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Association Between Serum Concentration of Infliximab and Efficacy in Adult Patients With Ulcerative Colitis

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BACKGROUND & AIMS: We analyzed data collected during the Active Ulcerative Colitis Trials (ACT-1 and ACT-2) to assess relationships between serum concentrations of infliximab and outcomes of adults with moderate-to-severe ulcerative colitis. **METHODS:** We compared serum concentrations of infliximab with outcomes of 728 patients with moderately-to-severely active ulcerative colitis who participated in ACT-1 or ACT-2; efficacy data were collected at weeks 8, 30, and 54 (for ACT-1 only). Relationships between serum concentration of infliximab and efficacy outcomes were assessed using trend, logistic regression, and receiver operating characteristic curve analyses. We also evaluated factors that affected the relationship between exposure and response. **RESULTS:** Median serum concentrations of infliximab at weeks 8, 30, and/or 54 were significantly higher in patients with clinical response, mucosal healing, and/or clinical remission than in patients who did not meet these response criteria. There were statistically significant relationships between quartile of infliximab serum concentration and efficacy at these time points ($P < .01$). Infliximab therapy was effective for a smaller proportion of patients in the lowest quartile, and these patients had lower serum levels of albumin and a higher incidence of antibodies to infliximab than patients in other quartiles. Although the relationship between exposure to infliximab and response varied among patients, approximate serum concentrations of 41 μg/mL infliximab at week 8 of induction therapy and 3.7 μg/mL at steady-state during maintenance therapy produced optimal outcomes in patients. **CONCLUSIONS:** Serum concentrations of infliximab are associated with efficacy in patients with moderate-to-severe ulcerative colitis; however, complex factors determine the relationship between exposure to this drug and response. A prospective evaluation of the value of measuring serum concentrations of infliximab should be performed before these data can be included in patient management strategies. Clinicaltrials.gov numbers: NCT00036439 and NCT00096655.

Keywords: Anti–Tumor Necrosis Factor; Monoclonal Antibody; Pharmacokinetics; Inflammatory Bowel Disease.

Infliximab is a recombinant chimeric IgG-1κ monoclonal antibody that neutralizes the biologic activity of tumor necrosis factor (TNF)-α. Infliximab is approved for the treatment of patients with moderate-to-severe ulcerative colitis (UC) based on the results of the Active Ulcerative Colitis Trials 1 and 2 (ACT-1 and ACT-2), which evaluated 728 patients with moderate-to-severe disease. In these studies, patients treated with infliximab at weeks 0, 2, and 6 and every 8 weeks thereafter were more likely to show clinical response, clinical remission, and mucosal healing at weeks 8, 30, and 54 than patients assigned to placebo.[1,2]

Previous pharmacokinetic (PK) evaluations of infliximab use in patients with UC have shown a linear relationship between dose and serum infliximab concentration,[3] and that the systemic disposition of infliximab is influenced by body weight, serum albumin level, and the formation of antibodies to infliximab (ATI).[4] In addition, serum infliximab concentrations have been found to influence the response to treatment in Crohn's disease,[5,6] rheumatoid arthritis,[7] and psoriasis.[8]

Therapeutic drug monitoring potentially can improve outcomes in patients receiving TNF antagonists, particularly in those who have lost response to these agents owing to inadequate serum drug concentrations.[9] As such, knowledge of the target serum infliximab concentrations required for efficacy in both induction and maintenance may improve clinical decision making in UC.

Several studies have reported a positive association between infliximab concentration and efficacy outcomes in patients with inflammatory bowel disease (IBD);[10–14] however, there are limited reports on specific concentration thresholds for optimal efficacy in UC. In 1 study that identified specific infliximab cut-off levels, the analysis was based on concentration data predominantly from patients with Crohn's disease and included relatively few patients with UC (n = 13).[14] Given the differences in pathophysiology and response to treatment between Crohn's disease

Abbreviations used in this paper: **ACT-1, Active Ulcerative Colitis Trial 1; ACT-2, Active Ulcerative Colitis Trial 2; ATI, antibodies to infliximab; AUC, area under the curve; CI, confidence interval; CPW2/6/14/30/54, pre-infusion concentration at weeks 2/6/14/30/54; CW8, concentration at week 8; IBD, inflammatory bowel disease; NPV, negative predictive value; PK, pharmacokinetic; PPV, positive predictive value; ROC, receiver operator characteristic; TNF, tumor necrosis factor; UC, ulcerative colitis.**

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and UC, it is reasonable to expect some potential differences in the exposure-response relationship of anti-TNF therapies when used to manage these conditions.[9] Hence, evaluation of the relationship between serum infliximab concentrations and efficacy based on data from well-controlled clinical trials in UC patients may help to identify target serum infliximab concentrations that can be used to guide therapeutic decisions in an effort to optimize clinical outcomes in these patients.

We performed post hoc analyses of data from the ACT-1 and ACT-2 trials to assess the relationship between serum infliximab concentrations and clinical outcomes and to identify clinically relevant drug concentrations to target in pursuit of better clinical outcomes.

Patients and Methods

Patients

ACT-1 and ACT-2 (Clinicaltrials.gov numbers: NCT00036439 and NCT00096655) were randomized, double-blind, placebo-controlled, phase 3 clinical trials conducted globally. A total of 728 patients were randomized at 62 sites in ACT-1 (N = 364) and at 55 sites in ACT-2 (N = 364). The institutional review board or ethics committee at each site approved the protocols, and all patients provided informed consent. A patient disposition flow chart for the present analyses is shown in Figure 1.

Study Design

The ACT-1 and ACT-2 trials were conducted in compliance with the principles of the Declaration of Helsinki and Good Clinical Practices. The design and conduct of these trials have been reported previously.[2] Briefly, all patients had an established diagnosis of moderately-to-severely active UC, with a Mayo score[15] of 6 to 12 points (range, 0–12; with higher scores indicating more severe disease activity), despite concurrent treatment with corticosteroids, azathioprine, or 6-mercaptopurine (ACT-1 and ACT-2), or mesalamine (ACT-2 only). Patients diagnosed with indeterminate colitis, Crohn's disease, or clinical findings suggestive of Crohn's disease (ie, fistula or granuloma on biopsy) were excluded. As previously described, concurrent therapy was not required at enrollment for patients who could not tolerate or who previously failed to respond to these medications.[2] Doses of concomitant medications remained constant except for corticosteroids, which were tapered to discontinuation after induction and during maintenance therapy (ie, from week 8 forward).[2]

Patients were randomized equally to receive intravenous infusions of infliximab 5 mg/kg, infliximab 10 mg/kg, or placebo at weeks 0, 2, and 6 and then every 8 weeks through week 22 (ACT-2) or week 46 (ACT-1) (Supplementary Figure 1). Although infliximab is indicated for the treatment of UC only as a 5-mg/kg dose regimen, for the purpose of these analyses, data from patients who received the 10-mg/kg dose regimen in the ACT-1 and ACT-2 trials were included for a more robust evaluation and interpretation of the concentration-response relationship.

Study Evaluations and Analyses

Clinical outcomes were assessed using the Mayo score at week 8 (ACT-1 and ACT-2), at week 30 (ACT-1 and ACT-2), and at week 54 (ACT-1 only). Clinical response, defined as a

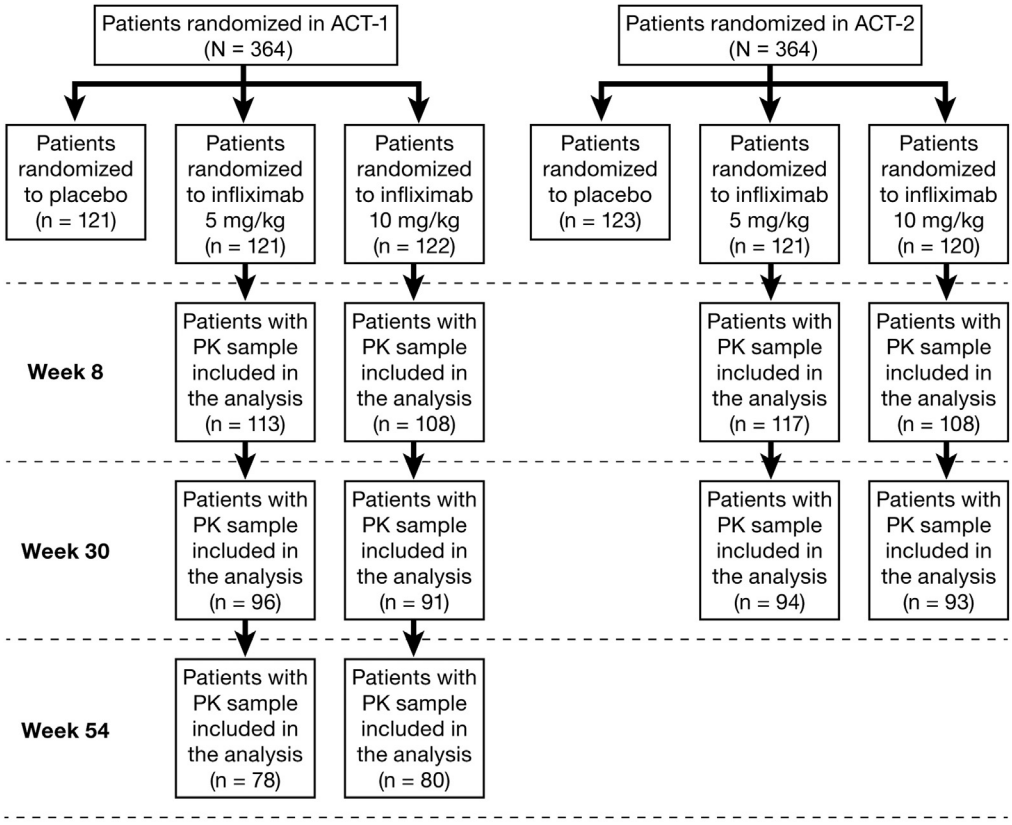

Figure 1. Patient disposition through the PK analytic time points of interest in the ACT-1 and ACT-2 trials.