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Infliximab's Pharmacokinetic and Pharmacodynamic Effects on Paediatric Ulcerative Colitis Patients

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Abstract

The colon is largely impacted by the chronic gastrointestinal inflammatory illness known as ulcerative colitis (UC). Patients with UC experience chronic inflammation of the colon's surface mucosa, crypt epithelium, and/or submucosa, which results in bloody diarrhoea, stomach pain, weight loss, and fever. Although UC symptoms are similar in both adults and children, pediatric-onset UC is more usually associated with acute severe exacerbations because it tends to be more severe than in adult patients. This study's primary goal is to evaluate infliximab pharmacokinetics in children with ulcerative colitis (UC).

Keywords: Infliximab; Ulcerative colitis; Monoclonal antibody; Pharmacokinetic; Therapeutic effect

Introduction

Chronic gastrointestinal inflammatory disease called ulcerative colitis (UC) primarily affects the colon. Patients with UC have bloody diarrhoea, stomach discomfort, weight loss, and fever as a result of chronic inflammation of the colon's surface mucosa, crypt epithelium, and/or submucosa. Although UC symptoms are comparable in both adults and children, pediatric-onset UC tends to be more severe than in adult patients and is therefore more frequently linked to acute severe exacerbations [1]. The main objective of this study is to assess infliximab pharmacokinetics in pediatric ulcerative colitis (UC). Similar treatment approaches and results are seen in both paediatric and adult UC patients, with disease activity serving as the primary motivating factor for juvenile therapy alternatives [2]. The following types of drugs are included in pharmacologic therapy for UC: 5-aminosalicylates, corticosteroids, thiopurine immunomodulators, calcineurin inhibitors, antibiotics, probiotics, and anti-tumor necrosis factor (TNF) medicines [3]. The anti-tumor necrosis factor monoclonal antibody infliximab (Janssen Biotech, Inc., Horsham, PA) is authorised for the treatment of a number of immune-mediated inflammatory diseases, including paediatric patients with UC who show an inadequate response to conventional therapy and are at least 6 years old. The choice of the dose and approval of infliximab for the treatment of juvenile patients with UC is an example of extending the efficacy of a biological previously licenced for use in a comparable indication in adults based on pharmacokinetics and exposure-response assessments [4].

Infliximab was found to have a favourable benefit-risk profile in a phase 3, randomised, open-label, parallel group study (study C0168T72) that prospectively assessed the safety and efficacy of the drug in paediatric patients with moderate-to-severely active UC. The drug was found to induce a response (defined as a decrease in Mayo score by both 30% and points along with a decrease in the rectal bleeding subs [5]. Pharmacokinetic analyses were also a part of this infliximab study for young patients with UC. The pharmacokinetic data in paediatric patients with UC were compared with infliximab pharmacokinetics seen in reference populations from earlier infliximab trials in paediatric patients with Crohn's disease (CD) and in adult patients with UC in order to improve the interpretation of clinical outcomes in this paediatric UC study [6,7].

Study design

Details about the study's design and patient eligibility have been disclosed. In a nutshell, this phase 3 randomised, open-label, parallel group multicenter study (NCT00336492, EudraCT 2006-000410-20) enrolled young patients aged 6 to 17 years with moderately to severely active UC (defined as a Mayo score of 6-12, including endoscopic subscore (2) who did not respond to, or tolerate, treatment with, 6-mercaptopurine (6-MP)/azathioprine (AZA), cortico Although corticosteroids may be decreased starting at week 0, and 6-MP/AZA and methotrexate could be stopped at any point throughout research participation, patients were permitted to remain stable dosages of their baseline concomitant UC medicines. Eight weeks following the final infliximab infusion, patients who did not respond to infliximab induction dose at week eight were to be assessed for safety; however, they were not to receive any more study agent. After losing response, patients who increased their infliximab dose and/or dosing interval were permitted to adjust their corticosteroid dose or begin therapy with 6-MP/AZA, methotrexate, and/or 5-aminosalicylate compounds if they later failed to recover or lost response.

Study Evaluation

The paediatric ulcerative colitis activity index (PUCAI), a validated technique for evaluating disease activity in paediatric UC patients that excludes an endoscopic examination, was also used to measure disease activity. The PUCAI is a scale that ranges from 0 to 85, with lower values indicating less severe illness. It is calculated as the sum of the following subscores: activity level (0-10), abdominal pain (0-10), stool consistency (0-10), and rectal haemorrhage (0-30). A 20-point decline is seen as a clinically significant (i.e., moderate) improvement on the PUCAI scale, which ranges from 35 to 64 and 65, respectively, to indicate moderate and severe disease activity [8-10].

Pharmacokinetics

For the purpose of measuring serum infliximab concentrations

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and infliximab antibody levels, blood samples were taken. Blood was obtained before to and one hour after the study agent infusions scheduled for weeks 0, 2, and 6 as well as at the non-infusion visits scheduled for weeks 8, 54, and 62 in order to measure infliximab concentration. Using serum samples obtained prior to infliximab infusions during visits planned for weeks 0, 30, 54, and 62, it was possible to detect the presence or absence of infliximab antibodies [11]. An antigen-bridging enzyme immunoassay was used to detect the presence of infliximab antibodies. If antibodies to infliximab were found on any visit, patients were labelled as "positive." It should be noted that this test may be hindered in its capacity to determine the presence of infliximab antibodies if there are measurable quantities of the drug in the blood. Descriptive statistics were used to compile the results of all studies provided here; formal statistical hypothesis testing was not done. In order to estimate the real proportion of paediatric patients who had a clinical response at week 8 with a 95% confidence interval, a sample size of 60 patients was intended. Based on the aggregated clinical response rate seen among all randomised adult patients with UC receiving infliximab 5 mg/kg in 2 independent studies, this sample size estimate used a clinical response rate of 67% at week 8. All treated participants were used in the analyses of the main endpoint and all other efficacy endpoints assessed at or before the week 8 visit. Patients who were randomised at week 8 served as the basis for analyses of effectiveness outcomes assessed beyond that time. The effectiveness analysis for outcomes assessed after week 8 did not include patients who received infliximab induction infusions but were not randomly assigned to maintenance medication. At the appropriate analysis time point, patients for whom the Mayo or PUCAI score could not be determined were deemed to have failed to achieve the effectiveness objective. Patients who underwent treatment failure, such as a colectomy or ostomy, stopped taking infliximab due to an unfavourable therapeutic effect, or started taking a prohibited medication change before the designated analysis time point, were also considered to have fallen short of the efficacy endpoints at that point. The pharmacokinetic analyses included all participants who had at least one detectable infliximab concentration and had at least one dose of infliximab. Serum infliximab concentrations were examined in relation to patient age (6-11 vs 12-17 years), concurrent immunomodulator usage (6-MP, AZA, and/or methotrexate) at baseline (yes versus no), and UC disease severity (left-sided colitis versus pancolitis). Ankylosing spondylitis, Crohn's disease, and rheumatoid arthritis are just a few of the many inflammatory disorders that may be treated with infliximab, a monoclonal anti-tumor necrosis factor alpha antibody. Infliximab is a chimeric monoclonal IgG1 antibody made up of human constant (75%) and murine variable (25%) regions that inhibits tumour necrosis factor (TNF-alpha or TNF-) 3. A recombinant cell line cultivated by continuous perfusion produces infliximab. One important proinflammatory cytokine in chronic inflammatory disorders is tumour necrosis factor-alpha (TNF-alpha). In inflammatory illnesses, when it triggers additional pro-inflammatory cascades, its hyperactivity and increased signalling pathways can be seen. Infliximab prevents TNF from interacting with its receptors by binding to both the soluble component and the membrane-bound precursor of TNF-1. It may also promote the lysis of cells that make TNF-1.

The FDA initially authorised infliximab in 1998 for intravenous injection under the brand name Remicade. It is approved to treat a number of inflammatory conditions, including adult or paediatric Chron's disease, adult or paediatric ulcerative colitis, rheumatoid arthritis when combined with methotrexate, ankylosing spondylitis, psoriatic arthritis, and plaque psoriasis. Multiple infusions of infliximab have been shown in clinical studies to reduce the signs and symptoms of inflammatory disorders and to induce remission in individuals who have not responded well to other first-line treatments for that ailment. There are now two biosilimar infliximab products on the US market that have a high degree of Remicade-like resemblance. They have been given approval for all of the reference product's legitimate indications. The first biosimilar medication, Inflectra, received approval in 2016. The FDA gave its clearance to Ixifi, a second Pfizer-developed biosimilar, in December 2017.

Pharmacodynamics

The activation of the pro-inflammatory cascade signalling is interfered with by infliximab. Inflamed cell infiltration into inflammatory areas has been demonstrated to be decreased by infliximab. The expression of molecules involved in cellular adhesion, such as E-selectin, intercellular adhesion molecule-1 (ICAM-1), and vascular cell adhesion molecule-1 (VCAM-1), chemoattraction, such as IL-8 and monocyte chemotactic protein (MCP-1), and tissue degradation, such as matrix metalloproteinase (MMP) 1 and 3, is also suppressed.

Discussion

Parental resistance to enrolling children in clinical trials, a lack of paediatric investigators with the necessary training, children's particular vulnerabilities, and ethical or methodological difficulties associated with conducting clinical trials in a paediatric population are just a few of the well-documented difficulties of conducting paediatric trials [12-14]. In addition to these difficulties, there are relatively less juvenile patients with inflammatory bowel disease (UC) compared to the equivalent adult group. Due to these restrictions, children clinical trials have a smaller patient pool than adult studies. As a result, it is crucial to make the most of the information gleaned from paediatric studies by combining it with adult research on the condition of interest. The United States Food and Medication Administration first explicitly promoted the idea of extending effectiveness data from adult to paediatric populations in 1994 when establishing and evaluating paediatric drug development programmes [15]. The specific strategy for extrapolating from adults to children is dependent on important presumptions about the history of the relevant disease and how it responds to intervention, as well as the exposure-response relationship between the intervention and effectiveness. Generally speaking, extrapolating efficacy or other data from an adult population to a paediatric population can increase access to treatments already available to the adult population, improve the efficiency of paediatric drug development, and ensure that these medications are used properly in children [16]. As a result, in the same research, it was expected that systemic infliximab exposure in paediatric patients aged 2 to 6 years would be around 40% lower than that in adults [17,18]. This difference is due to the nonlinear relationship between body weight and infliximab clearance combined with the linear dosing regimen (mg/kg), which results in a tendency toward lower serum infliximab exposure in children with lower body weights. Age was not a significant covariate once body weight was taken into account in this integrated analysis. These studies may point to the necessity for paediatric patients with UC who are less than 6 years old to receive a larger infliximab dosage (mg/kg) in order to obtain serum infliximab concentrations in this age group that are equivalent to those seen in older children and adults. In view of reports of lower efficacy of the 5-mg/kg infliximab regimen in younger children with inflammatory bowel disease, more research may be required to examine the effects of possible changes in

serum infliximab concentration on efficacy in this younger age group [19]. The results given here, which are based exclusively on the time of induction dosage, do not support the anticipation that the use of concurrent immunomodulators in conjunction with infliximab may be linked with slower clearance of infliximab and hence higher infliximab concentration. It's possible that this is due to the small sample sizes or the little time period used in the current comparison research. When given concurrently with an immunomodulator, the incidence of infliximab immunogenicity decreases, which is one method by which the influence of contemporaneous immunomodulators on infliximab pharmacokinetics has been explained.

Conclusion

An induction regimen of 5 mg/kg administered as an intravenous infusion at weeks 0, 2, and 6 followed by maintenance infusions of 5 mg/kg infliximab q8w appears to be appropriate for the treatment of UC in paediatric patients, according to an analysis of the pharmacokinetic, efficacy, and safety data from C0168T72 and supportive data from adult patients with UC. This analysis showed comparable pharmacokinetics and exposure-response between the paediatric and adult patients [20-22]. To more fully understand the pharmacokinetics of infliximab in younger paediatric patients with UC, more research on the drug's pharmacokinetics and exposure-response relationships in paediatric patients with UC younger than 6 years may be necessary.

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Conflict of Interest

Author declares no conflict of interest

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