Anti-Infliximab Antibodies in Patients with Rheumatoid Arthritis Who Require Higher Doses of Infliximab to Achieve or Maintain a Clinical Response

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ABSTRACT. ***Objective.*** To determine whether the need to use doses of infliximab greater than 3 mg/kg every 8 weeks to achieve or maintain clinical response in patients with rheumatoid arthritis (RA) is associated with differences in baseline clinical characteristics or anti-infliximab antibodies.

Methods. Baseline clinical characteristics and anti-infliximab levels were evaluated retrospectively in a cohort of 51 consecutive patients with RA treated with infliximab at a single center. Patients were divided into 2 groups for comparison: Group 1 patients achieved and maintained clinical responses with infliximab 3 mg/kg every 8 weeks; Group 2 patients required higher doses.

Results. Thirty-two (63%) patients required infliximab dose escalation (Group 2). There were no statistically significant differences in baseline or clinical characteristics between Group 1 and Group 2 patients. Anti-infliximab antibodies occurred in 47% of Group 2 versus 27% of Group 1 patients, with higher anti-infliximab antibody concentrations in Group 2 patients (mean ± SD: 18.3 ± 8.9 g/ml vs 7.5 ± 4.8 g/ml; p = 0.02). Patients who developed anti-infliximab antibodies were younger and receiving less prednisone at the time of infliximab initiation than patients who did not.

Conclusion. Finding higher anti-infliximab antibody concentrations in patients who needed dose escalation of infliximab to achieve or maintain clinical responses with lower serum trough levels of infliximab suggests that development of anti-infliximab antibodies may reduce clinical efficacy of infliximab in some patients with RA. (J Rheumatol 2006;33:31-6)

Key Indexing Terms:
RHEUMATOID ARTHRITIS INFLIXIMAB
ANTI-INFLIXIMAB ANTIBODIES DOSE ESCALATION CLINICAL RESPONSE

Tumor necrosis factor-α (TNF) inhibitors reduce signs and symptoms, improve patient-reported outcomes, and halt progressive joint damage in patients with rheumatoid arthritis (RA)[1-3]. Such inhibitors include the monoclonal antibodies infliximab and adalimumab and a recombinant soluble TNF receptor, etanercept.

Initially approved for the treatment of Crohn's disease, infliximab (Remicade®) is a chimeric murine/human monoclonal antibody against TNF that is indicated, in combination with methotrexate (MTX), for the treatment of patients with moderately-to-severely active RA who have had an inadequate response to MTX[4]. The recommended starting dose for patients with RA is 3 mg/kg given as an intravenous infusion followed with additional similar doses after 2 and 6 weeks and maintenance infusions every 8 weeks thereafter[4,5]. For patients who have an incomplete response, the dose may be increased to 10 mg/kg or treatments may be given as often as every 4 weeks[4]. Clinical efficacy is often judged after 14 or 22 weeks of infliximab therapy after patients have received one or more maintenance infusions.

A proportion of patients (45 to 73%) with RA require more intense infliximab dosing than the regimen outlined above to achieve or maintain satisfactory clinical responses[6-9]. The need for dose escalation may be explained, at least in part, by the development of antibodies against infliximab. Because infliximab is a chimeric molecule that is partially of murine origin, some patients develop human anti-chimeric antibodies (HACA, anti-infliximab antibodies) directed against infliximab[5,10-13].

Incidence of anti-infliximab antibody development depends on the dose and dosing regimen of infliximab, as well as use of concomitant corticosteroids or other immunosuppressant medications[5,10-13]. Higher concentrations of anti-infliximab antibodies have been linked to reduced efficacy in patients with Crohn's disease[11]. Baert, *et al* found a reduced duration of response in patients with anti-infliximab antibody concentrations ≥ 8.0 μg/ml compared with patients with lower anti-infliximab antibody concentrations (35 days vs 71 days; p < 0.001). Similarly, Farrell, *et al*[12] found that concentrations of anti-infliximab antibodies among patients

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with Crohn's disease who continued to respond to infliximab over 16 weeks were significantly lower than those of patients who had diminished clinical responses.

A potential association between the development of anti-infliximab antibodies and reduced efficacy is less well defined for patients with RA. A subset of RA patients treated with infliximab will develop anti-infliximab antibodies[3,4,14-16]. Antibodies to infliximab have been associated with altered infliximab pharmacokinetics and reduced serum infliximab concentrations over time in patients with RA[14]. Furthermore, undetectable serum concentrations of infliximab have been associated with a poorer clinical response in patients with RA[16]. Among 25 patients with RA who entered the Canadian Biologic Observational Switchover Survey[17], 9 of 18 patients who had discontinued infliximab because of lack of efficacy tested positive for antibodies to infliximab. However, in a study of 13 patients with RA who were retreated after developing antibodies to infliximab, American College of Rheumatology (ACR) scores did not correlate with antibody titers[14].

These data suggest that the presence of antibodies to infliximab could contribute to a less than optimal response to the drug. We investigated whether differences in baseline characteristics account for different dosing regimens required by patients with RA in order to achieve and maintain an adequate clinical response to infliximab and whether the need for infliximab dose escalation in these patients is associated with the presence of anti-infliximab antibodies.

MATERIALS AND METHODS

Study design. This was a retrospective analysis of the clinical characteristics, response to therapy, concomitant medications, infliximab doses, infliximab levels, and anti-infliximab antibodies in patients with RA at a single center. The first patients began infliximab treatment in March 2000; the first serum sample was collected in September 2003.

Patients. All patients met ACR criteria for RA[7] and were treated with infliximab at a single center. To be eligible for the study, all patients must have received infliximab for at least 22 weeks and have achieved a positive clinical response to infliximab (defined below). All patients provided written informed consent to donate blood prior to infliximab infusions for assessment of anti-infliximab antibodies and to use their sera and clinical data in this research. IRB Services (Aurora, ON) reviewed and approved this study.

The starting dose of infliximab in all patients was 3 mg/kg given intravenously (IV) and rounded to the nearest 100 mg, with loading doses given at weeks 0, 2, and 6, then every 8 weeks (q8wks) thereafter. Increases in doses were given for failure to achieve a clinical response on or after week 14 of therapy. A clinical response was defined as at least a 20% reduction from baseline in swollen joint count (44 joints assessed) and at least a 20% reduction in C-reactive protein, erythrocyte sedimentation rate, or health assessment questionnaire (HAQ) score[18]. This definition was selected because it is used by the Régie de l'Assurance-maladie du Québec (RAMQ), the government agency responsible for drug reimbursement, to approve continued payment and coverage. An infliximab dose increase was defined as either an increase greater than 20% of the dose per infusion for more than 2 infusions or a reduction in infusion interval to less than 8 weeks.

Patients were categorized by pattern of clinical response and infliximab dosing. Group 1 patients achieved and maintained clinical responses with their starting dose of 3 mg/kg infliximab q8wks. Group 2 patients included patients who required a dose increase either to achieve or maintain a clinical response. Group 2a patients did not achieve a clinical response by week 14 but subsequently achieved a clinical response to a higher dose of infliximab. Group 2b patients achieved an initial clinical response by week 14 but sometime thereafter required a dose increase to maintain a waning clinical response. Categorization of patients into Group 1, Group 2a, and Group 2b was done prior to, and was therefore not based on, analyses of baseline characteristics, serum infliximab, or anti-infliximab antibody test results.

Measurement of serum infliximab concentrations and anti-infliximab antibodies. Serum samples were tested for trough levels of infliximab and presence and concentrations of anti-infliximab antibodies. Peripheral blood samples of 5 to 10 ml were obtained just before infliximab infusions. Sera were separated by centrifugation and stored at -70°C in 1-5 ml aliquots. An aliquot from each serum sample was shipped overnight on dry ice to Prometheus Laboratories, Inc. (San Diego, CA, USA) for measurement of infliximab concentration and anti-infliximab antibodies. All samples were shipped and tested together.

Infliximab concentrations were measured using an enzyme-linked immunosorbent assay (ELISA) with a lower level of sensitivity of 1.40 μg/ml (Prometheus Laboratories, Inc.). Antibodies to infliximab were measured using a double antigen ELISA with infliximab bound to the plate as the capture antigen and biotinylated infliximab used to detect serum antibodies bound to the capture antigen (Prometheus Laboratories, Inc.). The lower level of sensitivity of the anti-infliximab antibody assay was 1.7 μg/ml, and the ceiling of detection was 26.33 μg/ml. Concentrations of anti-infliximab antibodies > 26.33 μg/ml were assigned a value of 26.33 μg/ml for purposes of data analyses.

Serum infliximab interferes with the anti-infliximab antibody assay[11]. For that reason, informative samples for the presence of anti-infliximab antibodies were defined as those that contained no measurable infliximab (i.e., < 1.40 μg/ml) or those that contained measurable anti-infliximab antibodies; samples that contained measurable infliximab but no anti-infliximab antibodies were judged to be non-informative.

Statistical analysis. Data were tabulated and summarized descriptively. Comparisons between groups were performed using Student's t test or Mann-Whitney test for continuous data and Fisher's test for categorical data.

RESULTS

Categorization of patients into Groups 1 and 2. Fifty-one consecutive patients were enrolled and characterized by patterns of clinical response and infliximab dosing (Table 1). Among the entire group of patients, the mean initial and maximum infliximab doses, expressed as mg/kg q8wks, were 3.3 mg/kg and 4.4 mg/kg, respectively ($p < 0.001$, 2-tailed paired t test). Thirty-two (63%) patients were characterized as Group 2 patients. About twice as many patients required an infliximab dose increase to maintain a clinical response than to achieve an initial clinical response; 41% of

Table 1. Infliximab dosing patterns in patients with RA.

	Group 1	Group 2	Group 2a	Group 2b
n (%) total patients)	19 (37)	32 (63)	11 (22)	21 (41)
Infliximab dose, mg/kg every 8 weeks, mean (SD)				
Baseline	3.6 (0.5)*	3.2 (0.4)	3.3 (0.6)	3.1 (0.2)
Maximum dose	3.5 (0.6)	4.9 (1.4)	5.1 (1.3)	4.7 (1.4)
Maximum infliximab dose, mean (SD) % of baseline dose	100 (12)	153 (33)	154 (22)	152 (39)

* $p = 0.008$, Group 1 versus Group 2; $p = 0.002$, Group 1 versus Group 2b, 2-tailed t test.

all patients were Group 2b patients and 22% were Group 2a. Group 1 patients received a slightly higher dose of infliximab at baseline than Group 2 patients (mean ± SD: 3.6 ± 0.5 vs 3.2 ± 0.4 mg/kg per infusion; p = 0.008, 2-tailed t test). The maximum infliximab dose for Group 2 patients was 153% of the starting dose and was similar in both Groups 2a and 2b (Table 1).

Clinical characteristics of Group 1 and 2 patients. Demographic and clinical characteristics at the time of initiation of infliximab therapy were similar between Group 1 and Group 2 patients, with no statistically significant differences (Table 2). The average age of patients was in the mid- to late-fifties. The majority of patients were females and had long-standing RA that was seropositive for rheumatoid factor and resistant to multiple disease modifying antirheumatic drugs. About one quarter of patients had taken prior biologic therapy. Over 90% of patients in each group were on concurrent MTX, with no differences in doses among the groups. More Group 1 than Group 2b patients (82% vs 57%) were taking concomitant prednisone at the time infliximab therapy was initiated, although the difference was not statistically significant (p = 0.08, Fisher's test). When used, doses of prednisone were similar in Group 1 and Group 2 patients.

Antibodies to infliximab. At least one serum sample was available for testing for anti-infliximab antibodies in all 51 patients. Two or more serum samples were available for 48 (94%) patients, with a mean of 3 samples per patient (range 1 to 5) for each group (Table 3). Overall, 33 patients (65%) had at least one informative sample.

Thirteen of 33 (39%) patients with informative samples tested positive for anti-infliximab antibodies; antibodies were seen more commonly in Group 2 than Group 1 patients (47% vs 29%), although the difference was not statistically significant (p = 0.3, 2-tailed Fisher's test). The concentration (mean ± SD) of anti-infliximab antibodies for Group 2 patients was more than twice as high as concentrations in Group 1 patients (18.3 ± 8.9 vs 7.5 ± 4.8 μg/ml, p < 0.001, 2-tailed t test). Group 2 patients were 3 times more likely to have anti-infliximab antibody concentrations higher than 8.0 μg/ml. Additionally, serum samples from Group 2 patients were more consistently positive for anti-infliximab antibodies than serum samples from Group 1 patients; of all informative serum samples from patients who had anti-infliximab antibodies, 96% of samples from Group 2 patients were positive for anti-infliximab antibodies (100% in Group 2a and 93% in Group 2b) compared with 42% of samples from Group 1 patients.

Clinical characteristics of anti-infliximab antibody positive and negative patients. Comparisons were made between baseline clinical characteristics of patients who developed anti-infliximab antibodies (n = 13) and those who did not (n

Table 3. Infliximab levels and anti-infliximab antibodies in patients with RA.

	Group 1 (n = 19)	Group 2 (n = 32)	Group 2a (n = 11)	Group 2b (n = 21)
Serum samples tested, mean (SD)	3.1 (1.1)	3.5 (0.9)	3.5 (1.0)	3.6 (0.8)
Patients with ≥ 1 informative sample, n (%)	14 (74)	19 (58)	8 (73)	11 (50)
Patients with anti-infliximab antibodies, n (%)	4 (29)	9 (47)	4 (50)	5 (45)
Maximum μg/ml concentration, mean (SD)	7.5 (4.8)*	18.3 (8.9)	15.3 (12.9)	20.7 (4.2)
Levels > 8 μg/ml, %	25	78	75	80

* p = 0.02, Group 1 vs Group 2; p = 0.005, Group 1 vs Group 2b, 2-tailed t test. SD: standard deviation.

Table 2. Demographic and clinical characteristics of patients with RA at baseline.

	Group 1 (n = 19)	Group 2 (n = 32)	Group 2a (n = 11)	Group 2b (n = 21)
Age, yrs, mean (SD)	59 (8)	54 (12)	56 (10)	53 (13)
Female, %	79	66	55	71
Weight, kg, mean (SD)	73 (14)	73 (17)	74 (18)	73 (17)
Duration of RA, yrs, mean (SD)	14 (10)	16 (10)	19 (11)	15 (10)
RF positive, %	84	79*	100*	70*
HAQ, mean (SD)	1.5 (0.7)	1.8 (0.7)	2.0 (0.5)	1.7 (0.8)
ESR, mm/h, median (range)	31 (1–89)	28 (6–73)	20 (12–50)	43 (6–73)
Swollen joint count, mean (SD)	21 (9)	20 (8)	19 (7)	20 (9)
No. of failed DMARD, mean (SD)	2.8 (1.4)	3.5 (1.8)	3.5 (1.8)	3.4 (1.8)
Failed previous biologic therapy, %	26	27	45	18
Taking MTX, %	100	91	91	91
Dose mg/week, median (range)	15 (7.5–25)	12.5 (5–20)	11.3 (5–20)	12.5 (5–25)
Taking prednisone (%)	84	66	82	57
Dose, mg/day, median (range)	6.8 (5–10)	10 (5–25)	10 (5–25)	10 (5–15)

* RF unknown for 3 Group 2 patients (2 Group 2a patients and one Group 2b patient). SD: standard deviation; HAQ: Health Assessment Questionnaire; ESR: erythrocyte sedimentation rate; DMARD: disease modifying antirheumatic drug; RF: rheumatoid factor.

= 20) (Table 4), excluding patients with non-informative samples (n = 18). Patients who developed anti-infliximab antibodies had similar baseline clinical characteristics to patients who did not, including baseline infliximab doses, except they were about 10 years younger (p = 0.003) and were taking about half the mean (± SD) dose of prednisone (3.7 ± 3.9 vs 7.4 ± 4.3 mg/day, p = 0.02, 2-tailed t test). The subset of patients with anti-infliximab antibodies concentrations greater than 8 μg/ml had a mean prednisone dose of 3.1 mg/day.

Serum trough levels of infliximab (Figure 1) were lower in patients who had anti-infliximab antibodies, compared with patients with no anti-infliximab antibodies or with non-informative serum samples [median (range) 0 (0-5.88) vs 2.2 (0-16.9) μg/ml; p = 0.003, 2-tailed Mann-Whitney test].

DISCUSSION

Our study addressed whether the need to use doses of infliximab greater than 3 mg/kg q8wks to achieve or maintain clinical response in patients with RA is associated with differences in baseline clinical characteristics of patients or the development of anti-infliximab antibodies. We found that 63% of patients in our cohort required infliximab dose escalation. The results of this study extend findings by others of anti-infliximab antibodies in RA by showing that anti-infliximab antibodies were present in 47% of patients who required a dose increase in infliximab and had informative serum samples. Anti-infliximab antibodies were present in concentrations more than twice as high and were more consistently detected in patients who required a dose escalation of infliximab compared to patients who did not. Patients who developed anti-infliximab antibodies were about 10 years younger (difference in mean ages) and were taking less prednisone at the time of infliximab initiation than patients who did not develop anti-infliximab antibodies. No other differences were identified in clinical characteristics at the time of infliximab initiation, including MTX doses and starting doses of infliximab. Median serum trough levels of infliximab were significantly lower in patients who had anti-infliximab antibodies, suggesting that high concentrations of anti-infliximab antibodies may have neutralized infliximab in this subset of patients.

Table 4. Demographic and clinical characteristics of patients positive and negative for anti-infliximab antibody.

	Anti-infliximab antibody positive (n = 13)	Anti-infliximab antibody negative (n = 20)
Required dose increase, n (%)	9 (69)	10 (50)
Age, yrs, mean (SD)	49 (9)	59* (10)
Female, %	77	60
Weight, kg, mean (SD)	69 (167)	74 (14)
Duration of RA, yrs, mean (SD)	13 (9)	16 (10)
HAQ, mean (SD)	1.7 (0.6)	1.7 (0.7)
ESR, mm/h, median (range)	31 (5–73)	26 (1–71)
Swollen joint count, mean (SD)	20 (7)	24 (10)
RF positive, %	92	79
Failed DMARD, mean (SD)	3.5 (1.8)	2.8 (1.4)
Failed previous biologic therapy, %	38	25
Baseline infliximab dose, mg/kg every 8 wks, mean (SD)	3.4 (0.5)	3.2 (0.4)
Baseline MTX, % receiving/mean (SD) dose mg/kg	100/13.6 (6.1)	100/15.3 (6.8)
Baseline prednisone, % receiving	54	85
Last prednisone, % receiving	31	60
Baseline prednisone, mg/day, mean (SD)	3.7 (3.9)	7.4††,††† (4.3)
Last prednisone, mg/day, mean (SD)	2.5 (4.0)	4.1 (4.3)
Serum samples tested, mean (SD)	3.7 (0.6)	3.2 (1.1)
Mos between infliximab initiation and last serum sample, median(range)	24 (6–43)	23 (5–45)

* p = 0.003; ** p = 0.02, anti-infliximab antibody positive vs antibody negative patients, 2-tailed t test and p = 0.02, baseline prednisone vs. last prednisone dose, 2-tailed paired t test.

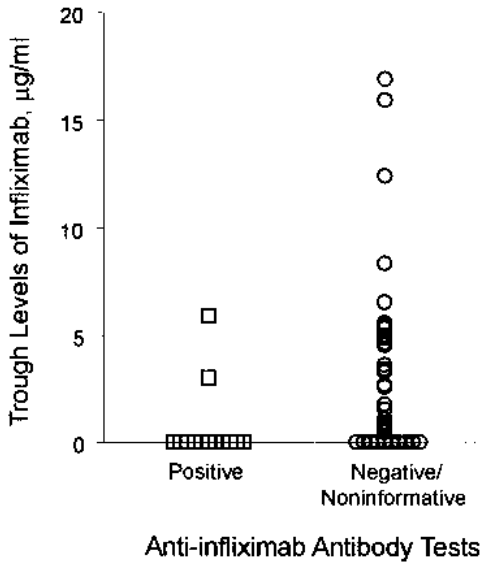

Figure 1. Median serum trough levels of infliximab. Infliximab levels were measured by ELISA in the serum of patients with anti-infliximab antibodies (open squares) and without anti-infliximab antibodies or with non-informative samples (open circles).

The frequency and degree of infliximab dose escalation in our study is remarkably similar to that reported in patients in other cohorts[6,8,9,19]. Gilbert, *et al*[19] found that infliximab dose escalation occurred during the first year of treatment in nearly 60% of 598 infliximab recipients identified from integrated pharmacy and medical claims from 61 US health plans. An increase in infliximab dose was also reported within the first year of therapy in 61% of 394 patients in 2 rheumatology practices and 56% of 1324 patients participating in a longitudinal study of RA outcomes[20].

The degree of infliximab dose escalation is similar to previous reports. The average final dose of infliximab in rheumatology patients reported by Stern and Wolfe was 5 mg/kg[20]. In a retrospective audit of 244 charts, a mean infliximab dose of 3.4 mg/kg q8wks at baseline increased to 4.1 mg/kg q8wks at the time of the last dose, after a mean of

14.8 months followup[6]. In our study, the mean infliximab dose of 3.3 mg/kg q8wks at baseline increased to 4.4 mg/kg q8wks, after a mean followup of 26.8 months.

Several factors have been associated with infliximab dose escalation. In the study by Gilbert, *et al*[19], 66.4% of patients aged 35-44 increased infliximab dose versus 39.3% in patients aged 65 and older (odds ratio, OR: 1.94). In the same study, patients using MTX during pretreatment period were more likely to require dose escalation than those without (OR: 1.48).

In our cohort, there were no statistically significant differences in Group 1 and Group 2 demographics and disease characteristics at the time of infliximab initiation, although prednisone therapy tended to be less in Group 2 patients. A lower proportion of Group 2b patients were on prednisone at the time of infliximab initiation compared with Group 1 patients, and the lower prednisone doses might have contributed to a need for higher doses of infliximab to control disease activity in some patients.

Another possible explanation for the requirement for infliximab dose escalation is the development of neutralizing anti-infliximab antibodies. Development of anti-infliximab antibodies has been reported in patients with Crohn's disease[11,13,21-25] and RA[3,5,15,16] after receiving infliximab. The incidence of anti-infliximab antibodies in the treatment of Crohn's disease in phase 2 and 3 trials with infliximab was 6-16%[24-27]. In the more recent ACCENT 1 clinical trial in Crohn's disease, 27% of patients developed anti-infliximab antibodies[13]. Among children and young adults with Crohn's disease, 25% of patients developed anti-infliximab antibodies[22]. The highest incidence of anti-infliximab antibodies (61%) occurred in patients with Crohn's disease who were treated with a mean of 3.9 infliximab infusions over a mean period of 10 months[11]. In our report, the overall incidence of anti-infliximab antibodies (excluding patients with non-informative samples) was 39%.

The proportion of patients with non-informative anti-infliximab antibody results in this study (35%) compares favorably with results of other studies, in which data were equivocal for 33% to 46% of patients tested[15,24]. However, in the report by Lipsky, *et al*[15], informative anti-infliximab antibody results were available for only 60 of 428 patients treated with infliximab, with non-informative testing in 86% of patients.

Differences in concurrent corticosteroids or other immunosuppressants, infliximab doses, or dosing schedules, and anti-infliximab antibody assays may contribute to the wide range in reported frequency of anti-infliximab antibodies[26]. Hanauer, *et al*[13] reported that development of antibodies to infliximab was lower in patients with Crohn's disease who received concurrent corticosteroid plus MTX therapy. Consistent with a negative effect of corticosteroids on anti-infliximab antibody formation, Farrell, *et al*[12] found that anti-infliximab antibody levels were lower in patients with Crohn's disease who received 200 mg pre-medication IV hydrocortisone prior to their infliximab infusion, but this did not eliminate anti-infliximab antibody formation. In contrast, Baert, *et al*[11] found no association with use of corticosteroids at the time of infliximab infusion and the development of anti-infliximab antibodies. In our report, the mean dose of prednisone at the time of infliximab initiation was lower in patients with RA who developed anti-infliximab antibodies (3.7 mg/day), compared with patients who did not (7.4 mg/day).

Another factor affecting the development of anti-infliximab antibodies is the concomitant use of immunosuppressive agents such as MTX[11-13]. In our report, 90% of the patients were receiving MTX, and there was no association between the dose of MTX therapy and the development of anti-infliximab antibodies.

The incidence of anti-infliximab antibody development depends on the dose and dosing regimen of infliximab[5,11,13,27]. In a study of 101 patients with active RA who received 5 infusions at 0, 2, 6, 10, and 14 weeks, the development of antibody to infliximab correlated inversely with dose: 57%, 25%, and 10% of patients tested positive after receiving 5 doses of 1 mg/kg, 3 mg/kg, or 10 mg/kg infliximab[5]. Episodic infliximab dosing is more immunogenic than more regular dosing regimens for patients with Crohn's disease. In a study of 573 patients with Crohn's disease[13], 28% of patients who received infliximab episodically developed antibodies to infliximab over a year, compared with 9% of patients who received 5 mg/kg and 6% of patients who received 10 mg/kg every 8 weeks. In another Crohn's disease study, among patients who were treated episodically with infliximab, 61% of 125 patients developed antibody to infliximab within 5 infusions[11]. In our study, all patients started with the same dose and regular dosing regimen.

The presence and level of anti-infliximab antibodies appear to play a role in reduced clinical efficacy in Crohn's disease[11,21], with reduced duration of response to treatment in 125 patients with Crohn's disease ($p < 0.001$)[11]. Patients with levels of anti-infliximab antibodies > 8.0 μg/ml before an infusion had a duration of clinical response that was approximately half the length of that in patients without antibodies (35 days vs 71 days)[11]. Hanauer, *et al*[21] found that fewer patients positive for anti-infliximab antibody attained clinical remission compared to patients who had negative or inconclusive antibody levels.

No prior studies have addressed the issue of clinical response in relation to the presence of anti-infliximab antibodies in RA. We report a higher proportion of Group 2 patients who tested positive for anti-infliximab antibodies, compared with Group 1 patients. Although not statistically significant, anti-infliximab antibodies were present in higher concentrations and were more consistently detectable in patients who required an infliximab dose increase compared with patients who did not require dose escalation. These

associations between the need for infliximab dose escalation and higher concentrations of anti-infliximab antibodies suggest the anti-infliximab antibodies may have interfered with infliximab efficacy in our patients.

Results reported by Hanauer, *et al*[13] support infliximab neutralization as a possible mechanism by which anti-infliximab antibodies mediate reduced clinical efficacy of infliximab. Median trough infliximab concentrations in patients positive for anti-infliximab antibodies were lower than in patients negative for anti-infliximab antibodies or with inconclusive anti-infliximab antibody results. Our findings are consistent with that report: median trough levels of infliximab were lower in patients with anti-infliximab antibodies than in patients without anti-infliximab antibodies or non-informative samples (0 vs 2.2 μg/ml, $p < 0.001$).

Although our study did not address the timing of the development of anti-infliximab antibodies, Baert, *et al* found that anti-infliximab antibodies were detected as early as 4 weeks after single infusion in about 45% of patients, and 61% of patients developed detectable anti-infliximab antibodies after the 5th infusion[11]. Early development of anti-infliximab antibodies suggests these antibodies could play a causal role in early treatment failures with infliximab, as well as in patients whose clinical benefit wanes over time.

Our study is the first to raise a possible causal relationship between the presence of high concentrations of antibodies to infliximab and the need for infliximab dose escalation in patients with RA.

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