Anti-TNFs in Pediatric Inflammatory Bowel Disease

Subjects: Gastroenterology & Hepatology

Contributor: Luis López-Fernández

Inflammatory bowel disease (IBD) is a chronic immune-mediated condition that affects the gastrointestinal tract. The incidence of the disease in children is increasing. However, most clinical trials in this disease have been carried out in adults, and the results have been extrapolated with minimal changes to determine treatment in children. Pediatric IBD (pIBD) is characterized by various factors, including a more severe phenotype than adult diseas. Since IBD is a chronic autoimmune disease, patients diagnosed during childhood live longer with the illness and consequently need treatment for longer. Biological drugs and, more specifically, anti-TNF drugs such as infliximab and adalimumab have proven efficient for treatment of IBD in adults and in children. However, the use of biological drugs differs between children and adults with IBD. For instance, the time between diagnosis and initiation of biological treatment is shorter in children than in adults. In addition, not all the biological drugs approved for adult IBD are approved for children.

biomarkers inflammatory bowel disease

1. Treatment of Pediatric IBD

The goal of the treatment of pediatric IBD is to induce and maintain clinical remission, achieve normal growth, provide optimal quality of life, promote psychological health, and reduce toxicity as much as possible. Additionally, the gold standard of optimal therapy is endoscopic mucosal healing, which makes it possible to modify the natural history of the disease and prevent complications of progressive bowel destruction. In observational adult studies, younger age at onset is repeatedly considered high-risk for poor prognosis, thus underlining the need for a highly effective treatment approach in children [1].

Treatment is selected based on the location, type of disease, severity of symptoms, and the goal of therapy (induction therapy or maintenance of remission). The pharmacological arsenal for pIBD treatment includes anti-inflammatory drugs such as aminosalicylates, corticosteroids, and immunomodulatory drugs (for example, thiopurines and methotrexate), which are used as maintenance therapy, and biologic drugs, which are used for induction and maintenance of remission. The doses and treatment guidelines for biologic drugs are very similar to those of adults, even though the metabolism and immune system of children may differ from those of adults [2][3][4].

The introduction of monoclonal antibodies against tumor necrosis factor (anti-TNF) revolutionized the treatment of IBD. Infliximab and adalimumab are the two anti-TNF agents approved by the United States Food and Drug Administration (FDA) and the European Medicines Agency for use in children, although adalimumab is not

approved in perianal pCD [5]. Infliximab is administered as an intravenous infusion and adalimumab is administered subcutaneously for induction and maintenance therapy. Studies have shown that early use of anti-TNF drugs in children with CD is associated with increased rates of remission and mucosal healing, as well as with modest improvement in linear growth [6][5][7][8].

Advances in the understanding of the etiology and pathogenesis of IBD in recent years have led to the development of new drugs based on inhibition of immune cells [9] or inhibition of cytokine signaling [10][11][12]. New categories of biologic drugs that have been shown to be effective and safe in adults are the new horizon for IBD treatment in children [5]. Some biological drugs that are currently approved in adults, such as vedolizumab or ustekinumab, are used off-label in children when treatment with infliximab or adalimumab fails [13].

Despite advances in medical treatment, surgery may still be warranted in refractory pIBD [1]. In pCD, the median time to first surgery is longer than in patients who debut in adulthood, although the need for surgery in pUC is earlier than in adults. Consequently, the risk of surgical resection before the age of 30 years is higher in children than in adults [14].

2. Clinical and Biochemical Biomarkers of Response to Anti-TNFs in pIBD

Anti-TNFα drugs have proven to be effective and safe for pIBD [15], although approximately one third of patients who initially respond to anti-TNF therapy lose that response over time [16][17]; and while various clinical and biochemical characteristics predict response to anti-TNF therapy, these are mainly based on studies in adult populations [18]. The characteristics include disease-related factors (such as disease phenotype, behavior, location, and severity), biochemical parameters (such as C-reactive protein, fecal calprotectin, and albumin levels) and drug-related characteristics (such as pharmacokinetic, pharmacodynamic, and immunogenic factors) [19][20][21][22][23]. The ECCO-ESPGHAN guideline update on management of CD in children recommends monitoring of fecal calprotectin or small bowel imaging as the best markers of treatment response [24].

The PANTS study is one of the few studies to evaluate the response to anti-TNFs in a population including children and adolescents over 6 years of age, although to date, no subanalysis of pediatric patients has been performed. Obesity, smoking, low albumin concentrations, higher baseline markers of disease activity, and development of immunogenicity were associated with low drug concentrations during induction, resulting in non-remission at week 54 after initiation of anti-TNF treatment [25].

The level of anti-TNF agent immediately before the following administration, known as the trough level, is increasingly used as a non-invasive biomarker. It is well known that serum levels of infliximab and adalimumab correlate with treatment response in patients with IBD [26][27] and pIBD [28][29][30][31]. Furthermore, these levels are associated with histological and endoscopic disease remission in both populations [32][33][34][35].

The therapeutic range of these drugs varies considerably, especially in pIBD. Most guidelines indicate that to achieve clinical remission of IBD, infliximab and adalimumab concentrations in the range of 3–7 and 5–12 µg/mL, respectively, are considered adequate [19][36][37][38][39]. The therapeutic ranges of both anti-TNF drugs may vary depending on the disease phenotype or on the treatment goals [25][35][40]. Further studies are needed to define optimal levels.

Anti-TNF drugs are antibodies against TNF that can induce the immune response and generate anti-drug antibodies (ADAs). ADAs bind to the anti-TNF drug, thus reducing free functional drug levels, neutralizing the therapeutic effect, and resulting in a loss of response [41]. ADA levels inversely correlate with drug levels and treatment response in adults [21][42], as well as in children [43][44][45][46].

For this reason, therapeutic drug monitoring (TDM) has been proposed as a means of optimizing biological therapies in both adults [47][48][49][50] and children [29][51][52][53] with IBD. This approach appears to be more advantageous in pediatric patients, since fluctuations in pharmacokinetic variables tend to be more pronounced in children than in adults, possibly owing to physiological differences, such as volume of distribution, and immaturity of enzyme systems and of clearance mechanisms [29]. In fact, Jongsma MME et al. reported that, over one year of treatment with infliximab, patients under 10 years of age require a more intensive treatment regimen than older patients and that these patients are more likely to develop antibodies to infliximab [54].

Data on the optimal timing of TDM are conflicting, since some professionals use reactive monitoring, i.e., measuring drug levels in the case of loss of response, whereas others use proactive monitoring, i.e., measuring them at preset time points [55]. Proactive monitoring has been shown to achieve clinical improvement and endoscopic remission in IBD patients treated with anti-TNFs [56][57][58], as well as in children [59][60]. However, this issue is quite controversial and, in fact, the recommendations form the ECCO for adults are indecisive [24].

The current recommendation in pIBD is to measure drug levels and ADA titers after the induction period, even though studies in this population are insufficient and data are conflicting [5][31][61]. The use of TDM in pIBD is increasing in clinical practice, and efficacy similar to that of adults has been demonstrated in children, with loss of response to anti-TNF therapy [28].

Considering the high cost and potentially severe side effects of anti-TNF biologics, the identification of underlying factors involved in the individual responses is sorely needed. The usefulness of TDM is therefore limited, as monitoring helps physicians to modify the existing treatment by adjusting the dose of the biological drug and/or the frequency of administration. However, to choose the best biological drug and the best starting dose, other types of biomarkers are needed. Moreover, these new biomarkers should be inexpensive and easy to implement in clinical routine, which is not always simple.

3. Genomic Biomarkers of Response to Anti-TNFs in pIBD

Pharmacogenomics may play an important role in predicting response, mainly before initiation of anti-TNF treatment in pIBD. Genetic variants and gene expression could be useful markers for predicting response to biological drugs in children with IBD. Since pediatric patients will have to live longer with the disease and will therefore need treatment for longer, identification of pharmacogenomic biomarkers with the aim of personalizing treatment is especially important in this population.

4. Other Biomarkers of Response to Anti-TNFs in pIBD

Regulatory T cells (Tregs) play an essential role in the pathogenesis of IBD, in which Treg counts are decreased [62]. Anti-TNF therapy is known to increase the number and function of Tregs in IBD [63]. The study of these cells may help to predict response to anti-TNF agents, because upregulation is not as efficient in non-responders as in responders [64][65].

Few studies have assessed Tregs in children, although preliminary results suggest an effect similar to that observed in adults. Ricardelli et al. showed that FOXP3+ T-cell counts were lower in the mucosal samples of children with active CD than in healthy controls. However, this difference disappeared after the initiation of infliximab [66].

Furthermore, intestinal microbiota may also modulate the immune system and play an acute role in IBD [67]. It has been suggested that defects in Treg function might induce changes in the gut microbiome, leading to loss of tolerance to commensal bacteria [68]. In children, Conte et al. observed higher numbers of mucosa-associated aerobic and facultative anaerobic bacteria in IBD patients than in healthy controls [69]. The authors also observed a decrease in counts of *Bacteroides vulgatus*. A subsequent study differentiating between CD and UC in children showed a decrease in counts of *Faecalibacterium prausnitzii* and an increase in those of *Escherichia coli* in children with CD [70]. However, no differences were found in the composition of microbiota in children with UC, in contrast with findings in adults [70].

Concerning anti-TNF therapy and the gut microbiome in children with IBD, a higher number of multiple short-chain, fatty-acid-producing bacteria has been associated with a sustained response to infliximab in pediatric CD [71]. In addition, infliximab increased the diversity of the gut microbiome, and its composition resembled that of healthy children. These results were recently confirmed in a larger cohort of pediatric CD patients, where bile salt hydrolase-producing bacteria are also enriched after treatment with infliximab [72].

The aforementioned data suggest that Treg count and functionality, as well as the gut microbiome, could act as relevant biomarkers of response to anti-TNFs. However, this observation is restricted to infliximab. More studies are necessary to validate these biomarkers and to find new ones associated with the different biological drugs used in pIBD.

The list of factors thought to affect the efficacy of anti-TNFs is growing. It was recently reported that vitamin D deficiency was associated with a higher risk of early discontinuation of anti-TNF therapy (14.5% vs. 0%) in children

with IBD [73].

References

1. Conrad, M.A.; Rosh, J.R. Pediatric Inflammatory Bowel Disease. Pediatr. Clin. N. Am. 2017, 64, 577–591.
2. Ygberg, S.; Nilsson, A. The developing immune system-from foetus to toddler. Acta Paediatr. 2012, 101, 120–127.
3. Filimoniuk, A.; Daniluk, U.; Samczuk, P.; Wasilewska, N.; Jakimiec, P.; Kucharska, M.; Lebensztejn, D.M.; Ciborowski, M. Metabolomic profiling in children with inflammatory bowel disease. Adv. Med. Sci. 2020, 65, 65–70.
4. Carr, E.J.; Dooley, J.; Garcia-Perez, J.E.; Lagou, V.; Lee, J.C.; Wouters, C.; Meyts, I.; Goris, A.; Boeckxstaens, G.; Linterman, M.A.; et al. The cellular composition of the human immune system is shaped by age and cohabitation. Nat. Immunol. 2016, 17, 461–468.
5. Aardoom, M.A.; Veereman, G.; de Ridder, L. A Review on the Use of Anti-TNF in Children and Adolescents with Inflammatory Bowel Disease. Int. J. Mol. Sci. 2019, 20, 2529.
6. Grover, Z. Predicting and preventing complications in children with inflammatory bowel disease. Transl. Pediatr. 2019, 8, 70–76.
7. Ruemmele, F.; Veres, G.; Kolho, K.; Griffiths, A.; Levine, A.; Escher, J.; Dias, J.A.; Barabino, A.; Braegger, C.; Bronsky, J.; et al. Consensus guidelines of ECCO/ESPGHAN on the medical management of pediatric Crohn's disease. J. Crohn's Colitis 2014, 8, 1179–1207.
8. Walters, T.D.; Kim, M.-O.; Denson, L.A.; Griffiths, A.M.; Dubinsky, M.; Markowitz, J.; Baldassano, R.; Crandall, W.; Rosh, J.; Pfefferkorn, M.; et al. Increased effectiveness of early therapy with anti-tumor necrosis factor-α vs an immunomodulator in children with Crohn's disease. Gastroenterology 2014, 146, 383–391.
9. Feagan, B.G.; Rutgeerts, P.; Sands, B.E.; Hanauer, S.; Colombel, J.-F.; Sandborn, W.J.; Van Assche, G.; Axler, J.; Kim, H.-J.; Danese, S.; et al. Vedolizumab as induction and maintenance therapy for ulcerative colitis. N. Engl. J. Med. 2013, 369, 699–710.
10. Feagan, B.G.; Sandborn, W.J.; Gasink, C.; Jacobstein, D.; Lang, Y.; Friedman, J.R.; Blank, M.A.; Johanns, J.; Gao, L.-L.; Miao, Y.; et al. Ustekinumab as Induction and Maintenance Therapy for Crohn's Disease. N. Engl. J. Med. 2016, 375, 1946–1960.
11. Nakase, H. Optimizing the Use of Current Treatments and Emerging Therapeutic Approaches to Achieve Therapeutic Success in Patients with Inflammatory Bowel Disease. Gut Liver 2020, 14, 7–19.

12. Sulz, M.C.; Burri, E.; Michetti, P.; Rogler, G.; Peyrin-Biroulet, L.; Seibold, F. Treatment Algorithms for Crohn's Disease. Digestion 2020, 101 (Suppl. S1), 43–57.
13. Shim, H.H.; Chan, P.W.; Chuah, S.W.; Schwender, B.J.; Kong, S.C.; Ling, K.L. A review of vedolizumab and ustekinumab for the treatment of inflammatory bowel diseases. JGH Open Open Access J. Gastroenterol. Hepatol. 2018, 2, 223–234.
14. Von Allmen, D. Pediatric Crohn's Disease. Clin. Colon Rectal Surg. 2018, 31, 80–88.
15. Corica, D.; Romano, C. Biological Therapy in Pediatric Inflammatory Bowel Disease. J. Clin. Gastroenterol. 2017, 51, 100–110.
16. Topf-Olivestone, C.; Turner, D. How effective is the use of long-term anti-TNF for paediatric IBD? Clues from real-life surveillance cohorts. Arch. Dis. Child. 2015, 100, 391–392.
17. Cameron, F.L.; Wilson, M.L.; Basheer, N.; Jamison, A.; McGrogan, P.; Bisset, W.M.; Gillett, P.M.; Russell, R.K.; Wilson, D.C. Anti-TNF therapy for paediatric IBD: The Scottish national experience. Arch. Dis. Child. 2015, 100, 399–405.
18. Gisbert, J.P.; Chaparro, M. Predictors of Primary Response to Biologic Treatment in Patients with Inflammatory Bowel Disease: From Basic Science to Clinical Practice. J. Crohn's Colitis 2020, 14, 694–709.
19. Ungar, B.; Levy, I.; Yavne, Y.; Yavzori, M.; Picard, O.; Fudim, E.; Loebstein, R.; Chowers, Y.; Eliakim, R.; Kopylov, U.; et al. Optimizing Anti-TNF-α Therapy: Serum Levels of Infliximab and Adalimumab Are Associated with Mucosal Healing in Patients with Inflammatory Bowel Diseases. Clin. Gastroenterol. Hepatol. 2016, 14, 550–557.e2.
20. Ding, N.S.; Hart, A.; De Cruz, P. Systematic review: Predicting and optimising response to anti-TNF therapy in Crohn's disease-algorithm for practical management. Aliment. Pharmacol. Ther. 2016, 43, 30–51.
21. Naviglio, S.; Giuffrida, P.; Stocco, G.; Lenti, M.V.; Ventura, A.; Corazza, G.R.; Di Sabatino, A. How to predict response to anti-tumour necrosis factor agents in inflammatory bowel disease. Expert Rev. Gastroenterol. Hepatol. 2018, 12, 797–810.
22. Laserna-Mendieta, E.J.; Lucendo, A.J. Faecal calprotectin in inflammatory bowel diseases: A review focused on meta-analyses and routine usage limitations. Clin. Chem. Lab. Med. 2019, 57, 1295–1307.
23. Scaldaferri, F.; D'Ambrosio, D.; Holleran, G.; Poscia, A.; Petito, V.; Lopetuso, L.; Graziani, C.; Laterza, L.; Pistone, M.T.; Pecere, S.; et al. Body mass index influences infliximab post-infusion levels and correlates with prospective loss of response to the drug in a cohort of inflammatory bowel disease patients under maintenance therapy with Infliximab. PLoS ONE 2017, 12, e0186575.

24. Van Rheenen, P.F.; Aloi, M.; Assa, A.; Bronsky, J.; Escher, J.C.; Fagerberg, U.L.; Gasparetto, M.; Gerasimidis, K.; Griffiths, A.; Henderson, P.; et al. The Medical Management of Paediatric Crohn's Disease: An ECCO-ESPGHAN Guideline Update. J. Crohn's Colitis 2021, 15, 171–194.
25. Kennedy, N.A.; Heap, G.A.; Green, H.D.; Hamilton, B.; Bewshea, C.; Walker, G.J.; Thomas, A.; Nice, R.; Perry, M.H.; Bouri, S.; 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, 341–353.
26. Cornillie, F.; Hanauer, S.B.; Diamond, R.H.; Wang, J.; Tang, K.L.; Xu, Z.; Rutgeerts, P.; Vermeire, S. Postinduction serum infliximab trough level and decrease of C-reactive protein level are associated with durable sustained response to infliximab: A retrospective analysis of the ACCENT I trial. Gut 2014, 63, 1721–1727.
27. Hendy, P.; Hart, A.; Irving, P. Anti-TNF drug and antidrug antibody level monitoring in IBD: A practical guide. Frontline Gastroenterol. 2016, 7, 122–128.
28. Van Hoeve, K.; Dreesen, E.; Hoffman, I.; Van Assche, G.; Ferrante, M.; Gils, A.; Vermeire, S. Higher Infliximab Trough Levels Are Associated with Better Outcome in Paediatric Patients with Inflammatory Bowel Disease. J. Crohn's Colitis 2018, 12, 1316–1325.
29. Van Hoeve, K.; Hoffman, I.; Vermeire, S. Therapeutic drug monitoring of anti-TNF therapy in children with inflammatory bowel disease. Expert Opin. Drug Saf. 2018, 17, 185–196.
30. Merras-Salmio, L.; Kolho, K.-L. Clinical Use of Infliximab Trough Levels and Antibodies to Infliximab in Pediatric Patients with Inflammatory Bowel Disease. J. Pediatr. Gastroenterol. Nutr. 2017, 64, 272–278.
31. Lucafò, M.; Curci, D.; Bramuzzo, M.; Alvisi, P.; Martelossi, S.; Silvestri, T.; Guastalla, V.; Labriola, F.; Stocco, G.; Decorti, G. Serum Adalimumab Levels After Induction Are Associated with Long-Term Remission in Children with Inflammatory Bowel Disease. Front. Pediatr. 2021, 9, 646671.
32. Chaparro, M.; Barreiro-de Acosta, M.; Echarri, A.; Almendros, R.; Barrio, J.; Llao, J.; Gomollón, F.; Vera, M.; Cabriada, J.L.; Guardiola, J.; et al. Correlation Between Anti-TNF Serum Levels and Endoscopic Inflammation in Inflammatory Bowel Disease Patients. Dig. Dis. Sci. 2019, 64, 846–854.
33. Nobile, S.; Gionchetti, P.; Rizzello, F.; Calabrese, C.; Campieri, M. Mucosal healing in pediatric Crohn's disease after anti-TNF therapy: A long-term experience at a single center. Eur. J. Gastroenterol. Hepatol. 2014, 26, 458–465.
34. Nuti, F.; Civitelli, F.; Bloise, S.; Oliva, S.; Aloi, M.; Latorre, G.; Viola, F.; Cucchiara, S. Prospective Evaluation of the Achievement of Mucosal Healing with Anti-TNF-α Therapy in a Paediatric Crohn's Disease Cohort. J. Crohn's Colitis 2016, 10, 5–12.

35. Yarur, A.J.; Jain, A.; Sussman, D.A.; Barkin, J.S.; Quintero, M.A.; Princen, F.; Kirkland, R.; Deshpande, A.R.; Singh, S.; Abreu, M.T. The association of tissue anti-TNF drug levels with serological and endoscopic disease activity in inflammatory bowel disease: The ATLAS study. Gut 2016, 65, 249–255.

36. Vande Casteele, N.; Ferrante, M.; Van Assche, G.; Ballet, V.; Compernolle, G.; Van Steen, K.; Simoens, S.; Rutgeerts, P.; Gils, A.; Vermeire, S. Trough Concentrations of Infliximab Guide Dosing for Patients with Inflammatory Bowel Disease. Gastroenterology 2015, 148, 1320–1329.e3.

37. Mitrev, N.; Vande Casteele, N.; Seow, C.H.; Andrews, J.M.; Connor, S.J.; Moore, G.T.; Barclay, M.; Begun, J.; Bryant, R.; Chan, W.; et al. Review article: Consensus statements on therapeutic drug monitoring of anti-tumour necrosis factor therapy in inflammatory bowel diseases. Aliment. Pharmacol. Ther. 2017, 46, 1037–1053.

38. Beltrán, B.; Iborra, M.; Sáez-González, E.; Marqués-Miñana, M.R.; Moret, I.; Cerrillo, E.; Tortosa, L.; Bastida, G.; Hinojosa, J.; Poveda-Andrés, J.L.; et al. Fecal Calprotectin Pretreatment and Induction Infliximab Levels for Prediction of Primary Nonresponse to Infliximab Therapy in Crohn's Disease. Dig. Dis. 2019, 37, 108–115.

39. Yanai, H.; Lichtenstein, L.; Assa, A.; Mazor, Y.; Weiss, B.; Levine, A.; Ron, Y.; Kopylov, U.; Bujanover, Y.; Rosenbach, Y.; et al. Levels of drug and antidrug antibodies are associated with outcome of interventions after loss of response to infliximab or adalimumab. Clin. Gastroenterol. Hepatol. Off. Clin. Pract. J. Am. Gastroenterol. Assoc. 2015, 13, 522–530.e2.

40. Courbette, O.; Aupiais, C.; Viala, J.; Hugot, J.-P.; Roblin, X.; Candon, S.; Louveau, B.; Chatenoud, L.; Martinez-Vinson, C. Trough Levels of Infliximab at W6 Are Predictive of Remission at W14 in Pediatric Crohn Disease. J. Pediatr. Gastroenterol. Nutr. 2020, 70, 310–317.

41. Nanda, K.S.; Cheifetz, A.S.; Moss, A.C. Impact of antibodies to infliximab on clinical outcomes and serum infliximab levels in patients with inflammatory bowel disease (IBD): A meta-analysis. Am. J. Gastroenterol. 2013, 108, 40–47.

42. Pallagi-Kunstár, É.; Farkas, K.; Szepes, Z.; Nagy, F.; Szűcs, M.; Kui, R.; Gyulai, R.; Bálint, A.; Wittmann, T.; Molnár, T. Utility of serum TNF-α, infliximab trough level, and antibody titers in inflammatory bowel disease. World J. Gastroenterol. 2014, 20, 5031–5035.

43. Cohen, R.Z.; Schoen, B.T.; Kugathasan, S.; Sauer, C.G. Management of Anti-drug Antibodies to Biologic Medications in Children with Inflammatory Bowel Disease. J. Pediatr. Gastroenterol. Nutr. 2019, 69, 551–556.

44. Naviglio, S.; Lacorte, D.; Lucafò, M.; Cifù, A.; Favretto, D.; Cuzzoni, E.; Silvestri, T.; Pozzi Mucelli, M.; Radillo, O.; Decorti, G.; et al. Causes of Treatment Failure in Children with Inflammatory Bowel Disease Treated with Infliximab. J. Pediatr. Gastroenterol. Nutr. 2019, 68, 37–44.

45. Ohem, J.; Hradsky, O.; Zarubova, K.; Copova, I.; Bukovska, P.; Prusa, R.; Malickova, K.; Bronsky, J. Evaluation of Infliximab Therapy in Children with Crohn's Disease Using Trough Levels Predictors. Dig. Dis. 2018, 36, 40–48.
46. Rolandsdotter, H.; Marits, P.; Sundin, U.; Wikström, A.-C.; Fagerberg, U.; Finkel, Y.; Eberhardson, M. Serum-Infliximab Trough Levels in 45 Children with Inflammatory Bowel Disease on Maintenance Treatment. Int. J. Mol. Sci. 2017, 18, 575.
47. Steenholdt, C.; Brynskov, J.; Thomsen, O.Ø.; Munck, L.K.; Fallingborg, J.; Christensen, L.A.; Pedersen, G.; Kjeldsen, J.; Jacobsen, B.A.; Oxholm, A.S.; et al. Individualised therapy is more cost-effective than dose intensification in patients with Crohn's disease who lose response to anti-TNF treatment: A randomised, controlled trial. Gut 2014, 63, 919–927.
48. Afif, W.; Loftus, E.V.J.; Faubion, W.A.; Kane, S.V.; Bruining, D.H.; Hanson, K.A.; Sandborn, W.J. Clinical utility of measuring infliximab and human anti-chimeric antibody concentrations in patients with inflammatory bowel disease. Am. J. Gastroenterol. 2010, 105, 1133–1139.
49. Overkleeft, R.; Tommel, J.; Evers, A.W.M.; den Dunnen, J.T.; Roos, M.; Hoefmans, M.-J.; Schrader, W.E.; Swen, J.J.; Numans, M.E.; Houwink, E.J.F. Using Personal Genomic Data within Primary Care: A Bioinformatics Approach to Pharmacogenomics. Genes 2020, 11, 1443.
50. Choi, S.Y.; Kang, B.; Lee, J.H.; Choe, Y.H. Clinical Use of Measuring Trough Levels and Antibodies against Infliximab in Patients with Pediatric Inflammatory Bowel Disease. Gut Liver 2017, 11, 55–61.
51. Carman, N.; Mack, D.R.; Benchimol, E.I. Therapeutic Drug Monitoring in Pediatric Inflammatory Bowel Disease. Curr. Gastroenterol. Rep. 2018, 20, 18.
52. Pinto Pais, I.; Espinheira, M.C.; Trindade, E.; Amil Dias, J. Optimizing Antitumor Necrosis Factor Treatment in Pediatric Inflammatory Bowel Disease with Therapeutic Drug Monitoring. J. Pediatr. Gastroenterol. Nutr. 2020, 71, 12–18.
53. Deora, V.; Kozak, J.; El-Kalla, M.; Huynh, H.Q.; El-Matary, W. Therapeutic drug monitoring was helpful in guiding the decision-making process for children receiving infliximab for inflammatory bowel disease. Acta Paediatr. 2017, 106, 1863–1867.
54. Jongsma, M.M.E.; Winter, D.A.; Huynh, H.Q.; Norsa, L.; Hussey, S.; Kolho, K.-L.; Bronsky, J.; Assa, A.; Cohen, S.; Lev-Tzion, R.; et al. Infliximab in young paediatric IBD patients: It is all about the dosing. Eur. J. Pediatr. 2020, 179, 1935–1944.
55. Papamichael, K.; Cheifetz, A.S.; Melmed, G.Y.; Irving, P.M.; Vande Casteele, N.; Kozuch, P.L.; Raffals, L.E.; Baidoo, L.; Bressler, B.; Devlin, S.M.; et al. Appropriate Therapeutic Drug Monitoring of Biologic Agents for Patients with Inflammatory Bowel Diseases. Clin. Gastroenterol. Hepatol. Off. Clin. Pract. J. Am. Gastroenterol. Assoc. 2019, 17, 1655–1668.e3.

56. Papamichael, K.; Vajravelu, R.K.; Vaughn, B.P.; Osterman, M.T.; Cheifetz, A.S. Proactive Infliximab Monitoring Following Reactive Testing is Associated with Better Clinical Outcomes Than Reactive Testing Alone in Patients with Inflammatory Bowel Disease. J. Crohn's Colitis 2018, 12, 804–810.
57. Kelly, O.B.; Donnell, S.O.; Stempak, J.M.; Steinhart, A.H.; Silverberg, M.S. Therapeutic Drug Monitoring to Guide Infliximab Dose Adjustment is Associated with Better Endoscopic Outcomes than Clinical Decision Making Alone in Active Inflammatory Bowel Disease. Inflamm. Bowel Dis. 2017, 23, 1202–1209.
58. Fernandes, S.R.; Bernardo, S.; Simões, C.; Gonçalves, A.R.; Valente, A.; Baldaia, C.; Moura Santos, P.; Correia, L.A.; Tato Marinho, R. Proactive Infliximab Drug Monitoring Is Superior to Conventional Management in Inflammatory Bowel Disease. Inflamm. Bowel Dis. 2020, 26, 263–270.
59. Lyles, J.L.; Mulgund, A.A.; Bauman, L.E.; Su, W.; Fei, L.; Chona, D.L.; Sharma, P.; Etter, R.K.; Hellmann, J.; Denson, L.A.; et al. Effect of a Practice-wide Anti-TNF Proactive Therapeutic Drug Monitoring Program on Outcomes in Pediatric Patients with Inflammatory Bowel Disease. Inflamm. Bowel Dis. 2021, 27, 482–492.
60. Assa, A.; Matar, M.; Turner, D.; Broide, E.; Weiss, B.; Ledder, O.; Guz-Mark, A.; Rinawi, F.; Cohen, S.; Topf-Olivestone, C.; 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, 985–996.e2.
61. Van Hoeve, K.; Dreesen, E.; Hoffman, I.; Van Assche, G.; Ferrante, M.; Gils, A.; Vermeire, S. Adequate Infliximab Exposure During Induction Predicts Remission in Paediatric Patients with Inflammatory Bowel Disease. J. Pediatr. Gastroenterol. Nutr. 2019, 68, 847–853.
62. Maul, J.; Loddenkemper, C.; Mundt, P.; Berg, E.; Giese, T.; Stallmach, A.; Zeitz, M.; Duchmann, R. Peripheral and intestinal regulatory CD4+ CD25(high) T cells in inflammatory bowel disease. Gastroenterology 2005, 128, 1868–1878.
63. Boschetti, G.; Nancey, S.; Sardi, F.; Roblin, X.; Flourié, B.; Kaiserlian, D. Therapy with anti-TNFα antibody enhances number and function of Foxp3 (+) regulatory T cells in inflammatory bowel diseases. Inflamm. Bowel Dis. 2011, 17, 160–170.
64. Li, Z.; Vermeire, S.; Bullens, D.; Ferrante, M.; Van Steen, K.; Noman, M.; Rutgeerts, P.; Ceuppens, J.L.; Van Assche, G. Restoration of Foxp3+ Regulatory T-cell Subsets and Foxp3- Type 1 Regulatory-like T Cells in Inflammatory Bowel Diseases During Anti-Tumor Necrosis Factor Therapy. Inflamm. Bowel Dis. 2015, 21, 2418–2428.
65. Li, Z.; Arijs, I.; De Hertogh, G.; Vermeire, S.; Noman, M.; Bullens, D.; Coorevits, L.; Sagaert, X.; Schuit, F.; Rutgeerts, P.; et al. Reciprocal changes of Foxp3 expression in blood and intestinal mucosa in IBD patients responding to infliximab. Inflamm. Bowel Dis. 2010, 16, 1299–1310.

66. Ricciardelli, I.; Lindley, K.J.; Londei, M.; Quaratino, S. Anti tumour necrosis-alpha therapy increases the number of FOXP3 regulatory T cells in children affected by Crohn's disease. Immunology 2008, 125, 178–183.
67. Marteau, P.; Lepage, P.; Mangin, I.; Suau, A.; Doré, J.; Pochart, P.; Seksik, P. Review article: Gut flora and inflammatory bowel disease. Aliment. Pharmacol. Ther. 2004, 20 (Suppl. S4), 18–23.
68. Macpherson, A.; Khoo, U.Y.; Forgacs, I.; Philpott-Howard, J.; Bjarnason, I. Mucosal antibodies in inflammatory bowel disease are directed against intestinal bacteria. Gut 1996, 38, 365–375.
69. Conte, M.P.; Schippa, S.; Zamboni, I.; Penta, M.; Chiarini, F.; Seganti, L.; Osborn, J.; Falconieri, P.; Borrelli, O.; Cucchiara, S. Gut-associated bacterial microbiota in paediatric patients with inflammatory bowel disease. Gut 2006, 55, 1760–1767.
70. Schwiertz, A.; Jacobi, M.; Frick, J.-S.; Richter, M.; Rusch, K.; Köhler, H. Microbiota in pediatric inflammatory bowel disease. J. Pediatr. 2010, 157, 240–244.e1.
71. Wang, Y.; Gao, X.; Ghozlane, A.; Hu, H.; Li, X.; Xiao, Y.; Li, D.; Yu, G.; Zhang, T. Characteristics of Faecal Microbiota in Paediatric Crohn's Disease and Their Dynamic Changes During Infliximab Therapy. J. Crohn's Colitis 2018, 12, 337–346.
72. Wang, Y.; Gao, X.; Zhang, X.; Xiao, F.; Hu, H.; Li, X.; Dong, F.; Sun, M.; Xiao, Y.; Ge, T.; et al. Microbial and metabolic features associated with outcome of infliximab therapy in pediatric Crohn's disease. Gut Microbes 2021, 13, 1–18.
73. Hizarcioglu-Gulsen, H.; Kaplan, J.L.; Moran, C.J.; Israel, E.J.; Lee, H.; Winter, H. The Impact of Vitamin D on Response to Anti-tumor Necrosis Factor-α Therapy in Children with Inflammatory Bowel Disease. J. Pediatr. Gastroenterol. Nutr. 2021, 72, e125–e131.