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MINIREVIEWS

Infliximab *vs* adalimumab: Points to consider when selecting anti-tumor necrosis factor agents in pediatric patients with Crohn's disease

Eun Sil Kim, Ben Kang

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Abstract

Biologic agents with various mechanisms against Crohn's disease (CD) have been released and are widely used in clinical practice. However, two anti-tumor necrosis factor (TNF) agents, infliximab (IFX) and adalimumab (ADL), are the only biologic agents approved by the Food and Drug Administration for pediatric CD currently. Therefore, in pediatric CD, the choice of biologic agents should be made more carefully to achieve the therapeutic goal. There are currently no head-to-head trials of biologic agents in pediatric or adult CD. There is a lack of accumulated data for pediatric CD, which requires the extrapolation of adult data for the positioning of biologics in pediatric CD. From a pharmacokinetic point of view, IFX is more advantageous than ADL when the inflammatory burden is high, and ADL is expected to be advantageous over IFX in sustaining remission in the maintenance phase. Additionally, we reviewed the safety profile, immunogenicity, preference, and compliance between IFX and ADL and provide practical insights into the choice of anti-TNF therapy in pediatric CD. Careful evaluation of clinical indications and disease behavior is essential when prescribing anti-TNF agents. In addition, factors such as the efficacy of induction and maintenance of remission, safety profile, immunogenicity, patient preference, and compliance play an important role in evaluating and selecting treatment options.

Key Words: Anti-tumor necrosis factor; Infliximab; Adalimumab; Crohn's disease; Pediatric

Core Tip: In pediatric Crohn's disease (CD), the choice of biologic agents should be made more carefully to achieve the therapeutic goal. This review article focuses on comparing the efficacy of induction and maintenance of remission, safety profile, immunogenicity, preference, and compliance between infliximab and adalimumab in pediatric CD.

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INTRODUCTION

Crohn's disease (CD) has become an important concern of clinicians owing to its rapidly increasing prevalence and incidence worldwide, including in emerging industrial countries[1]. Even though the incidence rate in Western countries has stabilised, most studies have revealed a statistically significant increase in the incidence of pediatric CD[2,3]. Pediatric patients with CD are more likely to have complications such as growth impairment, delayed puberty, psychosocial problems, aggressive disease course, and extensive gastrointestinal involvement than adult patients[4].

After infliximab (IFX) was approved by the Food and Drug Administration (FDA) in 1998[5], biologic agents with various mechanisms have been released and are widely used in clinical practice[6]. Among this broad spectrum of biologics, anti-tumor necrosis factor-α (TNF-α) agents have been classically used as first-line biologics for the treatment of moderate-to-severe CD refractory to conventional therapy[7]. Anti-TNF agents modulate the inflammatory response by binding to the TNF receptor on the cell membrane. IFX is a purified, recombinant DNA-derived chimeric human-mouse immunoglobulin G monoclonal antibody. Adalimumab (ADL) is a human monoclonal antibody that binds specifically to TNF-α[8,9]. Anti-TNF agents, such as IFX and ADL, are the only biologic agents that are currently approved by the FDA for pediatric patients with CD (Table 1)[10,11]. Therefore, the initial biologic agents to modify the disease course of CD and to achieve the therapeutic goal should be chosen more carefully in pediatric patients with CD.

Although head-to-head trials are the gold standard method for determining which treatment option is more effective, to date, no head-to-head trials have directly compared biologic agents. Until direct comparative studies of which biologic agents should be used first are performed, several points must be considered when selecting the initial biologic agent. In this study, we provide practical insights into the choice of anti-TNF therapy in pediatric CD. We reviewed the comparative efficacy, safety profile, immunogenicity, preference, and compliance between IFX and ADL.

MAIN STUDIES IN PEDIATRIC CD ASSESSING THE EFFICACY OF ANTI-TNFα THERAPIES

Anti-TNFα therapies have been well studied in adults and have showed efficacy in both the induction and maintenance of remission[12,13]. Targan *et al*[14] found that after a single 5 mg/kg IFX infusion, more than 80% of patients had a clinical response after four weeks. In the ACCENT-I study in which 58% of 573 patients with CD who had a response after the first dose of IFX were randomised, the IFX 5 mg/kg and 10 mg/kg groups were more effective in achieving clinical remission at week 54 than the placebo group[15].

After IFX and ADL were approved for use in the treatment of pediatric CD in 2006 and 2012, respectively, more than 20 years of data, including those from clinical trials, have been accumulated. There is evidence from randomised controlled trials (RCT) involving open-label induction and randomised dose-ranging maintenance therapies (Table 2). Four RCTs conducted on pediatric CD treated with anti-TNF agents showed the clinical remission rate in both the induction and maintenance periods[16-19].

The first RCT with IFX in pediatric patients with CD showed clinical response and remission in the induction and maintenance phases[16]. Among 112 patients, 99 patients (88.4%) responded to IFX, and 66 patients (58.9%) showed clinical remission at week 10. Patients responding to IFX were randomly assigned to receive IFX 5 mg/kg every 8 or 12 wk. By week 54, 63.5% of patients receiving IFX every eight weeks had a clinical response, and 55.8% achieved clinical remission, which is significantly higher than the clinical remission rate of 23.5% in those who received IFX every 12 wk. Ruemmele *et al*[17] also demonstrated the efficacy of IFX in pediatric patients with CD. Forty patients received IFX according to the induction regimen (weeks 0, 2, and 6) and were then randomly assigned to maintenance therapy of

Table 1 Biologic agents currently used or under study for the treatment of pediatric Crohn's disease

Class	Biologics	FDA approval for CD	Pediatric CD indications
Anti-TNF	Infliximab	Adult: 1998; Pediatric: 2006	Moderate to severe diseases refractory to conventional therapy[10]
	Adalimumab	Adult: 2007; Pediatric: 2012	First-line therapy for patients with CD who are at risk for progressive disease or for whom corticosteroids may exacerbate underlying conditions[10]; Prophylactic therapy for preventing postoperative recurrence in high-risk patients[10]
Anti-α4β7 integrin	Vedolizumab	Adult: 2014; Pediatric: N/A	Guideline recommendations for this pediatric indication are not yet available
IL-12/23 p40 inhibitor	Ustekinumab	Adult: 2016; Pediatric: N/A	Second-line biologic therapy after anti-TNF agent failure[11]

FDA: Food and Drug Administration; CD: Crohn's disease; TNF: Tumor necrosis factor; IL: Interleukin; N/A: Not applicable.

Table 2 Studies evaluating infliximab efficacy in pediatric Crohn's disease in the induction and maintenance phases

Ref.	Study group	Anti-TNF-α	Participants	Study design and aims	Definition of the outcome	Number of patients (*n*)	Age at diagnosis (yr)	Time	Clinical response	Clinical remission
Hyams *et al* [16], 2007	REACH	IFX	CD with a PCDAI > 30	Comparison of IFX maintenance intervals; every 8 *vs* 12 wk. Primary responders were randomised at week 10	Response: ΔPCDAI = -15. Remission: PCDAI ≤ 10	Total: 103. Every 8 wk: 52. Every 10 wk: 51	13.3	Week 10. Week 54	88.4%. Every 8 wk: 63.5%. Every 12 wk: 33.3% (P = 0.002)	58.9%. Every 8 wk: 55.8%. Every 12 wk: 23.5% (P < 0.001)
Ruemmele *et al*[17], 2009	GFHGNP	IFX	CD	Comparison of IFX infusion every 8 wk at maintenance *vs* IFX on demand. Primary responders were randomised at week 10	Remission: Harvey Bradshaw index < 5	Total: 40. Every 8 wk: 18. On demand: 13	13.9	Week 10. Week 60	N/A	85%. Every 8 wk: 83%. On demand: 61% (P = 0.001)
Hyams *et al* [18], 2012	IMAgINE	ADL	Moderate-to-severe CD	Comparison of ADL dose; HD (40 mg or 20 mg for body weight ≥ 40 kg or < 40 kg) *vs* LD (20 mg or 10 mg for body weight ≥ 40 kg or < 40 kg). Primary responders were randomised at week 4	Response: ΔPCDAI = -15. Remission: PCDAI ≤ 10	Total: 188. HD: 93. LD: 95	HD: 13.7 ± 2.52. LD: 13.5 ± 2.47	Week 26. Week 52	HD: 59.1%, LD: 48.4%. HD: 41.9%, LD: 28.4%	HD: 38.7%; LD: 28.4%. HD: 33.3%; LD: 23.2%
Assa *et al* [19], 2019	PAILOT	ADL	Biologic-naïve CD	Comparison of proactive TDM *vs* reactive TDM. Primary responders were randomised at week 4	Remission: PCDAI ≤ 10	Total: 78. Proactive: 38. Reactive: 40	Proactive: 12.9 ± 2.6. Reactive: 13.5 ± 2.7	Week 4. Week 72	NA	NA. Proactive TDM: 82%; Reactive TDM: 48%

CD: Crohn's disease; RCT: Randomised controlled trial; IFX: Infliximab; PCDAI: Pediatric Crohn's disease activity index; NA: Not applicable; ADL: Adalimumab; HD: High dose; LD: Low dose; TDM: Therapeutic drug monitoring.

IFX infusion every two months or an on-demand regimen. Around 85.0% of patients achieved clinical remission during IFX induction therapy. After the induction phase, the relapse rate was significantly higher in the on-demand group (91.7%) than in the IFX-maintenance group (23.1%).

A double-blind RCT evaluating the efficacy and safety of a dose-dependent maintenance regimen with ADL following open-label, weight-adjusted induction therapy (IMAgINE-1) was conducted on both IFX-naïve patients and patients who did not respond to IFX therapy[18]. In patients who had a clinical response in the induction phase, 38.7% and 33.5% of clinical remission was observed at week 26 and week 52, respectively. In addition, there was no statistically significant difference between the high- and low-dose groups. In a recently published RCT conducted in anti-TNF-naïve pediatric patients with CD, the clinical remission rate after the induction phase was much higher than that in the IMAgINE-1 study (48%-82% *vs* 38.7%)[19]. These results are in line with findings from previous adult studies[12,13] and highlight the importance of the choice of initial biologic agents according to risk stratification.

ANTI-TNFα AND ITS INDICATIONS FOR PEDIATRIC CD

The indications for the use of biologic agents have changed over the last two decades since the introduction of anti-TNF agents for the treatment of pediatric CD. Previously, anti-TNF agents were considered when disease activity was not controlled despite conventional therapies such as immunomodulators (IMMs), the so-called step-up strategy[16]. However, the guidelines recently published by the European Society of Pediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN) recommended early anti-TNF treatment within < 3 mo after diagnosis for the induction of remission in moderate-to-severe pediatric CD with a high risk of complications such as extensive disease, deep colonic ulcers, perianal disease, stricturing (B2), or penetrating disease (B3), growth impairment, the so-called top-down strategy[20]. The RISK study demonstrated that early induction therapy with anti-TNF agents was associated with higher corticosteroid- and surgery-free remission rated at 1 year compared to induction with exclusive enteral nutrition (EEN) and corticosteroids[21]. Kugathasan *et al*[22] also reported that early induction therapy with anti-TNF agents significantly lowered the risk of penetrating (B3) complications, however did not seems to reduce the risk of stricturing (B2) complications. In addition, even in patients with low risk of poor outcome, anti-TNF therapy should be considered in patients with severe growth impairment or who have not achieved clinical (pediatric CD activity index < 10) and biochemical remission (fecal calprotectin < 250 μg/g) despite induction therapy with EEN or corticosteroids[20].

Walters *et al*[21] reported that early anti-TNF therapy was more effective at maintaining remission than IMM monotherapy [relative risk (RR), 1.41; 95%CI: 1.14-1.75; P = 0.0017]. In addition, a prospective study in 76 pediatric patients with CD compared the step-up group and the top-down group in terms of endoscopic healing[23]. Compared with that in the step-up strategy, the rate of achieving endoscopic healing at week 54 was higher in the top-down group of pediatric patients with CD (42% *vs* 72%, P = 0.007), which means that seizing the therapeutic window of opportunity in pediatric CD should be considered earlier than generally accepted[24]. Based on these results, guidelines suggest that either IFX or ADL can be provided to pediatric patients with CD who have not previously received anti-TNF therapy, taking into account the efficacy, route of administration, and preference.

Standard dosing of IFX is weight-based at 5 mg/kg at weeks 0, 2, and 6, followed by maintenance treatment every 8 wk. In the case of ADL, patients weighing < 40 kg received 80/40 mg, and those weighing ≥ 40 kg received 160/80 mg in the first 2 wk. Thereafter, patients weighing < 40 kg were administered 20 mg, and patients weighing ≥ 40 kg were administered 40 mg every 2 wk. Dose escalation is considered in patients who lose response to standard anti-TNF treatment; adjustment of the infusion interval to 4 or 6 wk or an increment in the dose of 10 mg/kg for IFX; and adjustment of the administration interval to every week for ADL. Especially, children at risk for accelerated IFX clearance during induction [*i.e.*, patients < 30 kg, those with extensive disease, and those with low serum albumin] require dose escalation to achieve target trough levels (TLs) or their first proactive therapeutic drug monitoring (TDM) at the second or third anti-TNF infusion[25].

EFFICACY OF ANTI-TNF THERAPY IN PEDIATRIC CD

Comparative efficacy of anti-TNF agents for induction of remission in CD

Head-to-head trials, in which each drug or treatment strategy is compared formally, are the gold standard method for comparing distinct therapies[26]. However, there are currently no head-to-head trials of biologic agents in pediatric or adult CD. Owing to the absence of results, the choice of IFX or ADL relied on expert opinion, real-world data, or indirect comparison of biologic agents. Unfortunately, for pediatric patients with CD, there is a lack of accumulated data, which requires the extrapolation of adult data for the positioning of biologics in pediatric CD.

In 2018, the results of a network meta-analysis that indirectly compared the efficacy of FDA-approved biologic agents in the treatment of CD, which included IFX, ADL, vedolizumab, ustekinumab, and certolizumab pegol, were published[27,28]. When IFX and ADL were compared with respect to the efficacy of remission induction, IFX was ranked higher than ADL [surface under the cumulative ranking (SUCRA) 0.93 *vs* 0.75] for inducing clinical remission in biologic-naïve patients with moderate-to-severe CD. Additionally, IFX was predicted to be more effective in induction therapy than ADL; the rates of achieving clinical remission with induction therapy were 59.6% and 48.7% for IFX and ADL, respectively.

These findings are partly explained by differences in the pharmacokinetics or tissue penetration of IFX and ADL[29]. Drug levels of IFX and ADL show completely different patterns over time after administration. Intravenous (IV) formulations, such as IFX, show the highest concentrations with administration, and the concentrations gradually decrease over time, dropping to the lowest level just before the next administration, that is, to the TLs. In the case of subcutaneous (SC) formulations, including ADL, the concentrations at the time of administration, at the peak point, and at the lowest point are similar[30]. Because IFX has relatively large fluctuations in drug levels according to the drug infusion type, it is necessary to increase drug levels during the induction phase to maintain TLs,

whereas ADL maintains relatively constant drug concentrations.

Post-induction TLs, which can modulate inflammation in patients with high disease and inflammatory burdens, differ according to the type of anti-TNF agent used. In Figure 1A[31], we assumed the threshold of drug levels to control the inflammatory burden in the induction phase as the purple dotted line. IFX exhibits higher TLs than ADL during the induction phase, which is beneficial for maintaining post-induction TLs above the threshold required for treatment in patients with severe inflammation. Therefore, IFX might be more advantageous than ADL in patients with a high inflammatory burden owing to differences in the pharmacokinetics of the two anti-TNF agents during the induction period.

Specifically, a post-hoc analysis of the ACCENT-I study found that high IFX TLs after induction therapy were a key factor in maintaining response after one year of treatment[32]. The study revealed that more than 3.5 μg/mL of post-induction TLs of IFX was associated with a durable, sustained response to maintenance therapy. Feng *et al*[33] reported that post-induction TLs of IFX were correlated with endoscopic healing, and the median TLs in patients who achieved endoscopic healing after the induction of IFX were 7.5 μg/mL.

Similar to adult inflammatory bowel disease (IBD), higher post-induction IFX TLs were the only independent factor that predicted clinical or biochemical remission and durable sustained response during the first year of treatment in pediatric IBD[34]. Singh *et al*[35] reported that cut-off levels of > 3, > 4, > 7 μg/mL of IFX TLs had positive predictive values of 64%, 76%, and 100%, respectively, for predicting persistent remission in pediatric IBD. Recently, El-Matary *et al*[36] showed that higher post-induction IFX TLs had a strong relationship with the healing of the fistula in pediatric perianal CD. The post-induction IFX TLs in the clinical responder group were higher than those in the non-responder group (12.7 μg/mL *vs* 5.4 μg/mL, $P = 0.002$).

Likewise, post-induction TLs of ADL correlated with clinical and biochemical remission[37,38]. Zittan *et al*[37] reported that ADL TLs at week 4 were higher in the biological remission group than in the non-responder group of adult patients with CD (19.8 μg/mL *vs* 10.2 μg/mL, $P = 0.001$). After induction therapy, it was shown that similar to adult CD, there was a positive relationship between ADL TLs and clinical outcomes in pediatric CD[38]. The cut-off values of ADL TLs at weeks 4 and 8 to predict clinical and biological remission at week 24 were 22.5 μg/mL and 12.5 μg/mL, respectively.

Although the cut-off values of post-induction TLs for regulating the inflammatory burden at anti-TNF initiation are different for IFX and ADL, it is anticipated that the higher the post-induction TLs, the higher the clinical and endoscopic remission rate. Considering the pharmacokinetics of the route of administration, IFX can reach drug levels above the threshold in a shorter period of time than ADL and exhibits a rapid response of induction. Therefore, predictions based on the pharmacokinetics of anti-TNF agents and the difference in remission according to post-induction TLs show that IFX is more advantageous than ADL when the inflammatory burden is high.

Comparative efficacy of anti-TNF agents for maintenance of remission in CD

As with the selection of anti-TNF agents for the induction of remission, there are no head-to-head trials comparing the efficacy of maintenance therapy between IFX and ADL. According to a network meta-analysis study conducted in adults, ADL was superior to IFX in the maintenance phase, in contrast to the induction phase. In biologic-naïve adult patients with moderate-to-severe CD, the SUCRA of maintaining remission over one year was 0.97 and 0.68 for ADL and IFX, respectively[27,28].

These results can also be explained by the differences in the pharmacokinetics of IFX and ADL. For IV drugs, a clear distinction can be made among the peak, intermediate, and trough concentrations available for TDM. However, for SC drugs, there is no clear distinction among the peak, intermediate, and trough concentrations. In the case of SC drugs, the sampling time for TDM is less important because the TLs of SC drugs are kept relatively constant because not only is frequent administration required but also the absorption rate is relatively low[29].

Figure 1B shows the concentration changes in IFX and ADL during the maintenance phase, and the purple dotted line indicates the threshold for controlling the inflammatory burden during the maintenance phase[31]. The drug level of IFX tends to be lower than the threshold as it approaches the trough time, whereas the drug level of ADL is continuously maintained above the threshold because of the relatively constant levels of ADL. In the maintenance phase, it is important to keep the drug concentrations above the threshold to not only inhibit the formation of anti-drug antibodies (ADAs) but also to suppress the occurrence of loss of response and increase the durability of anti-TNF agents. Owing to the differences in the pharmacokinetics of the two anti-TNF agents, ADL might be more advantageous than IFX in the maintenance phase.

The association between IFX TLs in the maintenance phase and clinical outcomes has been demonstrated in many studies conducted on adults. One meta-analysis indicated that patients who achieved clinical remission had significantly higher IFX TLs than those who did not achieve remission during the maintenance phase (3.1 μg/mL *vs* 0.9 μg/mL)[39]. In addition, it has been shown in several studies that IFX TLs in the maintenance phase are an important prognostic factor in achieving endoscopic healing. Another study revealed that the only factor associated with endoscopic healing was an increase in IFX TLs > 0.5 μg/mL (likelihood ratio, 2.02; 95%CI: 1.01-4.08; $P = 0.048$) in patients with IBD[40]. Additionally, Yarur *et al*[41] demonstrated a correlation between IFX TLs and fistula healing [area under the curve (AUC), 0.82; $P < 0.0001$]. Likewise, higher maintenance IFX TLs were associated

with clinical and biochemical remission in pediatric patients with CD[42]. Recently, it has been reported that IFX TLs during maintenance treatment are important determinants of endoscopic healing as well as clinical remission in pediatric patients with CD. According to this study, IFX TLs to achieve endoscopic remission with 80% specificity were ≥ 5 μg/mL[43].

Similar to IFX, maintenance TLs of ADL were associated with clinical and laboratory responses in adult patients with CD[44]. The study showed that ADL TLs were associated with clinical remission (AUC, 0.748; $P < 0.001$), with an optimal cut-off value for predicting clinical remission of 5.85 μg/mL (sensitivity, 68%; specificity, 70.6%). In addition, Zittan *et al*[45] conducted a large, homogenous CD cohort study which revealed that patients with endoscopic healing have higher ADL TLs during the maintenance phase than those without endoscopic healing (14.7 μg/mL *vs* 3.4 μg/mL, $P < 0.001$). Similar results were found in studies conducted on pediatric patients with CD. The IMAgINE-1 study showed that patients with clinical remission at week 26 had slightly higher ADL TLs than those without remission (11.3 μg/mL *vs* 10.5 μg/mL, $P = 0.028$)[46]. Choi *et al*[47] reported that pediatric patients with endoscopic healing had significantly higher ADL TLs at week 16 than those without endoscopic healing (13.0 μg/mL *vs* 6.2 μg/mL, $P = 0.023$).

As can be inferred from the above studies, clinical remission and endoscopic healing can be achieved when the drug concentrations are sustained above the threshold despite the difference in the cut-off values for withstanding the inflammatory burden in the maintenance phase between IFX and ADL. Considering the pharmacokinetics of the maintenance phase, ADL maintains drug levels more constantly than IFX; therefore, it is expected that ADL is more advantageous in sustaining remission than IFX in the maintenance phase.

IMMUNOGENICITY OF ANTI-TNF AGENTS

Although anti-TNF agents are effective in patients with CD refractory to conventional therapy, loss of response increases over time, and approximately, half of patients among primary responders require dose escalation[48]. Among patients receiving anti-TNF agents, 60%-87% of patients show clinical remission or partial response in the induction phase, and less than 40% of patients maintain clinical remission at one year[49]. Immunogenicity due to the formation of ADAs to anti-TNF agents as the main reason for the loss of response.

Immunogenicity to anti-TNF agents develops when the immune system of patients recognises drugs as antigens and triggers the formation of ADAs. ADAs accelerate drug clearance by the reticuloendothelial system and neutralise drugs by binding to anti-TNF agents[50]. Additionally, suboptimal TLs of anti-TNF agents are associated with a more immunogenic state, which leads to lower efficacy and greater loss of response[37,51,52]. Higher body weight, the development of ADAs to anti-TNF agents, a low albumin level, and an elevated C-reactive protein level are the covariates that accelerate the clearance of anti-TNF agents[53-56].

Vermeire *et al*[57] reported that the rate of ADA formation in IBD patients receiving IFX was up to 65.3% and that in patients receiving ADL was 38.0%. Theoretically, as ADL is a humanised monoclonal antibody, it is thought that the incidence of immunogenicity in the human body is lower than that for IFX, which is a monoclonal chimeric anti-TNF antibody (partly murine, partly human). Therefore, ADL was superior to IFX in terms of immunogenicity.

ANTI-TNF AGENTS FOR GROWTH IMPROVEMENT

In Selecting Therapeutic Targets in IBD-II, restoration of normal growth was established as an intermediate target for pediatric patients[58]. Therefore, a very important goal in treatment for pediatric patients with CD is to normalise the linear growth.

To date, no study has compared the effects of IFX and ADL on the restoration of linear growth. Studies have shown that each of the two anti-TNF agents has a positive effect on the recovery of normal growth. In the case of IFX, there is a study published on the restoration of growth as well as clinical response and endoscopic healing in 195 pediatric patients with CD[59]. The effect on the recovery of linear growth was greater when IFX was administered at the Tanner 1-2 stage with growth potential than at the Tanner 4-5 stage. Another study showed that early administration of IFX within one month after diagnosis was more effective for linear growth than the conventional step-up therapy ($P = 0.026$) [60]. For Tanner stage 4-5 patients receiving IFX, there was no statistically significant difference in height z-score between patients with early IFX administration and those with the conventional step-up therapy ($P = 0.438$). However, in patients with Tanner 1-2, the restoration of growth was significantly improved in patients with early IFX administration ($P = 0.016$).

Similarly, it was reported that ADL was effective in restoring linear growth at weeks 26 and 52 compared with baseline in patients with growth impairment at diagnosis (median height z-score, baseline, -3.25; 26 wk, -0.34; 52 wk, 0.21, $P < 0.001$)[61]. Additionally, Matar *et al*[62] showed that ADL improves weight as body mass index as well as linear growth after 72 wk of treatment.

SAFETY AND ADVERSE EVENTS DURING ANTI-TNF THERAPY

From an immunological point of view, as TNFα is a cytokine responsible for macrophage activation, neutrophil recruitment, and granuloma formation, anti-TNF agents are associated with an increased risk of infection, especially granulomatous infection[63]. Dulai *et al*[64] reported that the rate of serious infectious disease in pediatric patients with IBD who were treated with anti-TNF agents was similar to that of pediatric patients who received IMMs [352/10000 *vs* 33/10000 patient-years of follow-up evaluation (PYF); 95%CI: 0.83-1.36] but significantly lower than that of adult patients (654/10000 PYF; 95%CI: 0.43-0.67). In addition, the risk of infection is higher when anti-TNF agents are administered in combination with IMMs than with anti-TNF monotherapy (RR, 1.19; 95%CI: 1.03-1.37)[65]. According to a network meta-analysis of adult studies that indirectly compared IFX and ADL, IFX had a lower risk of any infection (SUCRA, 0.83) than ADL (SUCRA, 0.22)[27].

Previous studies have shown the risk of malignancy and lymphoproliferative disorders with IBD treatment, particularly with thiopurine and anti-TNF agents. Based on a meta-analysis of 49 randomised placebo-controlled studies comprising 14590 adult patients, there was no evidence related to an increased risk of malignancy with the use of biologic agents including IFX or ADL (odds ratio, 0.90; 95%CI: 0.54-1.50)[66]. Studies with pediatric patients also showed similar results to those of adult studies. In a study conducted using the DEVELOP registry including 5776 pediatric patients with IBD treated with anti-TNF agents, malignancy occurred in 15 patients[67]. An increased risk of malignancy was found in patients treated with thiopurine when a stratified analysis of thiopurine exposure was performed regardless of biologic agents. Even though the standardised incidence of malignancy for thiopurine exposure was 2.43 when compared to the prevalence in healthy children, no significant increase in the incidence of malignancy was observed in children who were only exposed to IFX.

Recent studies showed that the most common complications in patients with IBD treated with anti-TNF agents were dermatologic complications such as psoriasis, eczema, and skin infection[68]. Similarly, the frequency of skin problems appears to be high in pediatric patients with CD on anti-TNF. When comparing patients treated with IFX and ADL, the rate was much higher in IFX-treated patients than in ADL-treated patients. In a pediatric retrospective, large cohort study comprising 409 patients, 11.5% of patients showed at least one dermatologic complication. Among them, 35 were treated with IFX and 12 with ADL. In particular, among patients who developed psoriasis, the proportion of patients treated with IFX was significantly higher than that of those treated with ADL (84.8% *vs* 15.2%, $P = 0.05$) [69]. Additionally, Hradsky *et al*[70] reported that the only predictive factor for any dermatologic complication in pediatric CD was IFX therapy (*vs* ADL, hazard ratio, 2.07; 95%CI: 1.03-4.17).

EFFECTS OF CONCOMITANT IMM TREATMENT

For patients starting on IFX, combination therapy with IMM including azathioprine (AZA) and methotrexate (MTX) is recommended. As the first RCTs regarding the comparison of combination therapy of IFX and AZA with monotherapy of IFX or AZA, the SONIC trials showed the superiority of combination therapy to monotherapy regarding clinical remission, endoscopic healing, pharmacokinetics, and immunogenicity in adult patients with CD[71]. At week 30, ADAs developed in only 0.9% of patients receiving combination therapy, whereas these were produced in 14.6% of patients receiving IFX monotherapy, leading to higher IFX TLs in the combination therapy group than in the IFX monotherapy group (3.5 μg/mL *vs* 1.6 μg/mL, $P < 0.001$). Additionally, the combination therapy group was more likely than the IFX or AZA monotherapy group to achieve corticosteroid-free clinical remission and endoscopic healing. Likewise, it was revealed that the combination of IFX plus MTX had a lower ADA development (4% *vs* 20%, $P = 0.01$) and higher IFX TLs (6.35 μg/mL *vs* 3.75 μg/mL, $P = 0.08$) than IFX monotherapy in the COMMIT trial conducted in adult[72].

No RCT has compared the effects of combination therapy with IFX and IMM and IFX monotherapy in pediatric CD. A retrospective study conducted on 229 pediatric patients with CD confirmed that combination therapy with IFX and AZA reduced the formation of ADAs and loss of response compared to IFX monotherapy[73]. Moreover, pediatric patients who were treated with IFX monotherapy had a lower probability of remaining ADA than patients with combination therapy at 12, 24, and 36 mo after induction of IFX (72.6% *vs* 93.4%, 57.7% *vs* 91.0%, and 48.1% *vs* 91.0%, respectively). Similarly, pediatric studies comparing combination of IFX plus IMM (including AZA and MTX) and IFX monotherapy reported results similar to those in adult studies[59,74,75]. Therefore, up-front anti-TNF agents in combination with IMMs should be considered in patients with high risk of poor outcomes such as perianal disease, structuring (B2) or penetrating (B3) disease behaviour or severe growth impairment.

A meta-analysis comparing the efficacy of combination therapy of ADL and IMMs and ADL monotherapy in adult CD revealed that the induction of remission rate of ADL monotherapy was lower than that of combination therapy with IMMs, although the maintenance of remission was comparable [76]. In contrast to the results of studies on adults, a post-hoc analysis of the IMAgINE-1 study found that combination therapy of ADL and IMMs is not superior to ADL monotherapy in terms of pharmacokinetics, efficacy, and safety in pediatric patients with CD[77]. Clinical response and remission rates

were comparable in patients treated with combination therapy and ADL monotherapy at weeks 4, 26, and 52. Regarding pharmacokinetics, there were no significant differences in the mean TLs between the two groups. These results are in line with the findings of other studies showing that combination therapy with ADL and IMMs was not more effective than ADL monotherapy in pediatric CD[48,78].

Therefore, the recently updated ESPGHAN guidelines for the medical treatment of CD in children and adolescents recommend combination therapy with IFX and IMMs, whereas ADL monotherapy can be an alternative to combination therapy with IMMs[20].

PREFERENCES OF PATIENTS AND PARENTS

There are several differences between IFX and ADL. However, the primary difference is the mode of administration. The IV delivery of biotherapeutics has the advantage of being able to elicit a relatively rapid induction of response and is suitable for administering a large volume of drugs. On the other hand, SC formulations have the advantage of requiring fewer frequent visits to the clinic and being less invasive than IV administration[79]. Because of these differences in the route of administration, not only the efficacy of anti-TNF agents but also the preference of patients and caregivers for the delivery of drugs should be considered.

In a study conducted on rheumatoid arthritis patients treated with anti-TNF agents, patients under the age of 61 years showed a tendency to prefer SC preparations to IV preparations owing to the convenience of administration[80]. Similarly, a study conducted on adult patients with CD in Switzerland also showed the same results. The patient's choice of a specific anti-TNF agent was influenced by the convenience of use (69%), time required for treatment (34%), frequency of drug administration (31%), scientific evidence for efficacy (19%), and fear of syringes (10%). For these reasons, most patients prefer SC rather than IV injection when choosing anti-TNF agents[81].

However, a recent study conducted on anti-TNF selection in Korea reported the opposite result. Among 189 anti-TNF naïve patients with CD, 63.5% of patients preferred IFX, and 36.5% of patients preferred ADL[82]. In contrast to Western studies, the reason for choosing the IV route of administration over the SC route was the reassurance from the presence of doctors (68.3%).

The differences in results of these studies seem to show differences between Western and Eastern countries in terms of culture and medical environments. Unlike Western countries, Asia has a cultural context in which patients have relative interdependence in the decision-making process during treatment[83]. Therefore, characteristics, daily life, preferences, and cultural differences between patients and caregivers should be considered when selecting biologic agents for the treatment of pediatric patients with CD. Clinicians should discuss the route of administration of biologic agents with patients and their caregivers before prescribing anti-TNF therapy.

ADHERENCE TO ANTI-TNF AGENTS

Low compliance and delayed administration of anti-TNF agents are highly related to the formation of ADAs, which can lead to adverse events and loss of response due to low TLs[84,85]. In the treatment of patients with CD, adherence to anti-TNF agents plays an important role in improving treatment efficacy and patient outcomes. The rate of adherence to anti-TNF agents is known to be approximately 70% in patients with CD[86]. When the adherence rates of IFX and ADL were compared, the adherence rate of IFX was 66%-85%, and that of ADL was 55[87-89], with an RR of 0.76 (95%CI: 0.64-0.91)[86].

The difference in adherence between IFX and ADL is thought to be caused by the route of administration, intervals of injection, and supervision of clinicians during the injection. Adherence could be controlled in favour of IFX because the administration of IV drugs requires patient visits to an outpatient clinic.

However, special circumstances, such as coronavirus disease 2019 (COVID-19), may lead to different results. In 2020, the Pediatric IBD Porto Group of ESPGHAN published a society paper[90]. While investigating and reporting the experience of pediatric IBD management during the COVID-19 situation in China and South Korea, it has been recommended that standard treatment be not stopped or delayed. During the COVID-19 pandemic period, anti-TNF infusion delays were reported in 28% of cases in China and 5% in Korea, and exacerbation of disease among delayers was reported in 21% and 23%, respectively. The difference in infusion delay between the two countries may have been contributed to some extent by social factors such as social distancing or lockdown. However, it can be assumed that the main reason is that self-injectable ADL is not available in China, and only IFX, which requires an outpatient visit and IV infusion, can be administered. Therefore, when contagious diseases such as COVID-19 are spreading, ADL might have an advantage in terms of adherence to IFX.

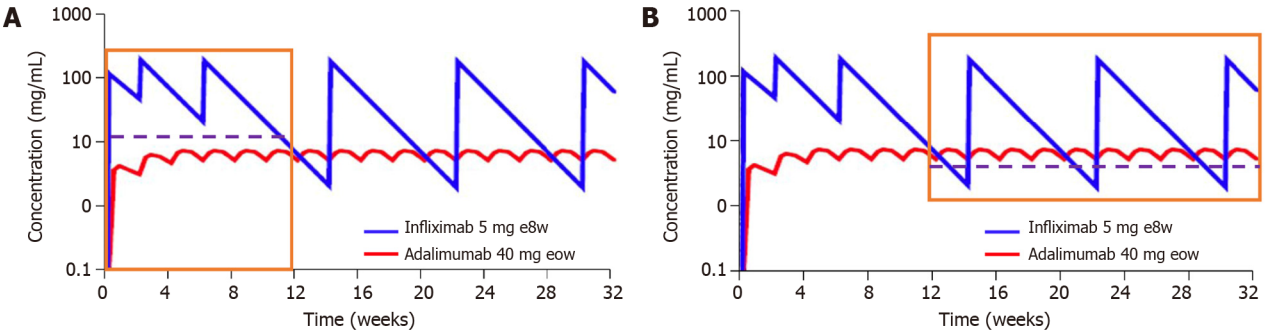
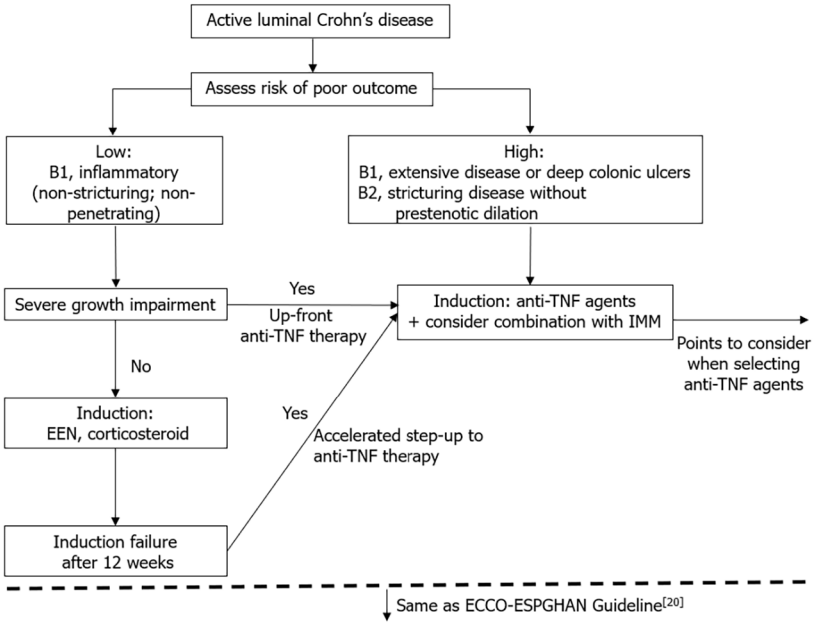


Figure 1 The pharmacokinetic profile of an intravenously or subcutaneously administered anti-tumor necrosis factor agent. A: According to a theoretical induction dosing regimen; B: According to a theoretical maintenance dosing regimen. TNF: tumor necrosis factor. Citation: Gibson DJ, Ward MG, Rentsch C, Friedman AB, Taylor KM, Sparrow MP, Gibson PR. Review article: determination of the therapeutic range for therapeutic drug monitoring of adalimumab and infliximab in patients with inflammatory bowel disease. *Aliment Pharmacol Ther* 2020; 51: 612-628. Copyright ©John Wiley & Sons Ltd. 2020. Published by John Wiley & Sons[31].



Factors	Infliximab	Adalimumab
Inflammatory burden	Superior	Inferior
Rapid response to induction	Superior	Inferior
Any infection	Superior	Inferior
Adherence	Superior	Inferior
Growth improvement	Equivalent	Equivalent
Malignancy	Equivalent	Equivalent
Sustaining remission in maintenance phase	Inferior	Superior
Immunogenicity	Inferior	Superior
Dermatologic complications	Inferior	Superior
Preference	Depend on culture and medical environment	

Figure 2 Summary flowchart of medical management of pediatric luminal Crohn's disease and points to consider when selecting anti-tumor necrosis factor agents. TNF: Tumor necrosis factor; EEN: Exclusive enteral nutrition; IMM: Immunomodulators. Citation: van Rheenen PF, Aloi M, Assa A, Bronsky J, Escher JC, Fagerberg UL, Gasparetto M, Gerasimidis K, Griffiths A, Henderson P, Koletzko S, Kolho KL, Levine A, van Limbergen J, Martin de Carpi FJ, Navas-López VM, Oliva S, de Ridder L, Russell RK, Shouval D, Spinelli A, Turner D, Wilson D, Wine E, Ruemmele FM. The Medical Management of Paediatric Crohn's Disease: an ECCO-ESPGHAN Guideline Update. *J Crohns Colitis* 2020. Copyright ©Oxford University Press 2020. Published by Oxford University Press[20].

CONCLUSION

Anti-TNF agents have proven to be effective in endoscopic, clinical, and biochemical remission in pediatric patients with moderate-to-severe CD. However, careful anti-TNF therapy is required because of the limitations of biologics approved for pediatric patients. Careful evaluation of clinical indications and disease behavior is essential when prescribing anti-TNF agents. In addition, factors such as the efficacy of induction and maintenance of remission, safety profile, immunogenicity, patient preference, and compliance play an important role in evaluating and selecting treatment options (Figure 2)[20]. Larger cohorts and clinical trials comparing groups based on risk stratification are needed to provide more effective and personalised treatment strategies for pediatric patients.

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FOOTNOTES

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REFERENCES

1 **Ng SC**, Shi HY, Hamidi N, Underwood FE, Tang W, Benchimol EI, Panaccione R, Ghosh S, Wu JCY, Chan FKL, Sung JJY, Kaplan GG. Worldwide incidence and prevalence of inflammatory bowel disease in the 21st century: a systematic review of population-based studies. *Lancet* 2017; **390**: 2769-2778 [PMID: 29050646 DOI: 10.1016/S0140-6736(17)32448-0]

2 **Benchimol EI**, Fortinsky KJ, Gozdyra P, Van den Heuvel M, Van Limbergen J, Griffiths AM. Epidemiology of pediatric inflammatory bowel disease: a systematic review of international trends. *Inflamm Bowel Dis* 2011; **17**: 423-439 [PMID: 20564651 DOI: 10.1002/ibd.21349]

3 **Sýkora J**, Pomahačová R, Kreslová M, Cvalínová D, Štych P, Schwarz J. Current global trends in the incidence of pediatric-onset inflammatory bowel disease. *World J Gastroenterol* 2018; **24**: 2741-2763 [PMID: 29991879 DOI: 10.3748/wjg.v24.i25.2741]

4 **Rosen MJ**, Dhawan A, Saeed SA. Inflammatory Bowel Disease in Children and Adolescents. *JAMA Pediatr* 2015; **169**: 1053-1060 [PMID: 26414706 DOI: 10.1001/jamapediatrics.2015.1982]

5 US Department of Health & Human Services. Drugs @ FDA-label and approval history. In: Food and Drug Administration. [cited 2022 December 28]. Available from: http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.Label_ApprovalHistory#apphis/

6 **Allen PB**, Bonovas S, Danese S, Peyrin-Biroulet L. Evolving primary and secondary endpoints in randomized controlled trials leading to approval of biologics and small molecules in IBD: an historical perspective. *Expert Opin Biol Ther* 2020; **20**: 151-161 [PMID: 31815548 DOI: 10.1080/14712598.2020.1702020]

7 **Nielsen OH**, Ainsworth MA. Tumor necrosis factor inhibitors for inflammatory bowel disease. *N Engl J Med* 2013; **369**: 754-762 [PMID: 23964937 DOI: 10.1056/NEJMct1209614]

8 **Kornbluth A**. Infliximab approved for use in Crohn's disease: a report on the FDA GI Advisory Committee conference. *Inflamm Bowel Dis* 1998; **4**: 328-329 [PMID: 9836088 DOI: 10.1002/ibd.3780040415]

9 **Baker DE**. Adalimumab: human recombinant immunoglobulin g1 anti-tumor necrosis factor monoclonal antibody. *Rev Gastroenterol Disord* 2004; **4**: 196-210 [PMID: 15580154]

10 **Ruemmele FM**, Veres G, Kolho KL, Griffiths A, Levine A, Escher JC, Amil Dias J, Barabino A, Braegger CP, Bronsky J, Buderus S, Martín-de-Carpi J, De Ridder L, Fagerberg UL, Hugot JP, Kierkus J, Kolacek S, Koletzko S, Lionetti P, Miele E, Navas López VM, Paerregaard A, Russell RK, Serban DE, Shaoul R, Van Rheenen P, Veereman G, Weiss B, Wilson D, Dignass A, Eliakim A, Winter H, Turner D; European Crohn's and Colitis Organisation; European Society of Pediatric Gastroenterology, Hepatology and Nutrition. Consensus guidelines of ECCO/ESPGHAN on the medical management of pediatric Crohn's disease. *J Crohns Colitis* 2014; **8**: 1179-1207 [PMID: 24909831 DOI: 10.1016/j.crohns.2014.04.005]

11 **Mack DR**, Benchimol EI, Critch J, deBruyn J, Tse F, Moayyedi P, Church P, Deslandres C, El-Matary W, Huynh H, Jantchou P, Lawrence S, Otley A, Sherlock M, Walters T, Kappelman MD, Sadowski D, Marshall JK, Griffiths A. Canadian Association of Gastroenterology Clinical Practice Guideline for the Medical Management of Pediatric Luminal Crohn's Disease. *Gastroenterology* 2019; **157**: 320-348 [PMID: 31320109 DOI: 10.1053/j.gastro.2019.03.022]

12 **Cholapranee A**, Hazlewood GS, Kaplan GG, Peyrin-Biroulet L, Ananthakrishnan AN. Systematic review with meta-analysis: comparative efficacy of biologics for induction and maintenance of mucosal healing in Crohn's disease and ulcerative colitis controlled trials. *Aliment Pharmacol Ther* 2017; **45**: 1291-1302 [PMID: 28326566 DOI: 10.1111/apt.14030]

13 **Hazlewood GS**, Rezaie A, Borman M, Panaccione R, Ghosh S, Seow CH, Kuenzig E, Tomlinson G, Siegel CA, Melmed GY, Kaplan GG. Comparative effectiveness of immunosuppressants and biologics for inducing and maintaining remission in Crohn's disease: a network meta-analysis. *Gastroenterology* 2015; **148**: 344-54.e5; quiz e14 [PMID: 25448924 DOI: 10.1053/j.gastro.2014.10.011]

14 **Targan SR**, Hanauer SB, van Deventer SJ, Mayer L, Present DH, Braakman T, DeWoody KL, Schaible TF, Rutgeerts PJ. A short-term study of chimeric monoclonal antibody cA2 to tumor necrosis factor alpha for Crohn's disease. Crohn's Disease cA2 Study Group. *N Engl J Med* 1997; **337**: 1029-1035 [PMID: 9321530 DOI: 10.1056/NEJM199710093371502]

15 **Hanauer SB**, Feagan BG, Lichtenstein GR, Mayer LF, Schreiber S, Colombel JF, Rachmilewitz D, Wolf DC, Olson A, Bao W, Rutgeerts P; ACCENT I Study Group. Maintenance infliximab for Crohn's disease: the ACCENT I randomised trial. *Lancet* 2002; **359**: 1541-1549 [PMID: 12047962 DOI: 10.1016/S0140-6736(02)08512-4]

16 **Hyams J**, Crandall W, Kugathasan S, Griffiths A, Olson A, Johanns J, Liu G, Travers S, Heuschkel R, Markowitz J, Cohen S, Winter H, Veereman-Wauters G, Ferry G, Baldassano R; REACH Study Group. Induction and maintenance infliximab therapy for the treatment of moderate-to-severe Crohn's disease in children. *Gastroenterology* 2007; **132**: 863-73; quiz 1165 [PMID: 17324398 DOI: 10.1053/j.gastro.2006.12.003]

17 **Ruemmele FM**, Lachaux A, Cézard JP, Morali A, Maurage C, Giniès JL, Viola S, Goulet O, Lamireau T, Scaillon M, Breton A, Sarles J; Groupe Francophone d'Hépatologie, Gastroentérologie et Nutrition Pédiatrique. Efficacy of infliximab in pediatric Crohn's disease: a randomized multicenter open-label trial comparing scheduled to on demand maintenance therapy. *Inflamm Bowel Dis* 2009; **15**: 388-394 [PMID: 19023899 DOI: 10.1002/ibd.20788]

18 **Hyams JS**, Griffiths A, Markowitz J, Baldassano RN, Faubion WA Jr, Colletti RB, Dubinsky M, Kierkus J, Rosh J, Wang Y, Huang B, Bittle B, Marshall M, Lazar A. Safety and efficacy of adalimumab for moderate to severe Crohn's disease in children. *Gastroenterology* 2012; **143**: 365-74.e2 [PMID: 22562021 DOI: 10.1053/j.gastro.2012.04.046]

19 **Assa A**, Matar M, Turner D, Broide E, Weiss B, Ledder O, Guz-Mark A, Rinawi F, Cohen S, Topf-Olivestone C, Shaoul R, Yerushalmi B, Shamir R. 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 [PMID: 31194979 DOI: 10.1053/j.gastro.2019.06.003]

20 **van Rheenen PF**, Aloi M, Assa A, Bronsky J, Escher JC, Fagerberg UL, Gasparetto M, Gerasimidis K, Griffiths A, Henderson P, Koletzko S, Kolho KL, Levine A, van Limbergen J, Martin de Carpi FJ, Navas-López VM, Oliva S, de Ridder L, Russell RK, Shouval D, Spinelli A, Turner D, Wilson D, Wine E, Ruemmele FM. The Medical Management of Paediatric Crohn's Disease: an ECCO-ESPGHAN Guideline Update. *J Crohns Colitis* 2020 [PMID: 33026087 DOI: 10.1093/ecco-jcc/jjaa161]

21 **Walters TD**, Kim MO, Denson LA, Griffiths AM, Dubinsky M, Markowitz J, Baldassano R, Crandall W, Rosh J, Pfefferkorn M, Otley A, Heyman MB, LeLeiko N, Baker S, Guthery SL, Evans J, Ziring D, Kellermayer R, Stephens M, Mack D, Oliva-Hemker M, Patel AS, Kirschner B, Moulton D, Cohen S, Kim S, Liu C, Essers J, Kugathasan S, Hyams JS; PRO-KIIDS Research Group. 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 [PMID: 24162032 DOI: 10.1053/j.gastro.2013.10.027]

22 **Kugathasan S**, Denson LA, Walters TD, Kim MO, Marigorta UM, Schirmer M, Mondal K, Liu C, Griffiths A, Noe JD, Crandall WV, Snapper S, Rabizadeh S, Rosh JR, Shapiro JM, Guthery S, Mack DR, Kellermayer R, Kappelman MD, Steiner S, Moulton DE, Keljo D, Cohen S, Oliva-Hemker M, Heyman MB, Otley AR, Baker SS, Evans JS, Kirschner BS, Patel AS, Ziring D, Trapnell BC, Sylvester FA, Stephens MC, Baldassano RN, Markowitz JF, Cho J, Xavier RJ, Huttenhower C, Aronow BJ, Gibson G, Hyams JS, Dubinsky MC. Prediction of complicated disease course for children newly diagnosed with Crohn's disease: a multicentre inception cohort study. *Lancet* 2017; **389**: 1710-1718 [PMID: 28259484 DOI: 10.1016/S0140-6736(17)30317-3]

23 **Kang B**, Choi SY, Kim HS, Kim K, Lee YM, Choe YH. Mucosal Healing in Paediatric Patients with Moderate-to-Severe Luminal Crohn's Disease Under Combined Immunosuppression: Escalation versus Early Treatment. *J Crohns Colitis* 2016; **10**: 1279-1286 [PMID: 27095752 DOI: 10.1093/ecco-jcc/jjw086]

24 **Kang B**, Choe YH. Early Biologic Treatment in Pediatric Crohn's Disease: Catching the Therapeutic Window of Opportunity in Early Disease by Treat-to-Target. *Pediatr Gastroenterol Hepatol Nutr* 2018; **21**: 1-11 [PMID: 29383299 DOI: 10.5223/pghn.2018.21.1.1]

25 **Clarkston K**, Tsai YT, Jackson K, Rosen MJ, Denson LA, Minar P. Development of Infliximab Target Concentrations During Induction in Pediatric Crohn Disease Patients. *J Pediatr Gastroenterol Nutr* 2019; **69**: 68-74 [PMID: 31232885 DOI: 10.1097/MPG.0000000000002304]

26 **Armstrong K**. Methods in comparative effectiveness research. *J Clin Oncol* 2012; **30**: 4208-4214 [PMID: 23071240 DOI: 10.1200/JCO.2012.42.2659]

27 **Singh S**, Fumery M, Sandborn WJ, Murad MH. Systematic review and network meta-analysis: first- and second-line biologic therapies for moderate-severe Crohn's disease. *Aliment Pharmacol Ther* 2018; **48**: 394-409 [PMID: 29920733 DOI: 10.1111/apt.14852]

28 **Singh S**. Network meta-analysis to inform positioning of biologics in patients with Crohn's disease: Promise and perils. *Best Pract Res Clin Gastroenterol* 2019; **38-39**: 101614 [PMID: 31327401 DOI: 10.1016/j.bpg.2019.05.001]

29 **Nestorov I**. Clinical pharmacokinetics of tumor necrosis factor antagonists. *J Rheumatol Suppl* 2005; **74**: 13-18 [PMID: 15742459]

30 **Vande Casteele N**, Gils A. Pharmacokinetics of anti-TNF monoclonal antibodies in inflammatory bowel disease: Adding value to current practice. *J Clin Pharmacol* 2015; **55** Suppl 3: S39-S50 [PMID: 25707962 DOI: 10.1002/jcph.374]

31 **Gibson DJ**, Ward MG, Rentsch C, Friedman AB, Taylor KM, Sparrow MP, Gibson PR. Review article: determination of the therapeutic range for therapeutic drug monitoring of adalimumab and infliximab in patients with inflammatory bowel disease. *Aliment Pharmacol Ther* 2020; **51**: 612-628 [PMID: 31961001 DOI: 10.1111/apt.15643]

32 **Cornillie F**, Hanauer SB, Diamond RH, Wang J, Tang KL, 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 [PMID: 24474383 DOI: 10.1136/gutjnl-2012-304094]

33 **Feng T**, Chen B, Ungar B, Qiu Y, Zhang S, He J, Lin S, He Y, Zeng Z, Ben-Horin S, Chen M, Mao R. Association of Infliximab Levels With Mucosal Healing Is Time-Dependent in Crohn's Disease: Higher Drug Exposure Is Required

Postinduction Than During Maintenance Treatment. *Inflamm Bowel Dis* 2019; **25**: 1813-1821 [PMID: 30934050 DOI: 10.1093/ibd/izz061]

34 **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 [PMID: 30633108 DOI: 10.1097/MPG.0000000000002265]

35 **Singh N**, Rosenthal CJ, Melmed GY, Mirocha J, Farrior S, Callejas S, Tripuraneni B, Rabizadeh S, Dubinsky MC. Early infliximab trough levels are associated with persistent remission in pediatric patients with inflammatory bowel disease. *Inflamm Bowel Dis* 2014; **20**: 1708-1713 [PMID: 25153505 DOI: 10.1097/MIB.0000000000000137]

36 **El-Matary W**, Walters TD, Huynh HQ, deBruyn J, Mack DR, Jacobson K, Sherlock ME, Church P, Wine E, Carroll MW, Benchimol EI, Lawrence S, Griffiths AM. Higher Postinduction Infliximab Serum Trough Levels Are Associated With Healing of Fistulizing Perianal Crohn's Disease in Children. *Inflamm Bowel Dis* 2019; **25**: 150-155 [PMID: 29912413 DOI: 10.1093/ibd/izy217]

37 **Zittan E**, Steinhart AH, Goldstein P, Milgrom R, Gralnek IM, Silverberg MS. Post-Induction High Adalimumab Drug Levels Predict Biological Remission at Week 24 in Patients With Crohn's Disease. *Clin Transl Gastroenterol* 2021; **12**: e00401 [PMID: 34613952 DOI: 10.14309/ctg.0000000000000401]

38 **Rinawi F**, Ricciuto A, Church PC, Frost K, Crowley E, Walters TD, Griffiths AM. Association of Early Postinduction Adalimumab Exposure With Subsequent Clinical and Biomarker Remission in Children with Crohn's Disease. *Inflamm Bowel Dis* 2021; **27**: 1079-1087 [PMID: 32978946 DOI: 10.1093/ibd/izaa247]

39 **Moore C**, Corbett G, Moss AC. Systematic Review and Meta-Analysis: Serum Infliximab Levels During Maintenance Therapy and Outcomes in Inflammatory Bowel Disease. *J Crohns Colitis* 2016; **10**: 619-625 [PMID: 26763722 DOI: 10.1093/ecco-jcc/jjw007]

40 **Paul S**, Del Tedesco E, Marotte H, Rinaudo-Gaujous M, Moreau A, Phelip JM, Genin C, Peyrin-Biroulet L, Roblin X. Therapeutic drug monitoring of infliximab and mucosal healing in inflammatory bowel disease: a prospective study. *Inflamm Bowel Dis* 2013; **19**: 2568-2576 [PMID: 24013361 DOI: 10.1097/MIB.0b013e3182a77b41]

41 **Yarur AJ**, Kanagala V, Stein DJ, Czul F, Quintero MA, Agrawal D, Patel A, Best K, Fox C, Idstein K, Abreu MT. Higher infliximab trough levels are associated with perianal fistula healing in patients with Crohn's disease. *Aliment Pharmacol Ther* 2017; **45**: 933-940 [PMID: 28211593 DOI: 10.1111/apt.13970]

42 **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**: 541-548 [PMID: 30970435 DOI: 10.5009/gnl18129]

43 **Kang B**, Choi SY, Choi YO, Lee SY, Baek SY, Sohn I, Choe BH, Lee HJ, Choe YH. Infliximab Trough Levels Are Associated With Mucosal Healing During Maintenance Treatment With Infliximab in Paediatric Crohn's Disease. *J Crohns Colitis* 2019; **13**: 189-197 [PMID: 30452616 DOI: 10.1093/ecco-jcc/jjy155]

44 **Mazor Y**, Almog R, Kopylov U, Ben Hur D, Blatt A, Dahan A, Waterman M, Ben-Horin S, Chowers Y. Adalimumab drug and antibody levels as predictors of clinical and laboratory response in patients with Crohn's disease. *Aliment Pharmacol Ther* 2014; **40**: 620-628 [PMID: 25039584 DOI: 10.1111/apt.12869]

45 **Zittan E**, Kabakchiev B, Milgrom R, Nguyen GC, Croitoru K, Steinhart AH, Silverberg MS. Higher Adalimumab Drug Levels are Associated with Mucosal Healing in Patients with Crohn's Disease. *J Crohns Colitis* 2016; **10**: 510-515 [PMID: 26783345 DOI: 10.1093/ecco-jcc/jjw014]

46 **Sharma S**, Eckert D, Hyams JS, Mensing S, Thakkar RB, Robinson AM, Rosh JR, Ruemmele FM, Awni WM. 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 [PMID: 25723614 DOI: 10.1097/MIB.0000000000000327]

47 **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 [PMID: 32329259 DOI: 10.3346/jkms.2020.35.e114]

48 **De Bie CI**, Hummel TZ, Kindermann A, Kokke FT, Damen GM, Kneepkens CM, Van Rheenen PF, Schweizer JJ, Hoekstra JH, Norbruis OF, Tjon A Ten WE, Vreugdenhil AC, Deckers-Kocken JM, Gijsbers CF, Escher JC, De Ridder L. The duration of effect of infliximab maintenance treatment in paediatric Crohn's disease is limited. *Aliment Pharmacol Ther* 2011; **33**: 243-250 [PMID: 21083595 DOI: 10.1111/j.1365-2036.2010.04507.x]

49 **Ding NS**, 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 [PMID: 26515897 DOI: 10.1111/apt.13445]

50 **Moss AC**, Brinks V, Carpenter JF. Review article: immunogenicity of anti-TNF biologics in IBD - the role of patient, product and prescriber factors. *Aliment Pharmacol Ther* 2013; **38**: 1188-1197 [PMID: 24118102 DOI: 10.1111/apt.12507]

51 **Vermeire S**, Noman M, Van Assche G, Baert F, D'Haens G, Rutgeerts P. Effectiveness of concomitant immunosuppressive therapy in suppressing the formation of antibodies to infliximab in Crohn's disease. *Gut* 2007; **56**: 1226-1231 [PMID: 17229796 DOI: 10.1136/gut.2006.099978]

52 **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 Disease. *Gut Liver* 2021; **15**: 588-598 [PMID: 33024062 DOI: 10.5009/gnl20134]

53 **Brandse JF**, Mould D, Smeekes O, Ashruf Y, Kuin S, Strik A, van den Brink GR, D'Haens GR. A Real-life Population Pharmacokinetic Study Reveals Factors Associated with Clearance and Immunogenicity of Infliximab in Inflammatory Bowel Disease. *Inflamm Bowel Dis* 2017; **23**: 650-660 [PMID: 28195852 DOI: 10.1097/MIB.0000000000001043]

54 **Fasanmade AA**, Adedokun OJ, Blank M, Zhou H, Davis HM. Pharmacokinetic properties of infliximab in children and adults with Crohn's disease: a retrospective analysis of data from 2 phase III clinical trials. *Clin Ther* 2011; **33**: 946-964 [PMID: 21741088 DOI: 10.1016/j.clinthera.2011.06.002]

55 **Ternant D**, Aubourg A, Magdelaine-Beuzelin C, Degenne D, Watier H, Picon L, Paintaud G. Infliximab pharmacokinetics in inflammatory bowel disease patients. *Ther Drug Monit* 2008; **30**: 523-529 [PMID: 18641542 DOI: 10.1097/FTD.0b013e318180e300]

56 **Dotan I**, Ron Y, Yanai H, Becker S, Fishman S, Yahav L, Ben Yehoyada M, Mould DR. Patient factors that increase infliximab clearance and shorten half-life in inflammatory bowel disease: a population pharmacokinetic study. *Inflamm Bowel Dis* 2014; **20**: 2247-2259 [PMID: 25358062 DOI: 10.1097/MIB.0000000000000212]

57 **Vermeire S**, Gils A, Accossato P, Lula S, Marren A. Immunogenicity of biologics in inflammatory bowel disease. *Therap Adv Gastroenterol* 2018; **11**: 1756283X17750355 [PMID: 29383030 DOI: 10.1177/1756283X17750355]

58 **Turner D**, Ricciuto A, Lewis A, D'Amico F, Dhaliwal J, Griffiths AM, Bettenworth D, Sandborn WJ, Sands BE, Reinisch W, Schölmerich J, Bemelman W, Danese S, Mary JY, Rubin D, Colombel JF, Peyrin-Biroulet L, Dotan I, Abreu MT, Dignass A; International Organization for the Study of IBD. STRIDE-II: An Update on the Selecting Therapeutic Targets in Inflammatory Bowel Disease (STRIDE) Initiative of the International Organization for the Study of IBD (IOIBD): Determining Therapeutic Goals for Treat-to-Target strategies in IBD. *Gastroenterology* 2021; **160**: 1570-1583 [PMID: 33359090 DOI: 10.1053/j.gastro.2020.12.031]

59 **Church PC**, Guan J, Walters TD, Frost K, Assa A, Muise AM, Griffiths AM. Infliximab maintains durable response and facilitates catch-up growth in luminal pediatric Crohn's disease. *Inflamm Bowel Dis* 2014; **20**: 1177-1186 [PMID: 24865777 DOI: 10.1097/MIB.0000000000000083]

60 **Choi J**, Kang B, Kim MJ, Sohn I, Lee HJ, Choe YH. Early Infliximab Yields Superior Long-Term Effects on Linear Growth in Pediatric Crohn's Disease Patients. *Gut Liver* 2018; **12**: 255-262 [PMID: 29298460 DOI: 10.5009/gnl17290]

61 **Walters TD**, Faubion WA, Griffiths AM, Baldassano RN, Escher J, Ruemmele FM, Hyams JS, Lazar A, Eichner S, Huang B, Li Y, Thakkar RB. Growth Improvement with Adalimumab Treatment in Children with Moderately to Severely Active Crohn's Disease. *Inflamm Bowel Dis* 2017; **23**: 967-975 [PMID: 28301428 DOI: 10.1097/MIB.0000000000001075]

62 **Matar M**, Shamir R, Lev-Zion R, Broide E, Weiss B, Ledder O, Guz-Mark A, Rinawi F, Cohen S, Topf-Olivestone C, Shaoul R, Yerushalmi B, Assa A. The Effect of Adalimumab Treatment on Linear Growth in Children With Crohn Disease: A Post-hoc Analysis of the PAILOT Randomized Control Trial. *J Pediatr Gastroenterol Nutr* 2020; **71**: 237-242 [PMID: 32324651 DOI: 10.1097/MPG.0000000000002728]

63 **Raychaudhuri SP**, Nguyen CT, Raychaudhuri SK, Gershwin ME. Incidence and nature of infectious disease in patients treated with anti-TNF agents. *Autoimmun Rev* 2009; **9**: 67-81 [PMID: 19716440 DOI: 10.1016/j.autrev.2009.08.006]

64 **Dulai PS**, Thompson KD, Blunt HB, Dubinsky MC, Siegel CA. Risks of serious infection or lymphoma with anti-tumor necrosis factor therapy for pediatric inflammatory bowel disease: a systematic review. *Clin Gastroenterol Hepatol* 2014; **12**: 1443-51; quiz e88 [PMID: 24462626 DOI: 10.1016/j.cgh.2014.01.021]

65 **Singh S**, Facciorusso A, Dulai PS, Jairath V, Sandborn WJ. Comparative Risk of Serious Infections With Biologic and/or Immunosuppressive Therapy in Patients With Inflammatory Bowel Diseases: A Systematic Review and Meta-Analysis. *Clin Gastroenterol Hepatol* 2020; **18**: 69-81.e3 [PMID: 30876964 DOI: 10.1016/j.cgh.2019.02.044]

66 **Bonovas S**, Fiorino G, Allocca M, Lytras T, Nikolopoulos GK, Peyrin-Biroulet L, Danese S. Biologic Therapies and Risk of Infection and Malignancy in Patients With Inflammatory Bowel Disease: A Systematic Review and Network Meta-analysis. *Clin Gastroenterol Hepatol* 2016; **14**: 1385-1397.e10 [PMID: 27189910 DOI: 10.1016/j.cgh.2016.04.039]

67 **Hyams JS**, Dubinsky MC, Baldassano RN, Colletti RB, Cucchiara S, Escher J, Faubion W, Fell J, Gold BD, Griffiths A, Koletzko S, Kugathasan S, Markowitz J, Ruemmele FM, Veereman G, Winter H, Masel N, Shin CR, Tang KL, Thayu M. Infliximab Is Not Associated With Increased Risk of Malignancy or Hemophagocytic Lymphohistiocytosis in Pediatric Patients With Inflammatory Bowel Disease. *Gastroenterology* 2017; **152**: 1901-1914.e3 [PMID: 28193515 DOI: 10.1053/j.gastro.2017.02.004]

68 **Fréling E**, Baumann C, Cuny JF, Bigard MA, Schmutz JL, Barbaud A, Peyrin-Biroulet L. Cumulative incidence of, risk factors for, and outcome of dermatological complications of anti-TNF therapy in inflammatory bowel disease: a 14-year experience. *Am J Gastroenterol* 2015; **110**: 1186-1196 [PMID: 26195181 DOI: 10.1038/ajg.2015.205]

69 **Sridhar S**, Maltz RM, Boyle B, Kim SC. Dermatological Manifestations in Pediatric Patients with Inflammatory Bowel Diseases on Anti-TNF Therapy. *Inflamm Bowel Dis* 2018; **24**: 2086-2092 [PMID: 29718343 DOI: 10.1093/ibd/izy112]

70 **Hradsky O**, Kazeka D, Copova I, Lerchova T, Mitrova K, Pospisilova K, Sulovcova M, Zarubova K, Bronsky J. Risk factors for dermatological complications of anti-TNF therapy in a cohort of children with Crohn's disease. *Eur J Pediatr* 2021; **180**: 3001-3008 [PMID: 33876264 DOI: 10.1007/s00431-021-04077-0]

71 **Colombel JF**, Sandborn WJ, Reinisch W, Mantzaris GJ, Kornbluth A, Rachmilewitz D, Lichtiger S, D'Haens G, Diamond RH, Broussard DL, Tang KL, van der Woude CJ, Rutgeerts P; SONIC Study Group. Infliximab, azathioprine, or combination therapy for Crohn's disease. *N Engl J Med* 2010; **362**: 1383-1395 [PMID: 20393175 DOI: 10.1056/NEJMoa0904492]

72 **Feagan BG**, McDonald JW, Panaccione R, Enns RA, Bernstein CN, Ponich TP, Bourdages R, Macintosh DG, Dallaire C, Cohen A, Fedorak RN, Paré P, Bitton A, Saibil F, Anderson F, Donner A, Wong CJ, Zou G, Vandervoort MK, Hopkins M, Greenberg GR. Methotrexate in combination with infliximab is no more effective than infliximab alone in patients with Crohn's disease. *Gastroenterology* 2014; **146**: 681-688.e1 [PMID: 24269926 DOI: 10.1053/j.gastro.2013.11.024]

73 **Kansen HM**, van Rheenen PF, Houwen RHJ, Tjon A Ten W, Damen GM, Kindermann A, Escher JC, Wolters VM; Kids with Crohn's, Colitis (KiCC) Working Group for Collaborative Paediatric IBD Research in the Netherlands. Less Anti-infliximab Antibody Formation in Paediatric Crohn Patients on Concomitant Immunomodulators. *J Pediatr Gastroenterol Nutr* 2017; **65**: 425-429 [PMID: 28945207 DOI: 10.1097/MPG.0000000000001551]

74 **Grossi V**, Lerer T, Griffiths A, LeLeiko N, Cabrera J, Otley A, Rick J, Mack D, Bousvaros A, Rosh J, Grossman A, Saeed S, Kay M, Boyle B, Oliva-Hemker M, Keljo D, Pfefferkorn M, Faubion W, Kappelman MD, Sudel B, Markowitz J, Hyams JS. Concomitant Use of Immunomodulators Affects the Durability of Infliximab Therapy in Children With Crohn's Disease. *Clin Gastroenterol Hepatol* 2015; **13**: 1748-1756 [PMID: 25911120 DOI: 10.1016/j.cgh.2015.04.010]

75 **van Rheenen H**, van Rheenen PF. Long-Term Efficacy of Anti-Tumor Necrosis Factor Agents in Pediatric Luminal Crohn's Disease: A Systematic Review of Real-World Evidence Studies. *Pediatr Gastroenterol Hepatol Nutr* 2020; **23**: 121-131 [PMID: 32206624 DOI: 10.5223/pghn.2020.23.2.121]

76 **Kopylov U**, Al-Taweel T, Yaghoobi M, Nauche B, Bitton A, Lakatos PL, Ben-Horin S, Afif W, Seidman EG. Adalimumab monotherapy versus combination therapy with immunomodulators in patients with Crohn's disease: a

systematic review and meta-analysis. *J Crohns Colitis* 2014; **8**: 1632-1641 [PMID: 25067824 DOI: 10.1016/j.crohns.2014.07.003]

77 **Hyams JS**, Dubinsky M, Rosh J, Ruemmele FM, Eichner SF, Maa JF, Lazar A, Alperovich G, Mostafa NM, Robinson AM. The effects of concomitant immunomodulators on the pharmacokinetics, efficacy and safety of adalimumab in paediatric patients with Crohn's disease: a post hoc analysis. *Aliment Pharmacol Ther* 2019; **49**: 155-164 [PMID: 30506693 DOI: 10.1111/apt.15054]

78 **Matar M**, Shamir R, Turner D, Broide E, Weiss B, Ledder O, Guz-Mark A, Rinawi F, Cohen S, Topf-Olivestone C, Shaoul R, Yerushalmi B, Ben-Horin S, Assa A. 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* 2020; **26**: 1627-1635 [PMID: 31793630 DOI: 10.1093/ibd/izz294]

79 **Bittner B**, Richter W, Schmidt J. Subcutaneous Administration of Biotherapeutics: An Overview of Current Challenges and Opportunities. *BioDrugs* 2018; **32**: 425-440 [PMID: 30043229 DOI: 10.1007/s40259-018-0295-0]

80 **Chilton F**, Collett RA. Treatment choices, preferences and decision-making by patients with rheumatoid arthritis. *Musculoskeletal Care* 2008; **6**: 1-14 [PMID: 17726671 DOI: 10.1002/msc.110]

81 **Vavricka SR**, Bentele N, Scharl M, Rogler G, Zeitz J, Frei P, Straumann A, Binek J, Schoepfer AM, Fried M; Swiss IBDnet and Swiss IBD Cohort Study Group. Systematic assessment of factors influencing preferences of Crohn's disease patients in selecting an anti-tumor necrosis factor agent (CHOOSE TNF TRIAL). *Inflamm Bowel Dis* 2012; **18**: 1523-1530 [PMID: 21987429 DOI: 10.1002/ibd.21888]

82 **Kim ES**, Kim KO, Jang BI, Lee CK, Kim HJ, Lee KM, Kim YS, Eun CS, Jung SA, Yang SK, Lee J, Kim TO, Jung Y, Seo GS, Yoon SM; IBD Study Group of the Korean Association for the Study of the Intestinal Diseases (KASID). Factors Contributing to the Preference of Korean Patients with Crohn's Disease When Selecting an Anti-Tumor Necrosis Factor Agent (CHOICE Study). *Gut Liver* 2016; **10**: 391-398 [PMID: 26347512 DOI: 10.5009/gnl15126]

83 **Alden DL**, Friend JM, Lee AY, de Vries M, Osawa R, Chen Q. Culture and medical decision making: Healthcare consumer perspectives in Japan and the United States. *Health Psychol* 2015; **34**: 1133-1144 [PMID: 26076003 DOI: 10.1037/hea0000229]

84 **Baert F**, Noman M, Vermeire S, Van Assche G, D' Haens G, Carbonez A, Rutgeerts P. Influence of immunogenicity on the long-term efficacy of infliximab in Crohn's disease. *N Engl J Med* 2003; **348**: 601-608 [PMID: 12584368 DOI: 10.1056/NEJMoa020888]

85 **Karmiris K**, Paintaud G, Noman M, Magdelaine-Beuzelin C, Ferrante M, Degenne D, Claes K, Coopman T, Van Schuerbeek N, Van Assche G, Vermeire S, Rutgeerts P. Influence of trough serum levels and immunogenicity on long-term outcome of adalimumab therapy in Crohn's disease. *Gastroenterology* 2009; **137**: 1628-1640 [PMID: 19664627 DOI: 10.1053/j.gastro.2009.07.062]

86 **Fidder HH**, Singendonk MM, van der Have M, Oldenburg B, van Oijen MG. Low rates of adherence for tumor necrosis factor-α inhibitors in Crohn's disease and rheumatoid arthritis: results of a systematic review. *World J Gastroenterol* 2013; **19**: 4344-4350 [PMID: 23885145 DOI: 10.3748/wjg.v19.i27.4344]

87 **Kane SV**, Chao J, Mulani PM. Adherence to infliximab maintenance therapy and health care utilization and costs by Crohn's disease patients. *Adv Ther* 2009; **26**: 936-946 [PMID: 19838649 DOI: 10.1007/s12325-009-0069-7]

88 **Kane S**, Dixon L. Adherence rates with infliximab therapy in Crohn's disease. *Aliment Pharmacol Ther* 2006; **24**: 1099-1103 [PMID: 16984504 DOI: 10.1111/j.1365-2036.2006.03092.x]

89 **Billioud V**, Laharie D, Filippi J, Roblin X, Oussalah A, Chevaux JB, Hébuterne X, Bigard MA, Peyrin-Biroulet L. Adherence to adalimumab therapy in Crohn's disease: a French multicenter experience. *Inflamm Bowel Dis* 2011; **17**: 152-159 [PMID: 21061388 DOI: 10.1002/ibd.21491]

90 **Turner D**, Huang Y, Martín-de-Carpi J, Aloi M, Focht G, Kang B, Zhou Y, Sanchez C, Kappelman MD, Uhlig HH, Pujol-Muncunill G, Ledder O, Lionetti P, Dias JA, Ruemmele FM, Russell RK; Paediatric IBD Porto group of ESPGHAN. Corona Virus Disease 2019 and Paediatric Inflammatory Bowel Diseases: Global Experience and Provisional Guidance (March 2020) from the Paediatric IBD Porto Group of European Society of Paediatric Gastroenterology, Hepatology, and Nutrition. *J Pediatr Gastroenterol Nutr* 2020; **70**: 727-733 [PMID: 32443020 DOI: 10.1097/MPG.0000000000002729]

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