Infliximab Dose and Clinical Status: Results of 2 Studies in 1642 Patients with Rheumatoid Arthritis

RICHARD STERN and FREDERICK WOLFE

ABSTRACT. ***Objective.*** Infliximab is an effective anti-tumor necrosis factor (TNF) agent widely used in the treatment of rheumatoid arthritis (RA). Initially recommended at a dose of 3 mg/kg, subsequent label revisions allowed doses up to 10 mg/kg or at 4-week intervals rather than the originally suggested 8-week intervals, if clinically indicated. The doses used have implications for efficacy and costs, but no data exist for actual dose used in the US. This study evaluates the dosage and rates of increase in infliximab-treated patients with RA.

Methods. Study 1: Review of patient charts and infusion records for 394 RA patients from 2 large rheumatology practices comprising 15 rheumatologists in Dallas, Texas. Study 2: Survey of 1324 RA patients using infliximab participating in a longitudinal study of RA outcomes. Patients completed a detailed questionnaire about clinical status and infliximab use.

Results. The results of the 2 studies were similar: the average infliximab dose was 5 mg/kg, increasing most rapidly until the end of the first years, after which the increase was slowed. Increases > 3 mg/kg occurred in 61% of patients in Study 1 and 56% in Study 2. The 8-week treatment interval was almost universally used, and more than 95% of infusions occurred in this interval. The most common reason for increase in dose was insufficient response. Among patients who completed 4 infusions, 75% remained on therapy at 2 years after infliximab start. The average improvement in Health Assessment Questionnaire disability score was 0.28.

Conclusion. Infliximab dose increases are common, particularly during the first year of treatment. The average dose is 5 mg/kg. Seventy-five percent of patients continue using infliximab 2 years after treatment onset. (J Rheumatol 2004;31:1538–45)

Key Indexing Terms:
INFLIXIMAB   DOSE   RHEUMATOID ARTHRITIS

Infliximab is a chimeric (mouse-human) IgGκ monoclonal antibody to tumor necrosis factor-α (TNF-α) approved for the treatment of rheumatoid arthritis (RA) since November 1999. It is indicated in combination with methotrexate (MTX) for reducing signs and symptoms of RA, inhibiting the progression of structural damage, and improving physical function in patients with moderately to severely active RA who have had an inadequate response to other disease modifying antirheumatic drugs (DMARD).

Several clinical trials have established the safety and efficacy of infliximab in the treatment of RA[1-6]. A 54-week study demonstrated sustained efficacy of the 3 mg/kg dose at 8-week intervals, and this dose has been established as the baseline dose for RA treatment[7]. Based on this study and other clinical trial data, the US Food and Drug Administration (FDA) approved the use of infliximab at the starting dose of 3 mg/kg. Infliximab is administered using a loading dosage at 3 mg/kg given at weeks 0, 2, and 6, followed by administration every 8 weeks thereafter. The recommendation as to dose was modified after infliximab had been released for use in the clinic to allow subsequent increases up to 10 mg/kg, as well as to allow reduction of the dosing interval to every 4 weeks, at the discretion of the treating physician based on the patient's response.

Not all patients respond adequately to the 3 mg/kg dose[8]. To date there are no data in the US showing the average dose and dosing interval used to treat RA in the usual clinical setting, although data from Sweden indicate that doses > 3 mg/kg are common[9]. We evaluated infliximab dosage and clinical status among US patients, where dose and use is less restrictive, using 2 different settings. In Study 1, we evaluated infliximab in 2 large multirheumatologist clinics where infusion centers were in use. In Study 2, we evaluated patients receiving infliximab who were participants in the National Data Bank for Rheumatic Diseases (NDB) longitudinal study of RA outcomes. We present data from these 2 studies to define the current use patterns of infliximab for the treatment of RA in the United States.

MATERIALS AND METHODS

Study 1

Patient population. Two large rheumatology practices comprising 15 rheumatologists in Dallas, Texas, agreed to participate in the first part of this study. Each practice has its own infliximab infusion center. A list of all patients receiving infliximab since the opening of the infusion center was provided by each practice and used to identify all patients receiving infliximab. All patients ≥ 18 years of age who met the 1987 American College of Rheumatology criteria for RA[10] and who currently or had previously received at least 4 infusions of infliximab met inclusion criteria for this study. Four infusions were chosen because increase in dose ordinarily does not occur before the completion of the loading dose. Patients who received infliximab for any reason other than RA were not studied. There were no restrictions on concomitant nonbiologic DMARD or previous treatment with etanercept or anakinra. Patients who had participated in an infliximab trial where the dose was fixed were excluded. All data were obtained from the office chart by the first author (RS).

Of 613 patients receiving infliximab infusions, 516 had a diagnosis of RA and were treated with infliximab between June 7, 2000, and March 10, 2003. Three patient charts could not be reviewed for the study period because they were at a satellite clinic and could not be obtained for review. These patients were excluded from analysis. Among others excluded, 80 had not yet completed 4 infusions, 10 were participants in a drug study, 25 had incomplete records, and 2 had concomitant illnesses.

A total of 394 patients completed at least 4 infusions, forming the basis of this report. All available demographic data were obtained from the chart, including age, sex, ethnicity, years of disease, and rheumatoid factor (RF) status. At each infusion visit, the status of infliximab therapy was noted, including the current dose, patient weight, date, infusion interval, change in dose, reason for dose change, days since first infusion, days since previous infusion, infusion reactions, date of discontinuation and reason, and erythrocyte sedimentation rate (ESR). The dose of prednisone, MTX, leflunomide, and other DMARD was recorded at each clinic visit. Quantitative clinical status measurements were not usually available.

Dose escalation. The normal starting dose of infliximab for RA was defined as 3 mg/kg every 8 weeks after a loading dose at Weeks 0, 2, and 6. A dose escalation was defined as an increase in dose of infliximab or a decrease in dosing interval ordered by the treating physician. The time to first dose escalation was recorded together with the reason, if documented in the chart. Categories for dose escalation included: incomplete clinical response, clinical response lasting < 8 weeks, previous clinical response but now incomplete clinical response, not specified, and other. The intended dose interval, per physician's orders, was recorded for each infusion. Discontinuations along with reasons for discontinuation were also recorded.

Study 2

Patients in this study were participants in the NDB longitudinal study of RA. The NDB is a rheumatic disease research data bank in which patients complete detailed self-report questionnaires at 6-month intervals. The characteristics of the NDB have been reported[11-13]. At each questionnaire assessment, demographic variables were recorded including sex, age, ethnic origin, education level, and current marital status. Study variables included the Stanford Health Assessment Questionnaire functional disability index (HAQ disability)[14,15], a visual analog scale (VAS) for pain, a VAS global disease severity, VAS sleep and fatigue scales[16], the Arthritis Impact Measurement Scales (AIMS)[17,18], anxiety and depression scales[19,20], and the Medical Outcome Study Short Form-36 mental and physical component scales (MCS and PCS)[21]. A lifetime comorbidity index was calculated from a list of 13 comorbid conditions by counting the number present for each patient.

Immediately following the semiannual questionnaire of July 2002, a supplemental questionnaire was mailed to patients known to be receiving infliximab. The questionnaire asked participants to obtain their height, weight, infliximab dose, and number of vials of infliximab from the medical staff at the time of their next infusion. The mean date of questionnaire completion was September 9, 2002. Of 1886 reports, usable replies were obtained from 1324 patients. Patients with usable reports were slightly older: 63.1 versus 61.4 years (p = 0.013); had lower HAQ scores: 1.1 vs 1.3 (p < 0.001); and were less likely to use prednisone: 42% vs 52% (p < 0.001). The patients were treated by and represented referrals to the NDB from 302 US rheumatologists.

Ongoing clinical status data were obtained from the semiannual survey of July 2002. In addition, baseline clinical data were available for 769 patients at the time they started infliximab in their rheumatologist's office. These patients were enrolled in the NDB as part of an infliximab safety registry.

Statistical analysis. In Study 1 longitudinal analysis was performed using Kaplan-Meier life tables and Cox regression as the primary methods of analysis. In Study 2, comparisons between dose groups used t-tests and chi-square analyses, as indicated. Linear, fractional polynomial, and locally weighted regression (lowess) were used to describe relationships between infliximab dose and predictor variables. Lowess regression is a locally weighted regression of the dependent variable on an independent variable. The smoothed result is displayed graphically. Analyses used Stata version 8.0[22]. All tests were 2-tailed and statistical significance was set at 0.05.

RESULTS

Study 1

Characteristics of the patients. Of the 394 patients, 314 (79.7%) were women and 280 (71.1%) were RF positive. The mean age at the date of first infusion was 56.3 years (SD 13.7), and the duration of RA at this time was 11.7 years (SD 10.6). There were 158 patients (40.0%) with missing data for disease duration because rheumatologists did not record this information in the charts. Of the 226 patients with ethnicity data, 73.9% were white, 13.3% were African American, 11.5% were Hispanic, and 1.3% were Asian or Pacific Islanders. Other data were complete.

Dosing interval. Almost all patients (95%) were kept on an 8-week dosing regime (Table 1), therefore increased frequency of treatment did not contribute substantially to overall dose escalation.

Dose increase. A total of 3327 infusions were recorded from June 7, 2000, to March 10, 2003. Figure 1 illustrates lowess regression used to describe the dose at each infusion over the almost 3 years of this study. Figure 2 models the relationship of dose to time using fractional polynomial regression. Both graphs show similar results; however, Figure 2 describes a prediction model that is not available for Figure 1.

Table 1. Interval between infliximab infusions for 394 patients with RA in Study 1.

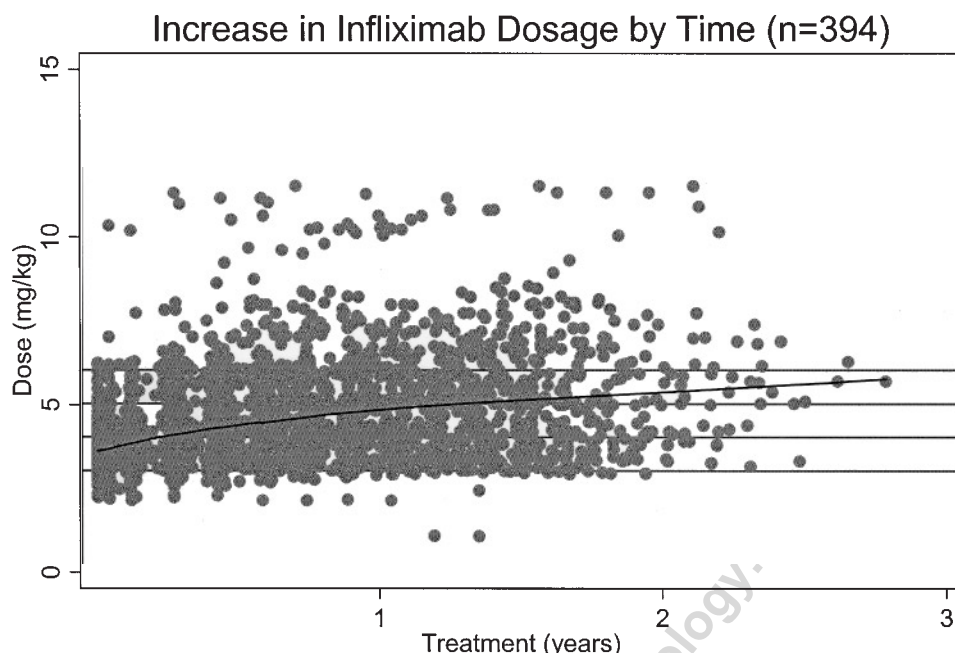| Interval Between Infusions, weeks	No. of observations	%
3	2	0.1
4	30	0.9
5	12	0.4
6	87	2.6
7	25	0.8
8	3169	95.3
Total	3325	100.0

Increase in Infliximab Dosage by Time (n=394)

Figure 1. Change in infliximab dose over time. Regression line is determined by locally weighted regression (lowess).

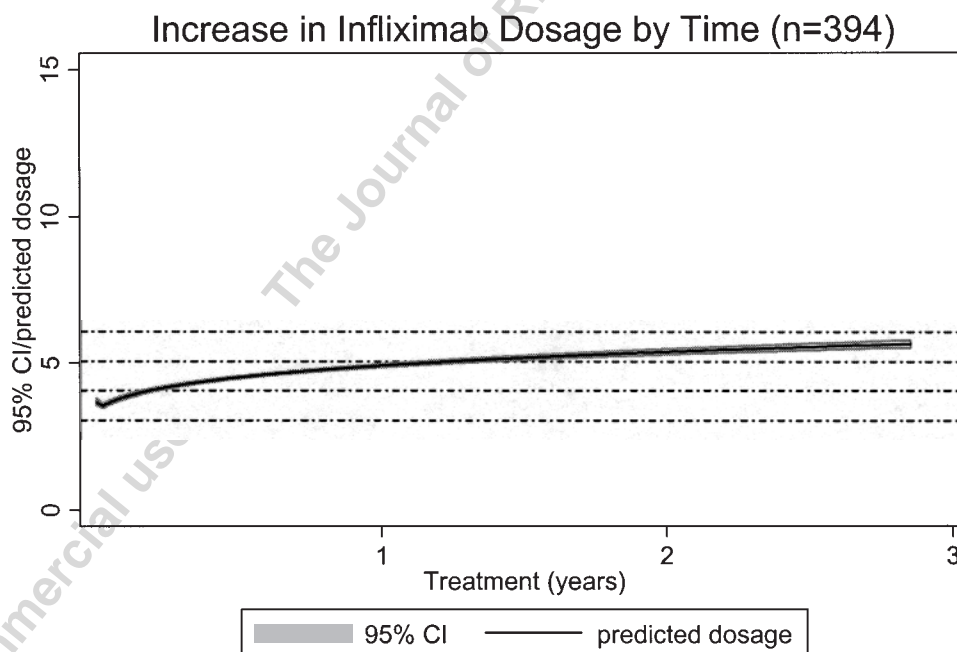

Increase in Infliximab Dosage by Time (n=394)

Figure 2. Change in infliximab dose over time modeled by fractional polynomial regression.

The average dose increase per year was 1.36 mg/kg to the 10th infusion (434 days) followed by an approximate plateau (Figures 1 and 2). At the start of therapy the mean infliximab dose was 3.6 (SD 0.6, range 2.2–6.2) mg/kg. At final observations, the mean dose was 4.9 (SD 1.6, range 1.1–11.5) mg/kg. At one year the mean was 4.9 mg/kg and at 2 years, 5.1 mg/kg.

We also estimated the mean doses at major timepoints

using area under the curve (AUC) measurements that allowed the inclusions of shorter intervals between treatments. As almost all of the treatments occurred at 8-week intervals, there was no significant difference in the mean doses presented above when the AUC method was used.

Reasons for dose increase. For the 239 patients who had a dose increase, 52.6% were for an overall insufficient clinical response, 27.2% were for a sufficient clinical response that lasted less than 8 weeks, 7.0% were given to previous responders whose response became incomplete. Miscellaneous reasons accounted for 7.8%, and 5.4% were not specified.

For variables that had no missing data, Cox regression showed that neither sex (male = 1) [hazard ratio (HR) 0.95, 95% CI 0.69 to 1.31], nor RF positivity (HR 1.19, 95% CI 0.89 to 1.59) nor clinic 1 versus clinic 2 (HR 0.83, 95% CI 0.64 to 1.09) influenced dose escalation.

Time to dose increase. As shown in Figure 3, the median time to dose escalation was 7 months, and 25% of patients were estimated to have had their first dose escalation by 102 days, 50% by 213 days, and 75% by 557 days. As indicated above, the 2 rheumatology clinics did not differ in their rate of time to first dose escalation (p = 0.18).

Discontinuation of therapy. Kaplan-Meier survival analysis indicated that 85.7% of patients continued therapy at 1 year and 75% of patients in Study 1 remained on therapy at 2 years (Figure 4). Fifty-seven (57) patients discontinued infliximab. Patients who discontinued infliximab had a higher probability of increasing infliximab dose (HR of 1.56, 95% CI 1.1–2.2)) compared to those remaining on infliximab. After comorbid medical conditions (such as infection, surgery, etc. — 29.8%), the most common reason for discontinuation was cost (22.8%), followed by lack of efficacy (21%) and adverse effects (17.5%) (Table 2).

Study 2

Study 2 addressed issues of infliximab dose increase in 1324 patients completing mailed surveys. As shown in Table 3, participants had evidence of active RA. The mean age at the time of infusion was 63.1 (SD 11.7) years and 78.7% were female. The mean duration of RA was 14.0 (10.9) years.

At a mean of 1.5 years after starting infliximab, the mean (SD) and median doses were 5.0 (2.0) and 4.6 mg/kg, respectively (Figure 5). On average, the dose increased by 0.4 mg/kg/year (95% CI 0.2–0.5), as shown in Figure 6. If it is assumed that the remainder of the 100 mg infliximab vial is used or charged for, the mean (SD) and median doses are 5.5 (SD 2.1) and 5.0 mg/kg, respectively. Assuming that the remainder of the 100 mg infliximab vial is always used, 43.9% of patients used 3 mg/kg and 56.1% used higher doses. The average doses in the 3 mg/kg and > 3 mg/kg group were 3.5 (0.5) and 6.3 (1.8) mg/kg, respectively.

Correlates of infliximab dose. Demographics were not associated with dose, but clinical variables (HAQ pain, global PCS, RA Disease Activity Index, etc.) and comorbidity were significantly more abnormal in patients using > 3 mg/kg

Time to infliximab dose escalation
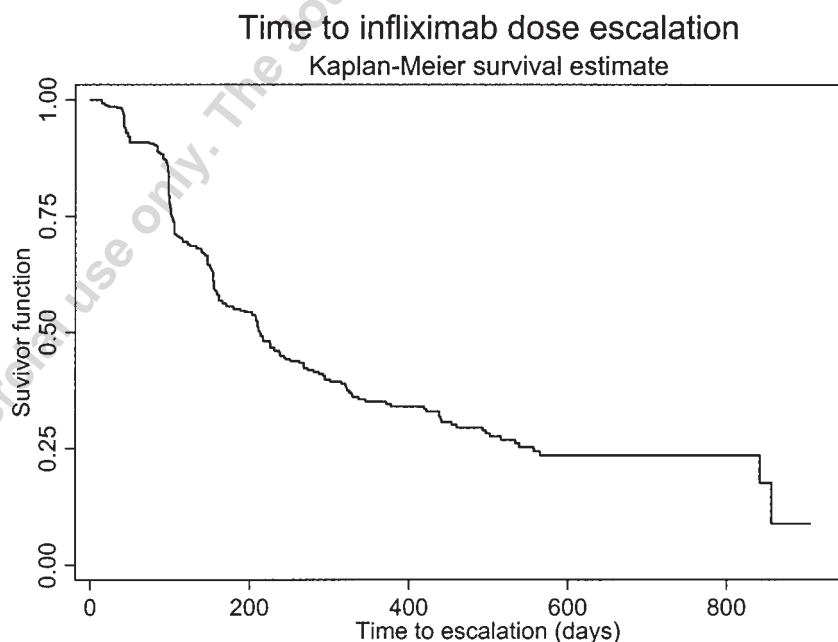### Kaplan-Meier survival estimate

Figure 3. Time until dose increase (Study 1). The median time to dose escalation was 7 months, and 25% of patients are estimated to have their first dose escalation by 102 days, 50% by 213 days, and 75% by 557 days.
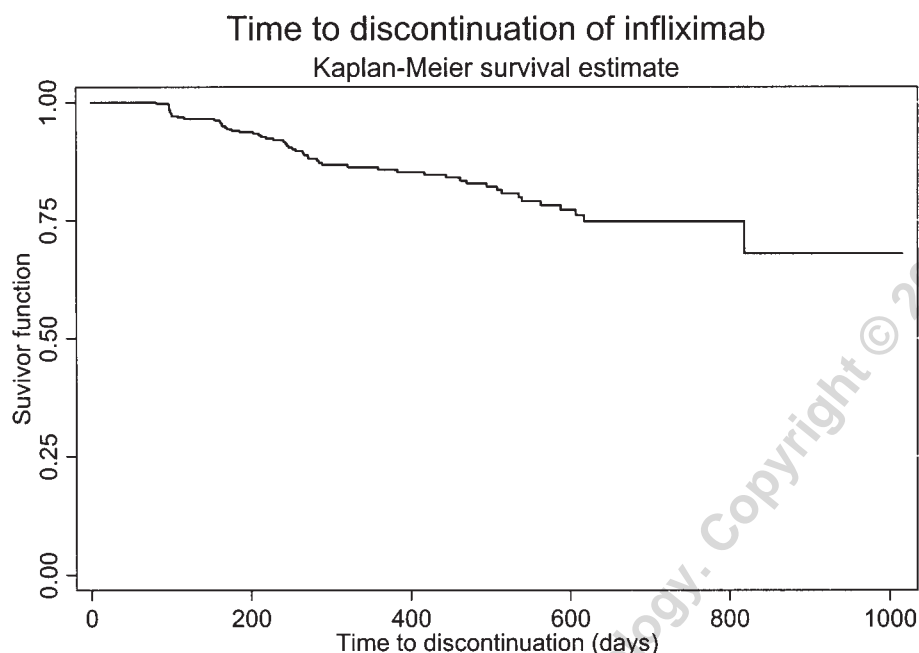
Time to discontinuation of infliximab
Kaplan-Meier survival estimate

Figure 4. Kaplan-Meier survival analysis indicated that 75% of patients in Study 1 remained on therapy at 2 years. Fifty-seven patients discontinued infliximab.

compared with those using 3 mg/kg (Table 4). The 17% of RA patients meeting survey criteria for fibromyalgia[23] were 2.1 times (95% CI 1.5–3.1) more likely to be receiving more than 3 mg/kg infliximab. The actual dose increase for this group compared with those without fibromyalgia was 0.9 (95% CI 0.6–1.3) mg/kg, and the actual dose was 5.8 (SD 2.4) mg/kg.

Among 556 patients whose data were available at the time they started infliximab in their rheumatologists' offices, HAQ (0–3), pain (0–10), and patient-global improved by 0.28, 1.46, and 0.98, respectively. Initial scores for HAQ, pain, and global did not predict (p > 0.5) subsequent infliximab dose, but improvement scores for pain (p = 0.007) and HAQ (p = 0.006) were associated with lower dosage.

DISCUSSION

The analyses of these 2 studies show similar results: the average infliximab dose is about 5 mg/kg, increasing most

rapidly until the end of the first year, after which the increase is slowed. Increases occurred in 61% of patients in Study 1 and 56% in Study 2. The 8-week interval was almost universally used, and more than 95% of infusions occurred in this interval. The most common reason for increase in dose was insufficient response.

In terms of increase in dose, the results of our studies are in agreement with those of van Vollenhoven, *et al*, who reported in a 2002 abstract that 45% of 184 Swedish patients had a dose increase > 3 mg/kg[9]. van Vollenhoven, *et al* also

Table 2. Reasons for infliximab discontinuation (Study 1).

Reason for Discontinuation	N	%
Insurance	13	22.8
Lack of efficacy	12	21.0
Adverse reaction	10	17.1
Lost to followup	2	3.5
Other medical reasons	17	29.8
Not specified	3	5.3
Total	57	100.0

Table 3. Demographic characteristics of 1324 NDB patients with RA in infliximab dose survey (Study 2).

Variable	Mean or %
Age, yrs	63.1
Sex, % male	21.3
Married, %	69.3
High school graduate, %	87.3
Non-Hispanic white, %	96.0
Disease duration, yrs	14.0
Pain, 0–10	3.8
HAQ, 0–3	1.2
Global severity, 0–10	3.5
Fatigue, 0–10	4.4
Sleep disturbance, 0–10	3.7
Anxiety, 0–10	3.4
Depression, 0–10	2.5
Physical component score, SF-36	32.2
Mental component score, SF-36	44.7
RADAI score, 0–10	3.4

RADAI: Rheumatoid Arthritis Disease Activity Index.

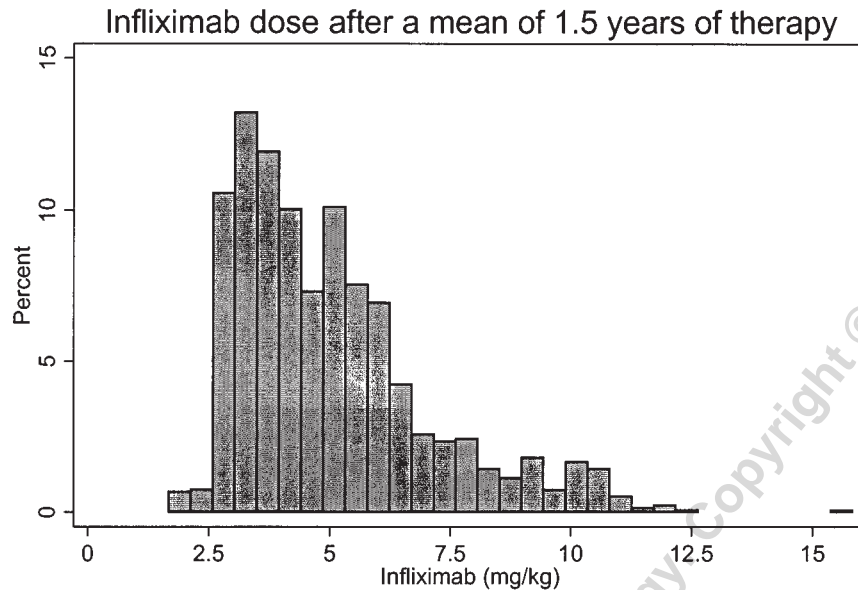## Infliximab dose after a mean of 1.5 years of therapy

Figure 5. Infliximab dose distribution in 1324 patients with RA (Study 2) at a mean of 1.5 years after starting infliximab; the mean (SD) and median doses were 5.0 (2.0) and 4.6 mg/kg, respectively.
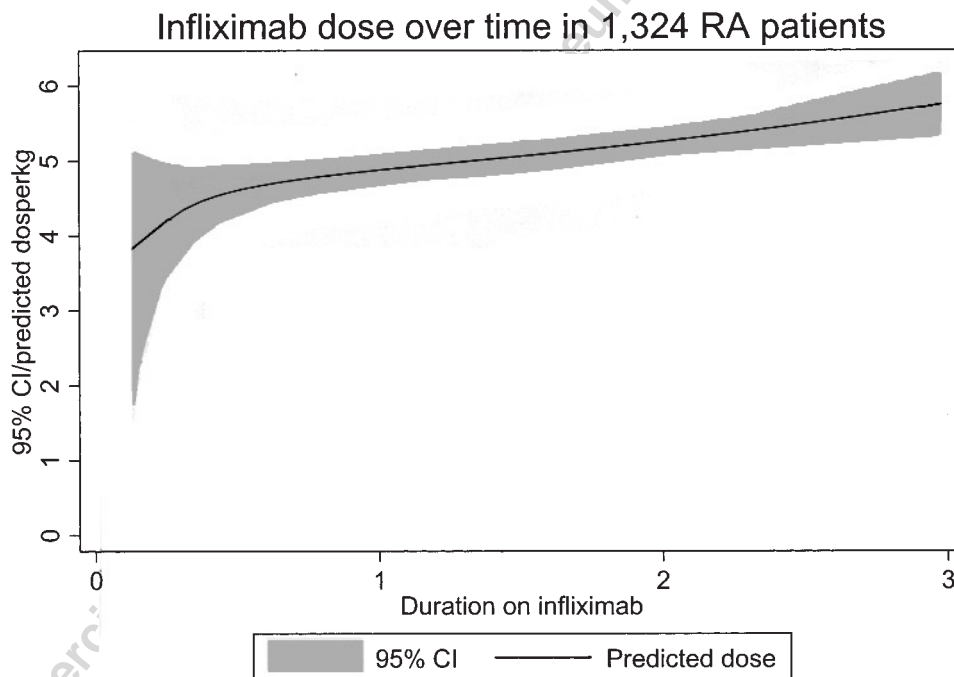
Infliximab dose over time in 1,324 RA patients

Figure 6. Pattern of infliximab dose increase modeled by fractional polynomial regression in Study 2. Most of the dose increase occurs in the first year. Data are sparse after the second year as shown by the wide confidence intervals.

reported improvement following dose increase, something that we think would have been true among the patients in our studies. However, we had no data to address this issue. We did find that higher doses were associated with worse clinical status. This is to be expected, as patients doing well would have no need for increased dose.

Dose increase may also have occurred in response to evidence that patients using higher dose of infliximab have fewer infliximab antibodies and have a better overall clinical response. The latter may be the result of low trough levels at the 3 mg/kg dose[8]. Lower trough levels may be associated with increased antibody formation and reduced clinical efficacy[24].

The results of this study have implications regarding the

fTable 4. Severity characteristics of infliximab-treated patients according to dose group (Study 2). Data reflect status at a mean of 8 weeks prior to completion of the infliximab supplemental survey.

Variable	Infliximab ≤ 3 mg/kg, N = 581, Mean or % SD		Infliximab > 3 mg/kg, N = 743, Mean or % SD		p
Age, yrs	63.4	12.0	62.8	11.4	0.407
Sex, % male	22.9		20.1		0.210
Lifetime comorbidity score, 0–11	1.7	1.5	2.2	1.6	< 0.001
Pain, 0–10	3.4	2.7	4.1	2.7	< 0.001
HAQ, 0–3	1.1	0.7	1.2	0.7	0.002
Global severity, 0–10	3.3	2.4	3.7	2.5	< 0.001
RADAI score, 0–10	2.9	1.9	3.7	2.0	< 0.001
Fatigue, 0–10	4.1	2.8	4.7	2.9	< 0.001
Fibromyalgia (survey criteria), %	10.5		20.2		< 0.001
Sleep disturbance, 0–10	3.5	3.0	3.8	3.1	0.200
Anxiety, 0–10	3.4	1.9	3.4	2.0	0.957
Depression, 0–10	2.4	1.7	2.5	1.8	0.517

RADAI: Rheumatoid Arthritis Disease Activity Index.

most appropriate dose of infliximab and also the increased cost associated with higher doses. It is important to recognize, however, that the dose of infliximab was always greater than 3 mg/kg because infliximab comes in 100 mg vials. Thus the actual dose used when the dose prescribed is 3 mg/kg is 3.5 mg/kg. In addition, while it is the case that higher doses are often used, titration with clinical activity scores such as the Disease Activity Score (DAS)[25,26] might allow lower doses and more effective utilization of infliximab[27].

Of interest, we were able to confirm in the 2 study populations that the level of HAQ improvement was similar to that seen in the infliximab clinical trials[1], and in this instance was a HAQ improvement of 0.28 units.

Our data represent the results of observational studies. In contrast to randomized clinical trials (RCT), where dose ranging does not usually occur, observational studies represent real-life conditions where patients and physicians change doses and discontinue therapy in response to clinical conditions. In that respect, observational studies offer insights into efficacy that may not be available in RCT. That 75% of patients remain on therapy after 2 years of treatment suggests longterm effectiveness. Increases in dose suggest that 3 mg/kg may not be an adequate dose for most patients. Although we have no data on this point, it is possible that higher doses used earlier in the course of treatment might result in better efficacy and longer duration of use.

Among the limitations of Study 1 is that it represents the work of only 2 groups of rheumatologists. It is possible that other groups might treat patients differently. However, the agreement between the smaller first study and much larger second study is quite good, offering reassurance on this point.

In Study 2 we did not report intervals between infusions, as we did not feel that we could adequately represent this timing with a cross-sectional study. However, 77% of patients reported a dose interval of 8 weeks or more. Therefore, it is possible that the average dose in Study 2 is slightly higher than what we have noted in the study results. In addition, ideas about infliximab dose and dose interval are changing, and the data presented here should be considered usual practice only at the time the study was conducted.

In summary, in agreement with non-US data, infliximab dose increases are common, particularly during the first year of treatment. The average dose is 5 mg/kg. Seventy-five percent of patients continue using infliximab 2 years after treatment onset.

REFERENCES

1. Lipsky PE, van der Heijde DMFM, St. Clair EW, et al. Infliximab and methotrexate in the treatment of rheumatoid arthritis. N Engl J Med 2000;343:1594-602.
2. Lipsky PE, Felson DT, Maini RN. Blocking tumor necrosis factor inhibits radiographic damage even in patients who show minimal or no clinical improvement: comment on the concise communication by Boers. Arthritis Rheum 2002;46:2817-8.
3. Maini R, St. Clair EW, Breedveld F, et al. Infliximab (chimeric anti-tumour necrosis factor alpha monoclonal antibody) versus placebo in rheumatoid arthritis patients receiving concomitant methotrexate: a randomised phase III trial. ATTRACT Study Group. Lancet 1999;354:1932-9.
4. St. Clair EW. Radiographic joint damage in rheumatoid arthritis: a community-based perspective. Arthritis Rheum 2001;44:1231-3.
5. St. Clair EW. Infliximab treatment for rheumatic disease: clinical and radiological efficacy. Ann Rheum Dis 2002;61 Suppl 2:ii67-9.
6. Maini RN, Breedveld FC, Kalden JR, et al. Therapeutic efficacy of multiple intravenous infusions of anti-tumor necrosis factor alpha monoclonal antibody combined with low-dose weekly methotrexate in rheumatoid arthritis. Arthritis Rheum 1998;41:1552-63.
7. Lipsky P, St. Clair EW, Furst D, et al. 54 week clinical and radiographic results from the ATTRACT trial: a phase III study of infliximab in patients with RA despite methotrexate [abstract]. Arthritis Rheum 1999;42 Suppl:S401.
8. St. Clair EW, Wagner CL, Fasanmade AA, et al. The relationship of serum infliximab concentrations to clinical improvement in rheumatoid arthritis: results from ATTRACT, a multicenter,

randomized, double-blind, placebo-controlled trial. Arthritis Rheum 2002;46:1451-9.

9. van Vollenhoven RF, Brannemark S, Klareskog L. Efficacy of infliximab (Remicade) dose increases: a nested case-control study [abstract]. Arthritis Rheum 2002;46 Suppl:S541.

10. Arnett FC, Edworthy SM, Bloch DA, et al. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. Arthritis Rheum 1988;31:315-24.

11. Wolfe F, Anderson J, Burke TA, Arguelles LM, Pettitt D. Gastroprotective therapy and risk of gastrointestinal ulcers: risk reduction by COX-2 therapy. J Rheumatol 2002;29:467-73.

12. Wolfe F, Flowers N, Burke TA, Arguelles LM, Pettitt D. Increase in lifetime adverse drug reactions, service utilization, and disease severity among patients who will start COX-2 specific inhibitors: quantitative assessment of channeling bias and confounding by indication in 6689 patients with rheumatoid arthritis and osteoarthritis. J Rheumatol 2002;29:1015-22.

13. Wolfe F, Flowers N, Anderson J. The National Rheumatic Disease Data Bank: case mix and severity characteristics of patients in rheumatological practice [abstract]. Arthritis Rheum 1998;41 Suppl:S132.

14. Fries JF, Spitz PW, Young DY. The dimensions of health outcomes: the Health Assessment Questionnaire, disability and pain scales. J Rheumatol 1982;9:789-93.

15. Fries JF, Spitz PW, Kraines RG, Holman HR. Measurement of patient outcome in arthritis. Arthritis Rheum 1980;23:137-45.

16. Wolfe F, Hawley DJ, Wilson K. The prevalence and meaning of fatigue in rheumatic disease. J Rheumatol 1996;23:1407-17.

17. Meenan RF, Gertman PM, Mason JH, Dunaif R. The Arthritis Impact Measurement Scales. Arthritis Rheum 1982;25:1048-53.

18. Meenan RF. The AIMS approach to health status measurement: conceptual background and measurement properties. J Rheumatol 1982;9:785-8.

19. Hawley DJ, Wolfe F. Depression is not more common in rheumatoid arthritis: a 10 year longitudinal study of 6608 rheumatic disease patients. J Rheumatol 1993;20:2025-31.

20. Hawley DJ, Wolfe F. Anxiety and depression in patients with RA: A prospective study of 400 patients. J Rheumatol 1988;15:932-41.

21. Ware JE, Sherbourne CD. The MOS 36-Item Short-Form Health Survey (SF-36). 1. Conceptual framework and item selection. Med Care 1992;30:473-83.

22. Stata Corporation. Stata statistical software: release 8.0. College Station, TX: Stata Corporation; 2003.

23. Wolfe F. Pain extent and diagnosis: development and validation of the regional pain scale in 12,799 patients with rheumatic disease. J Rheumatol 2003;30:369-78.

24. Baert F, Noman M, Vermeire S, et al. Influence of immunogenicity on the long-term efficacy of infliximab in Crohn's disease. N Engl J Med 2003;348:601-8.

25. van der Heijde DMFM, van't Hof MA, van Riel PLCM, van Leeuwen MA, van Rijswijk MH, van de Putte LBA. Validity of single variables and composite indices for measuring disease activity in rheumatoid arthritis. Ann Rheum Dis 1992;51:177-81.

26. van der Heijde DMFM, van't Hof MA, van Riel PLCM, et al. Judging disease activity in clinical practice in rheumatoid arthritis: first step in the development of a disease activity score. Ann Rheum Dis 1990;49:916-20.

27. den Broeder AA, Creemers MC, van Gestel AM, van Riel PL. Dose titration using the Disease Activity Score (DAS28) in rheumatoid arthritis patients treated with anti-TNF-alpha. Rheumatology Oxford 2002;41:638-42.