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Serum ɣ-Globulins Predictive Value on Anti- TNFα Response among Children with Inflammatory Bowel Disease

Valentina Giorgio[1]*; Elisa Blasi[1]; Stefano Nobile[1]; Sara De Giorgi[1]; Giuseppe Stella[1]; Gaia Margiotta[1]; Anna Basile[1]; Francesco Proli[1]; Franco Scaldaferri[2]; Antonio Gasbarrini[2]; Fiammetta Bracci[3]

[1]Department of Woman and Child Health and Public Health, Fondazione Policlinico Universitario A. Gemelli, IRCCS, Università Cattolica del Sacro Cuore, Rome, Italy.

[2]Department of Medical and Surgical Sciences, Fondazione Policlinico Universitario A. Gemelli, IRCCS, Università Cattolica del Sacro Cuore, Rome, Italy.

***Corresponding Author(s): Valentina Giorgio**

Department of Woman and Child Health and Public Health, Fondazione Policlinico Universitario A. Gemelli, IRCCS, Università Cattolica del Sacro Cuore, Rome, Italy.

Tel: +39333402067; Email: valentinagiorgio1@gmail.com

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Abstract

Objectives: loss of response to anti-TNFα treatment occurs frequently in Paediatric Inflammatory Bowel Disease (IBD) patients. Here, we assess the predictive value of serum ɣ-globulin and IgG concentrations for treatment failure and development of anti-drug antibodies (ADAs).

Methods: all children treated with either Infliximab or Adalimumab for IBD between November 2015 and April 2021 were included in the study. Serum ɣ-globulins, IgG, ADAs concentrations were collected at the beginning of biological, after 3 months, after 1 year since anti-TNF initiation and at the end of the follow-up period.

Results: 48 patients (25 CD, 23 UC) were included: 16 primary non responders (PNR), 9 obtained clinical and/or endoscopic remission (REM), 23 showed secondary loss of response (SLOR). Among SLOR, 10 patients obtained clinical remission intensifying biological therapy. Two final categories were identified: response (RES) and non-response (non-RES) at the end of follow-up. Clinical responsivity at 3- and 12-months follow-up evaluated with only PUCAI/PCDAI score was identified as *res* or *non-res*. At 3 months follow-up, high values of ɣ-globulins (>13 g/l) were significantly correlated with being *non-res* (p=0,007). The *non-res* group at 3,12 months showed non significantly higher IgG values at start therapy in comparison to res group. At 3,12 months and at the end of follow-up, IgG and ɣ-globulins values at start therapy resulted non significantly higher in those patients with ADAs>10 U/ml.

Conclusions: ɣ-globulins and IgG could potentially predict the lack of response at the end of induction of remission and the need of therapeutic scheme modulation, such as an intensified induction strategy.

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What is known

- a large fraction of patients with IBD are primary non responders without clinical benefit following the induction therapy, or subsequently lose response
- serum concentrations are valid tests to manage the biological therapy in case of persistence of disease activity.

What is new

- serum γ-globulin and IgG levels at start therapy are elevated in children with lack of response at the end of induction of remission, and there is a significant negative relationship between serum γ-globulin, IgG levels and anti-TNFα response.
- serum γ-globulin and IgG levels could predict loss of response to Anti-TNFα in children

Introduction

Pediatric Inflammatory bowel Disease (IBD) is a growing concern in pediatric health care.

The incidence of Crohn's Disease (CD) in the pediatric population is 2,5-11,4 per 100000 with an estimated prevalence of 58/100,000. In pediatric-onset CD the etiology is multifactorial, and the genetic component is more dominant and therefore recurrence within the family is more prevalent than in adults [1].

Childhood-onset CD is characterized by rapid early progression and it seems to be a more severe disease compared to adult-onset [2,3,4].

Ulcerative colitis (UC) develops during childhood in up to 25% of patients. In comparison with adult-onset disease, pediatric-onset UC is more often extensive and therefore, more likely to be associated with severe acute exacerbations [5].

However, with the introduction of biologics, such as Infliximab (IFX) and Adalimumab (Ada), more opportunities to induce and maintain remission have opened up. Indeed, anti-Tumor Necrosis Factor (TNF) therapy reduces both hospitalizations and the need of surgery, thus leading to new treatment targets, namely "mucosal healing" and "clinical remission". Nevertheless, a large fraction of patients with IBD are primary non responders without clinical benefit following the induction therapy, or subsequently lose response (secondary loss of response) and need to intensify or even discontinue therapy. Lastly, treatment failure with anti TNFα drugs can also be due to adverse events.

Both primary non-response (PNR) and secondary loss of response (SLOR) are due to pharmacokinetic problems, characterized by undetectable or subtherapeutic drug concentrations, and to the development of antidrug antibodies (ADAs), given the intrinsic risk of immunogenicity that biologic therapies involve.

In the pediatric population, the percentage of ADAs development to IFX is as high as 43%, [6] while to Adalimumab is up to 10.3% [7,8]. Moreover, recent evidence also suggests that insufficient anti-TNF exposure during induction and maintenance can lead to a higher risk to ADAs development [9].

Recent studies, mostly on adult population, identified epidemiological, clinical and laboratoristic factors as predictors of good response to anti-TNFα drugs. Among these factors: diagnosis at age < 40 years, association therapy with immunomodulators and no previous anti-TNFα drugs use, and predictors of scarce response such as a severe disease at diagnosis, a fibrostenotic disease or previous surgery in UC, male gender, a higher Body Mass Index, low body weight <30 Kg, hypoalbuminemia, and anemia at the beginning of anti- TNFα therapy [10-17].

A recent study on adult patients with IBD by Schoenefuss et al. also identified serum ɣ-globulins as predictors of secondary loss of response to anti-TNFα agents [18].

Since some clinical features and laboratory tests are known to influence the response to anti-TNFα agents while no pediatric studies are available, here we investigate whether serum levels of ɣ-globulins and IgG, largely used laboratory tests in routinely clinical practice, could predict the response to Infliximab and Adalimumab in pediatric patients affected by IBD. Furthermore, we aim to evaluate if an increase of serum ɣ-globulins and IgG could predict the development of drug antibodies. In turn, these findings would enable to personalize treatment strategies in pediatric IBD needing biological therapy.

Methods

This retrospective study included children with IBD who were treated with anti-TNFα agents (Infliximab, Adalimumab) between November 2015 and April 2021 at Fondazione Policlinico Universitario A. Gemelli IRCCS, Università Cattolica del Sacro Cuore of Rome, and Bambino Gesu` Children Hospital. The decision to start the biological therapy was dictated by the most recent ECCO-ESPGHAN guidelines available at the time of the beginning of therapy [1,5,9].

The therapeutic scheme for the induction of remission with IFX consisted in three endovenous doses of 5 mg/Kg at time 0, 2 and 6 weeks, followed by the maintenance of remission every 8 weeks at dose of 5 mg/Kg. An increase of doses to 10 mg/Kg or a reduction of intervals was adopted if this initial scheme resulted inefficient to maintain remission.

As regards Adalimumab, the therapeutic scheme consisted in a first dose of 80 mg subcutaneously (sc), followed by a dose of 40 mg sc after 2 weeks, then followed by doses of 20 mg sc every 2 weeks in children with weight < 35 Kg. The scheme 160-80 mg followed by 40 mg sc every 2 weeks was adopted if the weight was > 35 Kg [1,5].

We identified 3 groups of patients in according to clinical and/or endoscopic remission during therapy with anti-TNFα drugs **(Figure 1)**:

1. Children who presented "mucosal healing" and/or "clinical remission" (REM) at the time of study observation.
2. Children who presented lack of response to induction of remission (primary non-response, PNR) at 12-14 weeks from the beginning of therapy
3. Children who presented a loss of response after an initial response (secondary non-response, SLOR) during maintenance of remission.

"Mucosal Healing" was defined as a complete resolution of macroscopic and microscopic lesions at ileocolonoscopy in both CD and UC. "Clinical Remission" was evaluated by clinical activity disease indexes (Pediatric Ulcerative Colitis Activity Index, PUCAI, for UC and Pediatric Crohn's Disease Activity Index, PCDAI, for CD) and was defined as a PUCAI < 10 or a PCDAI ≤ 10 [5,20].

"Response" to anti-TNFα therapy was defined by a significant improvement of 20 or 12.5 points of PUCAI or PCDAI score respectively. PNR consisted in lack of improvement in clinical disease activity, evaluated with PUCAI or PCDAI score and/or positive endoscopic findings, during or at the end of therapeutic scheme for induction of remission.

SLOR was defined as a worsening of PUCAI or PCDAI score after an initial good response and/or positive endoscopic findings, which needed an intensification of biological therapy in term of increasing drug dose or reducing intervals between doses.

The patients' collected clinical data included: age at the beginning of anti-TNFα therapy, gender, type of IBD (CD, UC), type of anti-TNFα drug (IFX or Ada), previous anti-TNFα treatment, duration of disease from diagnosis to anti-TNFα initiation, clinical disease activity scores (PUCAI and PCDAI), and concomitant immunosuppressant or steroid therapy.

Moreover, laboratory data including serum ɣ-globulins (calculated multiplying the fraction of ɣ-globulins serum protein electrophoresis by the total serum protein), IgG, IFX and ADA serum levels and antibodies against IFX and Ada were collected.

Values of serum ɣ-globulins > 13 g/l and of IgG >16 g/l were considered pathological; antibodies against IFX and Ada were considered abnormal if > 10 U/Ml [21].

These findings were collected following this scheme, as per routine assessment at the Pediatric IBD clinic at Fondazione Policlinico Gemelli and Bambino Gesù Hospital:

- At the beginning of biological therapy (start therapy)
- At the end of scheme of induction of remission (3 months)
- After 1 year since anti-TNFα initiation (12 months)
- At the end of the observation period or at drug withdrawal of biological therapy in the case of PNR or SLOR.

Exclusion criteria included suspected or confirmed scarce compliance to biological therapy, confirmed infections or IBS-like symptoms which could explain the lack of improvement.

The study was approved by the local ethics committee.

Statistical Analysis

SPSS version 23 (IBM, Armonk, US) was used to compute statistics. Demographics and clinical characteristics of patients were retrieved from clinical charts and anonymized before statistical analysis was performed. Results are expressed as mean (standard deviation) or median (interquartile range) or percentage as appropriate based on data distribution. Associations with response to therapy were explored by means of univariate and multivariable analyses. T-test, Mann-Whitney U test, Kruskal Wallis test and Chi-square test were used as appropriate to compare independent groups. Logistic and multinomial regression analyses were performed to assess predictors of response to therapy. A linear regression analysis was computed to explore associations between the development of ADAs and serum ɣ-globulins and IgG values before the commencement of anti-TNF therapy. P-values <0.05 were considered statistically significant.

Results

Patients Characteristics

Fourty-eight patients (25 CD, 23 UC) treated with anti-TNFα agents were included. They were enrolled between November 2015 and April 2021. Twenty-five (52%) were male, and twenty-three (48%) were female. The median age at onset of disease was 13 years (IQR 12-15), and the median time of disease duration from diagnosis to anti-TNFα initiation was 7.5 months (IQR 3 – 26.3). Thirty-eight (79%) patients were treated with IFX and ten (21%) with Adalimumab as first biological agent. A combination of immunosuppressant agents (azathioprine or methotrexate) at the beginning of biological therapy was adopted in 15 (33%) patients (14 with azathioprine and 1 with methotrexate), while concomitant administration of steroids was reported in 15 (33%) patients (3 patients were on concomitant AZA and steroids).

Thirty-three out of fourty-eight patients (69%) were followed for > 1 year, and median follow up time was 29 months (interquartile range 20-44).

Characteristics of the study population at start, 3,12 months follow-up and the end of observation time are summarized in **Table 1.**

Based on clinical and/or endoscopic findings, we identified 3 groups at the end of observation time: 9/48 (18.8%) REM, 16/48 (33.3%) PNR, 23/48 (47.9%) SLOR. Among SLOR, 10 patients obtained clinical remission after intensification of biological therapy. Among all patients, 2 final categories were identified: response (RES) and non-response (nonRES) at the end of observation time (19 and 29 respectively). At the end of observation time, 3 patients of non-RES group switched biological therapy to Vedolizumab, 1 to Adalimumab and 1 to Thalidomide. Data are summarized in **Figure 1.**

Table 1: Clinical characteristics of patients during the study period. Patients characteristics at biological initiation, 3,12 months and at the end of follow-up. 5-ASA: Aminosalicylates PUCAI: Pediatric Ulcerative. Colitis Activity Index PCDAI: Pediatric Crohn's Disease Activity Index

	Start of anti-TNF therapy	3 months	12 months	End of follow-up
PCDAI, median (IQR)	15 (12-23)	5 (0-10)	1.25 (0-9.4)	2.5 (0-11.3)
PUCAI, mean (SD) or median (IQR)	55.0 (16.4)	15 (0-30)	5 (0-30)	0 (0-15)
Gamma-globulins (g/L), mean (SD)	13.0 (3.5)	13.1 (2.9)	13.6 (2.8)	13.9 (2.2)
Elevated gamma-globulins, n (%)	21 (45.7)*	24 (52.1)*	24 (55.8)*	21 (63.6)*
IgG (g/L), mean (SD)	13.3 (3.3)	13.9 (3.1)*	13.6 (2.9)*	14.0 (3.1)*
Elevated IgG, n (%)	5 (10.4)*	7 (25)*	5 (20)*	6 (27.3)*
Antibodies anti-IFX (mcg/ml), median (IQR)	/	8.4 (5.2-12.7)*	23.5 (9.3-53.1)*	24.0 (9.4-57.5)*
Elevated anti-IFX Ig, n (%)	/	7 (36.8)*	17 (77.3)*	13 (72.2)*

IFX levels within normal range, n (%)	/	3 (16.7)*	6 (27.3)*	7 (38.9)*
Antibodies anti-ADA (mcg/ml), median (IQR)	/	8.8 (8.4-9.1)	7.7 (/)*	10.3 (5.6)*
Elevated anti-ADA Ig, n (%)	/	0 (0)	0 (0)	4 (66.7)*
ADA levels within normal range, n (%)	/	1 (50)*	1 (100)*	5 (83.3)*
Combination therapy with AZA, MTX or steroids, n (%)	26 (54)	14 (31.8)*	7 (16.7)*	2 (6.3)*

* Some patients had unavailable data

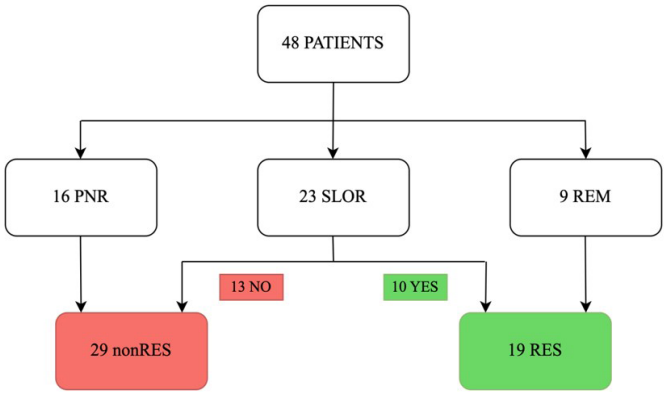

Table 1: Patients subgroups according to clinical and/or endoscopic remission during therapy with anti-TNFα)

Gamma Globulins

At start of anti-TNFα therapy, serum ɣ-globulins were available in 91% of patients.

Evaluating response at 3 months follow-up, ɣ-globulins at start > 13 g/l was significantly associated with being non-res (43.8% of patients with ɣ-globulins at start > 13 g/l were non-res, vs 8% of patients with ɣ-globulins at start < 13 g/l, p=0.007).

Evaluating response at 12 months follow-up, non-res patients had similar values of ɣ-globulins at start (26.1% of patients with ɣ-globulins at start < 13 g/l vs. 33.3 % of patients with ɣ-globulins at start > 13 g/l, (p>0.05).

At the end follow-up ɣ-globulins >13 g/l were reported in a similar proportion of patients (61.5% of RES versus 63.2% of nonRES, p>0.05).

Moreover, non-res group at 3 months follow-up presented higher ɣ-globulins values at start therapy in comparison to res group (p=0.0228). This data was not confirmed at 12 months follow-up.

At the end of follow-up, nonRES group presented higher ɣ-globulins values at start therapy in comparison to RES group without significance.

Immunoglobulins G

At start of anti-TNFα therapy, IgG were available in 62% of patients.

Evaluating response at 3 months follow-up, 12.5% of patients with IgG at start <16 g/l were non-res, while 50% of patients with IgG at start > 16 g/l were non-res (p=0.07).

At the end follow-up IgG >16 g/l were reported in 20% of nonRES, while in 7.1% of RES (p>0.05). Moreover, non-res group at 3, 12 months follow-up presented similar IgG values at start of anti-TNF therapy in comparison to res group (p>0.05).

At the end of follow-up nonRES group presented similar IgG value at start therapy in comparison to RES group (p>0.05).

Anti-Drug Antibodies

At 3 months follow-up all patients developing ADAs >10 U/ml (positive) were receiving Infliximab, whereas all patients treated with Adalimumab resulted negative for ADAs (p>0.05).

At 12 months follow-up, there was no significant difference between the proportion of res vs non-res who developed high ADAs levels (p>0.05). Similarly, at the end of follow-up we found no significant difference between res and non-res patients who developed high ADAs levels (83.3% of nonRES vs. 75% of RES, p>0.05).

Moreover at 3, 12 months and at the end of follow-up, IgG and ɣ-globulins values at start of anti-TNF therapy resulted slightly higher in patients with high vs. low ADAs levels (p>0.05).

Concerning the development of antibodies to IFX, there was no significant difference at linear regression analysis between patients who developed ADAs and those who did not in serum IgG and ɣ-globulins values at start of anti-TNF therapy.

With regard to antibodies to adalimumab, univariate analysis and linear regression analysis found no significant association between IgG and ɣ-globulins at commencement of anti-TNF therapy and the development of ADAs.

Combination Therapy

Among 14 patients who used combination therapy with Azathioprine, nine out 14 patients in combination therapy continued this strategy at least for 6 months from anti-TNFα initiation, but no significant difference in response at 3 and 12 months was noted compared to patients with anti-TNF monotherapy. Also, combination with steroids did not show significant differences in clinical response at 3- and 12-months follow-up.

The only patient in therapy with Methotrexate obtained clinical response.

Predictors of clinical response to therapy

At univariate analysis, there was no significant difference between responders and non-responders regarding variables before anti-TNF start: age at IBD onset, gender, duration of disease at anti-TNF start, initial PCDAI/PUCAI, levels of IgG and ɣ-globulins at anti-TNF start, combination therapy with AZA/MTX/steroids at anti-TNF start.

Similarly, we found no significant associations between response to therapy and variables at 3 months follow-up, 12 months follow up, end of follow up: combo therapy with immunosuppressants, levels of gammaGlobulins/IgG, antibodies vs IFX, IFX levels.

We run a logistic regression analysis to assess predictors of response to anti-TNF therapy and found no significant associations between levels of IgG and ɣ-globulins at anti-TNF start (among other clinical variables tested in different models) and responder status (data not shown).

Discussion

The key findings of our study are that higher ɣ-globulins and a higher trend of IgG levels at initiation of anti-TNFα drugs are associated with poor response to treatment and could lead to a lack of remission-at 3 months of biological therapy.

This data was not confirmed at 12 months follow-up, maybe explained by modification of therapies, and in particular by intensification of anti-TNFα scheme (increase of doses or reduction of intervals between doses) during the first year of treatment.

Since some centers could have limited laboratory services and specific more expensive tests -such as ADAs and drug levels- could not be available, it is possible to hypothesize that two routinary tests such as γ-globulins and IgG could be sufficient to predict short term response in pediatric IBD patients needing biological therapy.

To our knowledge, the present study is the first one strictly aiming to look at γ-globulins and IgG levels in children, as predictors of poor response to treatment.

Higher ɣ-globulins and IgG levels at initiation of biological therapy could lead to personalize treatment strategy in patients needing biologics. It could be possible to suggest starting anti-TNFα with an intensified induction of remission scheme, as previously suggested in pediatric studies [22].

A recent review by Hindryckx et al. showed the pharmacokinetic mechanisms behind the higher clearance rate of Infliximab in patients with acute severe UC. First an elevated amount of TNFα, due to high inflammation, binds a major amount of anti-TNFα drug, creating immunocomplexes that are subject to degradation, further facilitated by upregulation of the number of phagocytic mononuclear cells in response to systemic inflammation and increased activity of reticuloendothelial system macrophages. [23] Moreover, an intestinal mucosal damage facilitates the fecal loss of Infliximab. [24] Lastly, immunoglobulin G antibodies are involved into a recycling mechanism to escape from the lysosomal degradation, binding to the neonatal Fc receptor, located on the endothelial cell membranes. As Infliximab is an immunoglobulin G1 antibody, it participates to this recycle, leading to a longer drug half-life. If the intestinal epithelium is damaged, less Fc receptors are available and the higher concentration of endogenous immunoglobulin G that exists in the setting of severe inflammation may saturate neonatal Fc receptor binding sites. This leads to a less recycling of Infliximab and to a lower serum drug concentration [12,24].

A recent prospective study on 128 adult patients with IBD by Schoenefuss et al, identified serum gamma-globulins as predictors of secondary loss of response to anti-TNFα agents. They hypothesize that a higher B-cell activity produces more serum γ-globulins, and this could lead to an early development and increase of antibodies against Infliximab or Adalimumab. Moreover, they found that risk of SLOR in patients with high serum γ-globulins seems to be reduced significantly with the association of an immunosuppressant agent to the biological therapy [18].

Many studies indeed confirmed the superior efficacy of combination therapy with biological therapy and immunosuppressant in adults to reduce the risk of ADAs formation [10,25,26]. On the contrary, few pediatric studies are available, showing conflicting results on the outcome in patients treated with monotherapy or combination therapy. In our population we found no differences in term of response between patients undergoing combination therapy or not.

As regards to anti-drug antibodies development, ADAs were prevalent in patients using IFX in comparison to patients in therapy with Adalimumab. This is partially consistent with the other studies were in pediatric population the percentage of development of ADAs to IFX have been reported in up to 43%, [6] while to Ada in up to 10.3% [7,8].

It was also confirmed in a recent study by Kim et al. which reported development of ADAs in 13.2% of patients receiving IFX, while no antibodies were detected in patients receiving Ada [27]. In a review by Vermeire et al. on adult population it was found ADAs development in 0% to 65.3% of patients receiving IFX and in 0.3% to 38% of those receiving Ada [28]. This different prevalence can be explained by the characteristic of Ada to be a fully humanized monoclonal antibody and potentially less immunogenic then IFX.

Development of ADAs also seems to be correlated with lack of remission leading to a reduction of serum drug levels. In our study, we have found a higher prevalence of ADAs also in patients with clinical or/and endoscopic remission, and this could be explained by the potential transient nature of these antibodies. Indeed, Vande Casteele et al found that transient ADAs were reported in 28% of patients who developed ADAs during treatment with IFX and did not result in a worse clinical outcome, contrary to sustained high levels of ADAs which seems to be more associated with permanent SLOR [29].

In conclusion, we found that ɣ-globulins and IgG could potentially predict lack of response at the end of induction of remission and the need of modulating the therapeutic scheme. It seems that an intensified induction strategy may be proposed to these patients.

This finding has particular significance if translated in hospital settings limited laboratory services, where two routinary, easy-to-perform tests such as γ-globulins and IgG levels could be useful to predict anti-TNFα response and to personalize treatment strategy.

It has to be addressed that, even if multicentric, this is a retrospective study having as main limitation the small number of patients, giving the nature of pediatric IBDs.

Therefore, we plan to perform in the near future a prospective, multicenter pediatric study on a larger sample to confirm these findings and to understand if we can improve the clinical course of these patients with IBD, needing anti-TNFα therapy.

References

1. Ruemmele FM, Veres G, Kolho KL, Griffiths A, Levine A, et al. Consensus guidelines of ECCO/ESPGHAN on the medical management of pediatric Crohn's disease. J Crohns Colitis. 2014; 8: 1179-1207.
2. Van Limbergen J, Russell RK, Drummond HE, Aldhous MC, Round NK, et al. Definition of phenotypic characteristics of childhood-onset inflammatory bowel disease. Gastroenterology 2008; 135: 1114-1122.
3. Vernier-Massouille G, Balde M, Salleron J, Turck D, Dupas JL, et al. Natural history of pediatric Crohn's disease: a population-based cohort study. Gastroenterology. 2008; 135: 1106-1113.

4. Pigneur B, Seksik P, Viola S, Viala J, Beaugerie L, et al. Natural history of Crohn's disease: comparison between childhood- and adult-onset disease. Inflamm Bowel Dis. 2010; 16: 953-961.

5. Turner D, Ruemmele FM, Orlanski-Meyer E. Management of Paediatric Ulcerative Colitis, Part 1: Ambulatory Care-An Evidence-based Guideline From European Crohn's and Colitis Organization and European Society of Paediatric Gastroenterology, Hepatology and Nutrition. J Pediatr Gastroenterol Nutr. 2018; 67: 257-291.

6. Carman N, Mack DR, Benchimol EI. Therapeutic drug monitoring in pediatric inflammatory bowel disease. Curr Gastroenterol Rep. 2018; 20: 18

7. Sharma S, Eckert D, Hyams JS, Mensing S, Thakkar RB, 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: 783-792.

8. Matar M, Shamir R, Turner D, Broide E, Weiss B, et al. Combination therapy of adalimumab with an immunomodulator is not more effective than adalimumab monotherapy in children with Crohn's disease: a post hoc analysis of the PAILOT randomized controlled trial. Inflamm Bowel Dis. 2019; 26: 1627-1635.

9. Roblin X, Marotte H, Rinaudo M, Tedesco E, Moreau A, et al. Association between pharmacokinetics of adalimumab and mucosal healing in patients with inflammatory bowel diseases. Clin Gastroenterol Hepatol. 2014; 12: 80-84e2.

10. Panaccione R, Ghosh S, Middleton S, Márquez JR, cott BB, et al. Combination therapy with infliximab and azathioprine is superior to monotherapy with either agent in ulcerative colitis. Gastroenterology. 2014; 146: 392-400e3.

11. Macaluso FS, Fries W, Privitera AC, Cappello M, Siringo S, et al. A propensity score-matched comparison of infliximab and adalimumab in tumour necrosis factor-alpha inhibitor-naive and non-naive patients with crohn's disease: Real-life data from the sicilian network for inflammatory bowel disease. J. Crohns Colitis. 2019; 13: 209-217.

12. Ordas I, Mould DR, Feagan BG, Sandborn WJ. Anti-TNF monoclonal antibodies in inflammatory bowel disease: pharmacokinetics-based dosing paradigms. Clin Pharmacol Ther. 2012; 91: 635-646.

13. Vermeire S, Louis E, Carbonez A, Van Assche G, Noman M, et al. Demographic and clinical parameters influencing the short-term outcome of anti-tumor necrosis factor (infliximab) treatment in crohn's disease. Am J Gastroenterol. 2002; 97: 2357-2363.

14. Harper JW, Sinanan MN, Zisman TL. Increased body mass index is associated with earlier time to loss of response to infliximab in patients with inflammatory bowel disease. Inflamm. Bowel Dis. 2013; 19: 2118-2124.

15. Kennedy NA, Heap GA, Green HD, Hamilton B, Bewshea C, 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

16. Oussalah A, Evesque L, Laharie D, Roblin X, Boschetti G, et al. A multicenter experience with infliximab for ulcerative colitis: Outcomes and predictors of response, optimization, colectomy, and hospitalization. Am J Gastroenterol. 2010; 105: 2617-2625.

17. Fasanmade AA, Adedokun OJ, Ford J, Hernandez D, Johanns J, et al. Population pharmacokinetic analysis of infliximab in patients with ulcerative colitis. Eur J Clin Pharmacol. 2009; 65: 1211-1128.

18. Schoenefuss F, Hoffmann P. Serum gamma-globulin and albumin concentrations predict secondary loss of response to anti-TNF-alfa in inflammatory bowel disease patients. Eur J Gastroenterol Hepatol. 2019; 31: 1563-1568.

19. van Rheenen PF, Aloi M, Assa A, Bronsky J, Escher JC, et al. The Medical Management of Paediatric Crohn's Disease: an ECCO-ESPGHAN Guideline Update. J Crohns Colitis. 2021; 15: 171-194.

20. Hyams J, Markowitz J, Otley A, Rosh J, Mack D, et al. Evaluation of the Pediatric Crohn Disease Activity Index: A Prospective Multicenter Experience. J Pediatr Gastroenterol Nutr. 2005; 41: 416-21.

21. Vande Casteele N, Herfarth H, Katz J, Falck-Ytter Y, Singh S, et al. American Gastroenterological Association Institute technical review on the role of therapeutic drug monitoring in the management of inflammatory bowel diseases. Gastroenterology. 2017; 153: 835-857.

22. 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.

23. Hindryckx P, Novak G, Vande Casteele N, Laukens D, Parker C, et al. Review article: dose optimisation of infliximab for acute severe ulcerative colitis. Aliment Pharmacol Ther. 2017; 45: 617-630.

24. Brandse JF, Van Den Brink GR, Wildenberg ME, van der Kleij D, Rispens T, et al. Loss of infliximab into feces is associated with lack of response to therapy in patients with severe ulcerative colitis. Gastroenterology. 2015; 149: 350-355.

25. Nanda KS, Cheifetz AS, Moss AC. 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: 40-48.

26. Vermeire S, Noman M, Van Assche G, Baert F, D'Haens G, et al. Effectiveness of concomitant immunosuppressive therapy in suppressing the formation of antibodies to infliximab in Crohn's disease. Gut. 2007; 56: 1226-1231.

27. Kim JY, Lee Y, Choe BH, Kang B. Factors Associated with the Immunogenicity of Anti-Tumor Necrosis Factor Agents in Pediatric Patients with Inflammatory Bowel. Gut Liver. 2020.

28. Vermeire S, Gils A, Accossato P, Lula S, Marren A,et al. Immunogenicity of biologics in inflammatory bowel disease. Therap Adv Gastroenterol. 2018; 11.

29. Vande Casteele N, Gils A, Singh S, Ohrmund L, Hauenstein S, et al. Antibody response to infliximab and its impact on pharmacokinetics can be transient. Am J Gastroenterol. 2013; 108: 962-971.