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The Treatment of Pediatric Inflammatory Bowel Disease with Biologic Therapies

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Abstract

Purpose of Review Biologics for the treatment of inflammatory bowel disease (IBD) have been transformative to the therapeutic goals in the pediatric population. We review the biologics used to treat IBD, highlighting the importance of patient selection, dosing considerations, and therapeutic drug monitoring in children.

Recent Findings Infliximab is well-established as a safe and efficacious therapy for Crohn's disease and ulcerative colitis. Both dose escalation strategies and therapeutic drug monitoring increase the likelihood of response to anti-TNFα therapies. Early real-world experience of vedolizumab and ustekinumab in pediatric IBD shows promising results, including clinical response rates comparable to what is seen in adults, but there are limited data using them as first-line therapies.

Summary Biologic therapies have improved outcomes in pediatric IBD, including achieving mucosal healing as well as improved growth and pubertal development. Therapeutic drug monitoring improves likelihood of response to anti-TNFα therapies, but further studies for vedolizumab and ustekinumab are necessary.

Keywords Pediatric inflammatory bowel disease · Biologic therapy · Children · Crohn's disease · Ulcerative colitis · Therapeutic drug monitoring

Abbreviations

ASC	Acute severe colitis
CD	Crohn's disease
IBD	Inflammatory bowel disease
IBD-U	Inflammatory bowel disease–unclassified
HLH	Hemophagocytic lymphohistiocytosis
IFX	Infliximab
IMM	Immunomodulator
TNFα	Yumor necrosis factor alpha
UC	Ulcerative colitis

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Inflammatory bowel diseases (IBD), including Crohn's disease (CD), ulcerative colitis (UC), and IBD unclassified (IBD-U), are chronic inflammatory conditions of the gastrointestinal tract. The etiology is often complex, involving an altered immune response to environmental exposures in a genetically susceptible host. Symptoms vary, but can include abdominal pain, diarrhea, and rectal bleeding. The therapeutic goals in pediatric inflammatory bowel disease are to induce and maintain clinical remission, achieve mucosal healing, and improve quality of life, while minimizing the adverse effects of medications. Additionally, in children, disease control is critical due to the narrow window of opportunity to prevent delays in development, growth, and puberty.

The advent of biologic therapies has dramatically changed the landscape for treatment of both adult and pediatric IBD. Infliximab (IFX) is the first biopharmaceutical that was approved for IBD. Since its approval for adults in 2001 and pediatrics in 2006, many more biologic therapies have been developed and are now part of the armamentarium of IBD treatment. In this age of precision medicine, the ultimate goal is determining the most appropriate and effective therapy for the individual patient.

In this paper, we will review the role of biologic therapies in pediatric IBD, focusing on how early use of anti-tumor necrosis factor (TNF)-α antibodies affects outcomes in CD and UC and the use of therapeutic drug monitoring in optimizing treatment and in modulating rates of surgeries and hospitalizations.

Infliximab

TNFα, a prominent pro-inflammatory cytokine, is greatly increased in the lamina propria in the small and large intestine of patients with IBD [1]. IFX is a chimeric monoclonal IgG1 antibody to TNFα composed of a human constant and murine variable region. In 2006, infliximab was approved for treatment of moderate-to-severe pediatric CD and more recently UC. IFX was then followed by adalimumab, which is FDA approved for pediatric CD, with a clinical trial ongoing for pediatric UC. Besides neutralization of TNFα, infliximab also blocks leukocyte migration and induces apoptosis of T-lymphocytes and monocytes. A third mechanism of action involves complement fixation, complement-dependent cytotoxicity, and antibody-dependent cellular cytotoxicity.

Infliximab in Pediatric Crohn's Disease

The initial study of IFX in adult patients with Crohn's disease performed by Targan et al. demonstrated that clinical response was achieved in > 80% of patients 4 weeks after a single 5 mg/kg infusion [2]. This study was followed by the ACCENT-I study in which 58% of 573 adult patients who had a clinical response after the first infusion were randomized to either placebo or infliximab dosed at 5 mg/kg or 10 mg/kg [3]. Here, both doses were more effective in achieving clinical remission at week 54 than placebo.

The first randomized clinical trial with IFX in pediatric CD, the Randomized, Multicenter, Open Label Study to Evaluate the Safety and Efficacy of Anti-TNF Chimeric Monoclonal Antibody in Pediatric Subjects with Moderate-to-Severe Crohn's Disease (REACH) study, evaluated clinical response and remission at week 10 after an induction regimen of 5 mg/kg at 0, 2, and 6 weeks [4]. Clinical response was seen in 88% of patients, and these patients were randomized to receive infliximab every 8 or 12 weeks. By week 54, 63.5% of subjects allocated to every 8-week infusions had a clinical response, and 55.8% were in clinical remission, significantly higher than the clinical remission rate of 23.5% in those who received infliximab every 12 weeks.

Through these studies, it became clear that IFX was effective in improving clinical symptoms, but the question remained whether introducing anti-TNFα therapy early in the disease course would improve mucosal healing, resulting in less structural damage, fewer complications, and decreased surgical intervention for these children as compared to treatment later in the disease course. Through a multicenter inception cohort of pediatric CD, Walters et al. addressed this issue [5]. Subjects were enrolled in the prospective Risk Stratification and Identification of Immunogenetic and Microbial Markers of Rapid Disease Progression in Children with Crohn's Disease (RISK) study that includes 552 children < 17 years of age with newly diagnosed, inflammatory (non-penetrating and non-stricturing) CD. Subjects were matched in triads: (1) anti-TNFα monotherapy, (2) immunomodulator (IMM) only therapy, which included thiopurines or methotrexate, and (3) neither IMM or anti-TNFα therapy. By 1 year of follow up, anti-TNFα therapy was significantly more effective in achieving sustained remission than IMM (85.3% vs 60.3%) or neither therapy (54.4%).

Infliximab in Pediatric Ulcerative Colitis

Until the early 2000s, up to one-third of patients with moderate-to-severe UC required colectomy despite treatment with corticosteroids. However, over the past 20 years, infliximab has led to successful induction and maintenance of remission and mucosal healing in patients with ulcerative colitis and prevented the need for colectomy [6••]. A retrospective comparison of pediatric UC compared clinical outcomes in patients diagnosed between 2005–2010 and 2011–2016. This study found similar rates of hospitalization and flares in both eras despite an increased use of 5-ASA, infliximab, and thiopurines in the latter group. However, decreased rates of colectomies were reported in 2011–2016, and this was independently associated with infliximab use [7]. In another pediatric study from 2010, 74% of children with UC treated with infliximab were colectomy-free at 2 years of therapy [8]. It is important to note that approximately 50% of these patients required dose escalation of IFX to maintain remission, and this is discussed in more detail below.

IFX has also been shown to be effective in one of the most challenging populations, known as acute severe colitis (ASC). These patients typically present with severe and fulminant pancolitis (Pediatric Ulcerative Colitis Activity Index ≥ 65), can be accompanied by massive hemorrhage, toxic megacolon, and even multiorgan failure, and are high risk for colectomy. The current pediatric guidelines recommend initiation of IFX in patients who are anti-TNF therapy naïve, after a 3- to 5-day course of intravenous corticosteroids without response [9, 10••]. In a study of 128 patients with ASC, 76% of the 33 children who failed steroids responded to infliximab and avoided colectomy during that hospitalization [9]. In the year of follow-up though, 28% of these responders had ultimately undergone colectomy.

Patient Selection for Infliximab

As discussed above, the therapeutic approach in IBD has shifted over the last decade from reserving anti-TNFα therapy as a "last line" to initiating these agents as primary therapy. The decision to start IFX as a first line drug in both CD and UC is based on the patient's disease phenotype, including extent and location of disease, disease behavior, especially stricturing and/or penetrating disease, presence of growth delay, severe osteoporosis, or significant perianal disease, severity of endoscopic findings, and post-operatively to prevent disease recurrence. The goals of this approach are to achieve mucosal healing early and to maintain this state throughout the disease course.

The use of a precision medicine strategy to target patients based on clinical characteristics has been shown to be successful in both adult and pediatric IBD. Predictors of poor anti-TNFα response in patients with ulcerative colitis include severe disease, obesity, longer disease duration (> 2 years), prior intestinal surgery, malnutrition, hypoalbuminemia, and anemia [11]. Many of these clinical factors likely impact the pharmacokinetics of anti-TNFα treatments resulting in lower drug concentration during induction leading to nonresponse [12, 13]. In pediatrics, genetic, serologic, and microbiome signatures are also being investigated as biomarkers for predicting response to therapy. The larger RISK cohort analysis of 913 patients followed for 3 years demonstrated the importance of early anti-TNFα therapy as compared to later introduction of anti-TNFα therapy, especially in slowing progression to penetrating complications, and identified associated biomarkers [14•].

In addition to choosing which patients are most likely to respond to anti-TNFα, determining the appropriate dose is important to achieving optimal anti-TNFα response. Dose escalation has been a critical and successful strategy, largely due to our improved grasp of the pharmacokinetics of this agent, and has been guided by therapeutic drug monitoring (discussed more below). A prime example of this approach can be seen in patients with predominantly colonic disease, in whom intensified induction with higher dosing and more frequent intervals of infliximab can increase efficacy and sustain response [15]. This strategy is more likely to achieve remission and avoid colectomy [16].

Therapeutic Drug Monitoring of Infliximab in Pediatric IBD

The use of therapeutic drug monitoring (TDM) has dramatically changed our use of IFX and has led to improved response, sustained efficacy, and minimized some adverse drug effects. The trough and antibody levels can guide appropriate dosing and interval schedule, allowing for an individualized therapeutic plan. TDM can improve clinical, biochemical, and endoscopic outcomes, increase remission rates, and decrease the incidence of antibody formation resulting in loss of response to these drugs [17–23]. A recent retrospective study of 111 children with Crohn's disease treated with infliximab 5 mg/kg/dose at standard induction and maintenance schedule found that therapeutic trough levels > 8.3 μg/mL at week 6 was associated with clinical remission at week 14 [24]. Low or undetectable serum trough concentrations of infliximab are associated with loss of response to the drug, with worse clinical outcomes and disease activity. Antibodies to infliximab increase the clearance of the drug, which can lead to low trough levels [25]. In a retrospective study of 90 adults, an IFX trough level < 2.2μg/mL at week 14 was associated with discontinuation of infliximab due to loss of response or infusion reactions, even in patients who clinically improved after starting the medication [25].

The target infliximab trough may be different based on the patient's disease phenotype. Ungar et al. demonstrated that a level of 6–10 μg/mL is most likely to be associated with mucosal healing, [26] while higher IFX levels have been associated with successful treatment of perianal fistulae. In a cross-sectional study, those with healed fistulae had significantly higher median infliximab levels compared to those with active fistulae (15.8 vs 4.4 μg/mL ($P < 0.0001$)), suggesting that higher infliximab levels > 10 μg/mL may be beneficial for patients with this phenotype [27].

Infliximab Safety

A major concern for providers, patients, and patients' families is the safety profile of therapies. In general, the incidence of pediatric IBD-related malignancies, including colorectal cancer, lymphoma, or hepatosplenic T cell lymphoma and mortality are rare [28, 29]. The DEVELOP study is an ongoing multicenter prospective cohort study of the long-term safety and outcomes of pediatric IBD patients that began in 2007. Recent publication of > 10,000 patient-years of follow-up demonstrated that there was not an increased risk of malignancy or hemophagocytic lymphohistiocytosis (HLH) associated with infliximab exposure [30••]. Additionally, while malignancy in the patient population was rare, there was a trend toward higher rates of malignancy and HLH in patients with thiopurine exposure.

The potential side effects associated with IFX include acute infusion reactions that can resemble anaphylaxis. It is most commonly associated with the development of autoantibodies to infliximab and can occur in up to 15% of patients. [31] Delayed infusion reactions and other autoimmune phenomena, such as serum sickness, are rare. Clinically, these can present as myalgia, arthralgia, and other systemic symptoms. Other

conditions include drug-induced lupus, hemolytic anemia, demyelinating lesions, and optic neuritis. Psoriasis has been reported in up to 5% of adults with IBD on anti-TNFα therapy, but the prevalence in children with IBD is unknown [32]. Psoriasis may be able to be treated topically or with oral agents, and if it improves, IFX is most often able to be continued. In cases of severe psoriasis, IFX may need to be discontinued. In addition to the above side effects, there are several other autoimmune conditions that can be very rarely associated with IFX, and typically improve with withdrawal of infliximab.

Infection risk is potentially increased with anti-TNFα therapy, but the majority of infections are not serious nor requiring of hospitalization or IV antibiotics [33]. Other reported infections include herpes zoster, other viral infections, and bacterial infections, including sepsis, pneumonia, intra-abdominal abscesses, and other opportunistic bacterial, viral, fungal, and parasitic infections, although these are less common in children with IBD on anti-TNF therapy than in adults. In one study of the risks of serious infection with IBD therapies, the rate was similar among children on anti-TNFα and children on immunomodulators, but much lower than the rate seen in adults treated with anti-TNFα agents or children treated with steroids [34].

Adalimumab in Crohn's Disease

Adalimumab, a fully human monoclonal IgGI1 antibody to TNFα, is FDA approved for children with pediatric Crohn's disease. Beyond infliximab, it is the best-studied anti-TNF therapy for IBD. Similar to infliximab, adalimumab has been shown to be safe and efficacious for induction and maintenance of moderate-to-severe pediatric Crohn's disease, including perianal fistulizing disease, and improves linear growth and bone health. It is well tolerated, with a side effect profile similar to IFX [35–38]. Ease of self-administration with subcutaneous injections and the lack of infusion reactions are two of the advantages of adalimumab over infliximab. Recently, changed formulation and concentration of the medication have also improved pain associated with the injections.

For many providers and patients, the decision of when to choose adalimumab instead of infliximab as first-line therapy in moderate-to-severe CD can be difficult. Robust direct prospective comparisons of infliximab to adalimumab in children have not been performed; however, some observational cohort studies in adults suggest similar efficacy between the two in anti-TNFα-naïve CD patients [39, 40]. In addition, both drugs have similar lengths of duration or persistence as first-line therapies [41]. A comparative effectiveness study of infliximab versus adalimumab used electronic health record data to determine medication non-response in 1031 adults with CD. Adalimumab was associated with a higher likelihood of non-response at 1 year, compared to IFX, in both anti-TNFα-naïve and prior-anti-TNFα-exposed populations [42]. Nonresponse or loss of response to adalimumab has largely been attributed to differences in pharmacokinetics. A trial of escalating adalimumab maintenance dosing from every 2 weeks to every 1 week in non-responders, those with loss of response, or patients experiencing increased symptoms showed similar findings to dose escalation with IFX, including inducing clinical response and remission [43].

There is more debate about the efficacy of adalimumab after infliximab failure. One meta-analysis demonstrated that primary non-responders to IFX have 24% less likelihood of achieving remission on the second anti-TNF agents than for other indications [44]. In a study of pediatric CD patients predominantly with loss of response to IFX, remission was successfully reached with adalimumab in 34/53 patients and 50% sustained remission at 2-year follow-up [45].

Adalimumab in Ulcerative Colitis

While the results of a clinical trial for adalimumab in pediatric UC are not yet available, there are some retrospective data available, albeit in small sample sizes, to suggest that adalimumab can be effective for pediatric UC, including in the setting of infliximab failure [46]. Currently, guidelines and dosing are based on adult and observational studies. A meta-analysis of adult trials in UC suggested that adalimumab has inferior efficacy as compared to IFX for induction, but likely is equally effective for maintenance therapy [47]. A large observational Danish study found that there was a higher risk of disease-related and general hospitalizations in UC patients who were treated with adalimumab as first-line therapy as compared to patients treated with IFX [48]. Moreover, unlike infliximab, there is no evidence for the use of adalimumab as rescue therapy for patients with ASC. The American College of Gastroenterology guidelines for the management of hospitalized patients with ASC recommend infliximab and no other anti-TNFα agents, for this indication [49]. Recent European guidelines for the outpatient management of pediatric UC recommend use of adalimumab for patients who have developed loss of response or intolerance to infliximab and advise close monitoring of trough levels and antibodies. These guidelines do not recommend adalimumab for UC patients who have primary non-response to first-line therapy with infliximab [6]. As seen with infliximab, there are likely biomarkers and risk factors to be determined that would suggest the need for higher dosing of adalimumab, but data are lacking.

Therapeutic Drug Monitoring of Adalimumab in Pediatric IBD

As with infliximab, TDM with adalimumab has greatly improved clinical and endoscopic outcomes. In a randomized

controlled trial of TDM in pediatric Crohn's disease on adalimumab as first anti-TNFα therapy, children were assigned to proactive (obtaining trough levels at weeks 4, 8, and then every 8 weeks until week 72) versus reactive (trough levels obtained after clinical signs of loss of response) drug monitoring [50]. Patients in both arms had their dose and interval adjusted to maintain level > 5 μg/mL. Children with proactive monitoring achieved steroid-free clinical remission, normal CRP, and normal calprotectin at all visits up to week 72 ($n = 31/38$) more frequently than children who had reactive monitoring and dose adjustment ($n = 19/40$).

Vedolizumab

Vedolizumab is a humanized anti-α4β7 integrin immunoglobulin G1 monoclonal antibody that inhibits intestinal T lymphocyte migration into the tissue in order to downregulate intestinal inflammation. This mechanism of action is restricted to the gastrointestinal tract, potentially mitigating the risks of systemic immunosuppression, such as infections and potential malignancies, seen with other IBD therapies [51]. There are a limited number of vedolizumab studies in pediatric IBD populations. The two initial retrospective studies of vedolizumab in pediatrics demonstrated clinical response in the first 14–22 weeks of therapy in > 50% of patients with refractory IBD [52, 53]. A single-center cohort study of 21 pediatric patients with IBD who all failed at least one anti-TNFα agent and were largely steroid dependent demonstrated that 31.6% achieved clinical response by week 6, and by week 22, almost 58% of patients achieved remission with 20% of the cohort in steroid-free remission [52]. In a multicenter cohort study of 52 children with IBD, there was clinical remission in 4 of 5 anti-TNFα naïve subjects and in 76% and 42% of the refractory Crohn's disease and ulcerative colitis patients, respectively, by week 14 [53]. Prospective adult studies have demonstrated endoscopic and histologic remission in about 33% of patients with Crohn's disease after 1 year of vedolizumab therapy [54]. In a retrospective pediatric study of mucosal healing rates in patients with IBD treated with vedolizumab, 38% of patients achieved mucosal healing, with endoscopic remission seen more frequently in anti-TNFα-naïve patients than in anti-TNFα exposed [55].

One recent study compared the efficacy of vedolizumab versus adalimumab in adults with moderate-to-severe ulcerative colitis. The authors found that patients treated with vedolizumab had higher rates of clinical remission (37.2% vs 25.9%) and endoscopic improvement (39.7% vs. 27.7%); however, steroid-free remission was more commonly achieved in the adalimumab group [56]. More studies are necessary to determine the optimal primary strategy for these therapies.

Therapeutic Drug Monitoring of Vedolizumab

Due to the clear benefit of TDM in the use of anti-TNFα therapies for both Crohn's disease and ulcerative colitis, there has been great interest in positioning TDM to optimize the use of vedolizumab. Investigations into TDM for vedolizumab are less advanced than in anti-TNFα agents, but they have already started to demonstrate the ideal drug concentrations associated with clinical remission. One study of 55 adults with IBD treated with vedolizumab demonstrated that higher serum vedolizumab concentrations were associated with steroid-free endoscopic remission at 52 weeks of therapy [57]. Another prospective study examining maintenance therapy with vedolizumab demonstrated that patients with levels > 11.5 μg/mL were 2.4 times more likely to be in corticosteroid-free clinical and biochemical remission. A retrospective study suggested that a higher trough level > 25μg/mL was most optimal to predict histologic mucosal healing [58, 59]. Clinical factors associated with lower drug levels of vedolizumab and worse therapeutic outcomes include hypoalbuminemia and obesity, which were shown in the GEMINI studies to be predictors of accelerated clearance of vedolizumab [60]. While there is mounting literature to support an exposure-efficacy relationship for vedolizumab, there does not exist a consensus yet on target vedolizumab levels in adult populations with standard dosing, no less in pediatric populations that often receive weight-based dosing of vedolizumab rather than the standard 300-mg adult dose.

Risks of Vedolizumab

The safety profile of vedolizumab is overall favorable. Uncommon side effects may include nasopharyngitis, headache, arthralgia, and nausea to name a few. Other prior anti-integrin biologic agents, such as natalizumab, were very rarely associated with progressive multifocal leukoenceophalopathy due to JC virus infection. This has not been observed in patients on vedolizumab, likely due to the colon-specific integrin receptor it targets and therefore does not cross the blood-brain barrier [61].

Vedolizumab is not yet been FDA approved in children < 18 years of age, and long-term safety data are not available. Initially, vedolizumab was used primarily for medically refractory disease, so peri- and postoperative use of vedolizumab is not uncommon, and postoperative complications of surgery have been reported. One single-center study described more frequent postoperative complications in pediatric UC and CD patients treated with vedolizumab than a comparable vedolizumab-naïve patient population undergoing diverting ileostomy [62]. However, other centers' experiences have not reported similar findings and have not seen increased infections especially in the immediate 30-day post-operative period.[63,

{Lightner, 2018 #10893, 64, 65]. Meta-analyses do not demonstrate an increased risk of postoperative infection in vedolizumab-treated adults with IBD at this time [66].

Ustekinumab

Ustekinumab is a fully humanized monoclonal antibody against interleukins 12 and 23 via binding to their shared p40 subunit and inhibiting downstream Th1 and Th17 pathways. A large randomized, controlled trial of adults with Crohn's disease, with or without prior anti-TNFα failure, demonstrated that ustekinumab at week 6 was superior to placebo for induction of clinical response in both groups [67]. Further, initial ustekinumab responders were randomized to remain on the medication or switch to placebo, with the ustekinumab group showing significantly higher rates of clinical remission at week 44 (53.1% versus 35.9%) [68]. Additionally, the first multicenter, double-blind, randomized clinical trial of ustekinumab in adults with ulcerative colitis showed higher remission rates at week 8 after induction with either a standard 130-mg IV dose (15.6%) or a 6-mg/kg IV dose (15.5%) than with placebo (5.3%) [69]. Clinical remission was maintained at week 44 in 43.8% of those patients who responded to the induction dose and were continued on every 8-week maintenance dosing and in 38.4% of those patients continued on every 12-week maintenance dosing, compared to those who received maintenance placebo after initial response to induction with ustekinumab (24%). There have been no significant differences in rates of serious infections or other adverse events between ustekinumab- and placebo-treated adults reported.

Due to its recent FDA approval for use in adults with IBD, there is a paucity of data regarding ustekinumabuse in pediatric IBD. Ustekinumab has previously been shown to be safe and efficacious in the treatment of adolescents with plaque psoriasis [70]. In pediatric IBD, Dayan et al. reported steroid-free remission in 50% of biologic-exposed and 90% of biologic-naïve patients at 52 weeks in a single-center cohort of 52 patients [71]. Similarly, a multicenter retrospective cohort of 44 pediatric CD patients demonstrated 12-month clinical response and remission rates of 47.8% and 38.6%, respectively, with few adverse events reported [72].

Similar to vedolizumab, therapeutic drug monitoring and goal trough levels of ustekinumab in Crohn's disease and ulcerative colitis after induction have yet to be optimized. Analysis of pharmacokinetic data from phase 3 clinical trials has suggested that increased serum concentrations are associated with efficacy without increased safety events [73]

For now, ustekinumab is largely reserved for refractory Crohn's disease and ulcerative colitis, but not for acute severe colitis. It may be best suited for patients with intolerance to anti-TNFα or who had secondary loss of response. However, over time and with increased clinical real-world experience, it is likely to be used earlier in the disease course.

Conclusion

Biologic therapies have transformed the care for pediatric inflammatory bowel disease. While clinical trials in children are still limited, we have begun to stratify patients to determine who may be best suited for each medication and have developed dosing strategies to increase the efficacy of these agents. These approaches have greatly increased our ability to improve outcomes for children and avoid corticosteroid use as much as possible. Together, we have become closer to achieving personalized medicine for children with IBD, by identifying phenotypes that may respond to a specific therapy and how to optimize that treatment through therapeutic drug monitoring. The future of pediatric IBD treatment will continue to improve as we integrate genetic, microbial, and immunologic biomarkers to predict which patients will benefit from each of these targeted therapeutic options.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent All reported studies/experiments with human or animal subjects performed by the authors have been previously published and complied with all applicable ethical standards (including the Helsinki declaration and its amendments, institutional/national research committee standards, and international/national/institutional guidelines).

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