Pharmacokinetic and Pharmacodynamics Effects of Infliximab in Children with Ulcerative Colitis

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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: 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 sub mucosa. 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. 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 [2]. 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 [3].

Materials and Method

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, Eudra CT 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 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 [4].

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 [5].

Pharmacokinetics

For the purpose of measuring serum infliximab concentrations 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. An antigen-bridging enzyme immunoassay was used to detect the presence of infliximab antibodies [6]. 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 [7].

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 [8].

Result and 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. 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 [9].

Specific strategy

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. 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.

Weight and infliximab

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 [10].

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. 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.

Acknowledgement

Conflict of Interest

Author declares no conflict of interest.

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