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

Kim ES *et al.* Infliximab vs adalimumab in pediatric CD

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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 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-tumor necrosis factor (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: ³ Anti-tumor necrosis factor; Infliximab; Adalimumab; Crohn's disease; Pediatric

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Core Tip: ⁶ 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 ⁴ the efficacy of induction and maintenance of remission, safety profile, immunogenicity, ²⁸ preference, and compliance between infliximab and adalimumab in pediatric CD.

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-TNFA THERAPIES

Anti-TNFA 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 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-TNFA 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 rates 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 seem 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*^[23] 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^[24]. 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^[25]. 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^[26].

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^[27]. 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^[28,29]. 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^[30]. TLs 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^[31]. 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^[32], we assumed the threshold of TLs 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^[33]. 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*^[34] 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^[35]. Singh *et al*^[36] 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*^[37] 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^[38,39]. Zittan *et al*^[38] 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^[39]. 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^[28,29].

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^[30].

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^[32]. 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 $\mu\text{g/mL}$ vs 0.9 $\mu\text{g/mL}$)^[40]. 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 $\mu\text{g/mL}$ (likelihood ratio, 2.02; 95% CI: 1.01-4.08; $P = 0.048$) in patients with IBD^[41]. Additionally, Yarur *et al*^[42] 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^[43]. 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 $\geq 5 \mu\text{g/mL}$ ^[44].

Similar to IFX, maintenance TLs of ADL were associated with clinical and laboratory responses in adult patients with CD^[45]. 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 $\mu\text{g/mL}$ (sensitivity, 68%; specificity, 70.6%). In addition, Zittan *et al*^[46] 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 $\mu\text{g/mL}$ vs 3.4 $\mu\text{g/mL}$, $P < 0.001$). 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 $\mu\text{g/mL}$ vs 10.5 $\mu\text{g/mL}$, $P = 0.028$)^[47]. Choi *et al*^[48] reported that pediatric patients with endoscopic healing had significantly

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higher ADL TLs at week 16 than those without endoscopic healing (13.0 $\mu\text{g/mL}$ vs 6.2 $\mu\text{g/mL}$, $P = 0.023$).

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

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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^[49]. 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^[50]. 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^[51]. Additionally, suboptimal TLs of anti-TNF agents are associated with a more immunogenic state, which leads to lower efficacy and greater loss of response^[38,52,53]. 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^[54-57].

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Vermeire *et al*^[58] 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 ³ 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^[59]. 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. ¹ 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^[60]. 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 ($P = 0.026$)^[61]. For Tanner stage 4-5 patients receiving IFX, ² 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, $P < 0.001$)^[62]. Additionally, Matar *et al*^[63] 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 TNF α 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^[64]. Dulai *et al*^[65] 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)^[66]. 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)^[28].

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)^[67]. 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^[68]. 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^[69]. 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 ² 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 ² of patients treated with IFX was significantly higher than that of those treated with ADL (84.8% vs 15.2%, $P = 0.05$)^[70]. Additionally, Hradsky *et al*^[71] reported that the only predictive factor for any dermatologic complication in pediatric CD was IFX therapy (vs ADL, ⁴⁸ 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 ⁶² 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^[72]. 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 ¹³ 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 ²² (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^[73].

No RCT has compared the effects of ¹⁶ combination therapy with IFX and IMM and IFX monotherapy ¹⁵ 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^[74]. 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^[60,75,76]. 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^[77]. 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^[78]. 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^[49,79].

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^[80]. 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^[81]. 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^[82].

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^[83]. 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^[84]. 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^[85,86]. 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^[87]. When the adherence rates of IFX and ADL were compared, the adherence rate of IFX was 66%-85%, and that of ADL was 55^[88-90], with an RR of 0.76 (95%CI: 0.64-0.91)^[87].

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^[91]. 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.

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

compliance⁶ play an important role in evaluating and selecting treatment options (Figure 2)³[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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