 10.1080/14740338.2018.1413090

84. Ohem J, Hradsky O, Zarubova K, Copova I, Bukvovska P, Prusa R, et al. Evaluation of infliximab therapy in children with Crohn’s disease using trough levels predictors. *Dig Dis.* (2018) 36:40–8. doi: 10.1159/000477962

85. van Hoeve K, Dreesen E, Hoffman I, Van Assche G, Ferrante M, Gils A, et al. Adequate infliximab exposure during induction predicts remission in paediatric patients with inflammatory bowel disease. *J Pediatr Gastroenterol Nutr.* (2019) 68:847–53. doi: 10.1097/MPG.000000000002265

86. Choi SY, Kang B, Choe YH. Serum infliximab cutoff trough level values for maintaining hematological remission in pediatric inflammatory bowel disease. *Gut Liver.* (2019) 13:541–8. doi: 10.5009/gnl18129

87. Naviglio S, Lacorte D, Lucafo M, Cifì A, Favretto D, Cuzzoni E, et al. Causes of treatment failure in children with inflammatory bowel disease treated with infliximab: a pharmacokinetic study. *J Pediatr Gastroenterol Nutr.* (2019) 68:37–44. doi: 10.1097/MPG.000000000002112

88. Clarkson K, Tsai YT, Jackson K, Rosen MJ, Denson LA, Minar P. Development of infliximab target concentrations during induction in pediatric Crohn’s disease patients. *J Pediatr Gastroenterol Nutr.* (2019) 69:68–74. doi: 10.1097/MGP.0000000000003234

89. Gofin Y, Matar M, Shamir R, Assa A. Therapeutic drug monitoring increases drug retention of anti-tumor necrosis factor alpha agents in pediatric patients with Crohn’s disease. *Inflamm Bowel Dis.* (2020) 26:1276–82. doi: 10.1093/ibd/izz257

90. Choi SY, Choi YO, Choe YH, Kang B. Potential utility of therapeutic drug monitoring of adalimumab in predicting short-term mucosal healing and histologic remission in pediatric Crohn’s disease patients. *J Korean Med Sci.* (2020) 35:e114. doi: 10.3346/jkms.2020.35.e114

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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