EXTENDED REPORT

Double-blinded infliximab dose escalation in patients with rheumatoid arthritis

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Objective: To determine the efficacy, safety and pharmacokinetics of infliximab dose escalation in patients with rheumatoid arthritis (RA) who had an inadequate response to 3 mg/kg infliximab treatment or whose disease flared after initially responding.
Methods: Patients with active RA, despite receiving methotrexate, received infliximab 3 mg/kg at weeks 0, 2, 6 and 14 in one of the three arms of the START trial. Beginning at week 22, patients had their infliximab dose increased in a double-blind fashion in increments of 1.5 mg/kg if the total tender and swollen joint count did not improve by at least 20% from baseline (lack of response) or the improvement at week 22 or later worsened by 50% or more (criterion for flare).
Results: Of the 329 evaluable patients, 100 (30.4%) patients required dose escalation at or after week 22 because of flare or lack of response. The majority of patients (>80%) who received up to three dose escalations showed ≥20% improvement in the total tender and swollen joint count after their last dose escalation. Patients who required dose escalations generally had lower preinfusion serum infliximab concentrations than those who did not require them. The incidences of adverse events and serious adverse events for the patients who received dose escalation(s) were similar to those of patients who did not receive dose escalation.
Conclusion: Fewer than one-third of patients required a dose escalation. The majority of patients showed improvement after receiving increased doses of infliximab, without an increased risk of adverse events.

Infliximab has emerged as an effective treatment for rheumatoid arthritis (RA).[1–3] The recommended dosage of infliximab for RA is an induction regimen of 3 mg/kg followed by maintenance dosing every 8 weeks.[4] For patients with an incomplete response to 3 mg/kg infliximab, the product labelling for the United States allows for increasing the dose up to 10 mg/kg or reducing the interval between infusions to 4 weeks. Recent retrospective studies of governmental and private medical insurance databases, registries and medical records indicate that dose escalation of infliximab in patients with an inadequate response is not uncommon in actual clinical practice.[5–12]

Although infliximab dose titration may be commonly employed, only a few reports have systematically evaluated the efficacy and safety of this practice. In a retrospective analysis of data from the Stockholm TNFα Follow-up Registry (STURE), van Vollenhoven *et al* reported that dose increases of infliximab were associated with modest improvements in disease activity,[11] but the authors concluded that the improvements might have occurred without dose increases as part of the natural course of the disease. In a Belgian prospective study, Durez *et al* found that patients benefited from dose escalation of a single vial (100 mg) of infliximab without an increased incidence of adverse events.[5] However, in both of these studies, the decision to increase the infliximab dose was based on the subjective clinical judgment of the treating physician.

The reasons why some patients need dose escalations of infliximab are unclear. However, the results of studies of infliximab in RA[13] and Crohn's disease[14] suggest that clinical response may be related to trough serum concentrations. The Safety Trial for Rheumatoid Arthritis with Remicade Therapy (START) was designed to evaluate the risk of serious infections in patients with RA who received infliximab.[15] In this paper, we report the efficacy, safety and pharmacokinetic results from patients who were assigned to group 2, in which dose escalation was studied.

METHODS

The design and methods for the START trial have been reported previously.[15] Briefly, adult patients with active RA (six swollen and six tender joints) despite receiving methotrexate (MTX) were randomly assigned to one of three groups. Patients assigned to groups 1 and 3 received placebo or a stable dose of infliximab as described previously[15] and were not included in this analysis. Patients assigned to group 2 received infliximab 3 mg/kg at weeks 0, 2, 6 and 14. Beginning at week 22, patients in group 2 had their infliximab dose increased in a double-blinded fashion in increments of 1.5 mg/kg at weeks 22, 30, 38 and 46 if they met the criteria for lack of response or flare. The criterion for lack of response was <20% improvement from baseline in the combined tender joint count (TJC) and swollen joint count (SJC). The criterion for flare was a 50% or greater diminution in improvement in the combined TJC and SJC from baseline to the time at which response was initially achieved (at week 22 or thereafter). Patients who did not respond at week

Abbreviations: ACR 20, American College of Rheumatology 20% response criteria; CRP, C reactive protein; IVRS, interactive voice response system; MTX, methotrexate; RA, rheumatoid arthritis; SJC, swollen joint count; START, Safety Trial for Rheumatoid Arthritis with Remicade Therapy; TJC, tender joint count; TNFα, tumour necrosis factor α

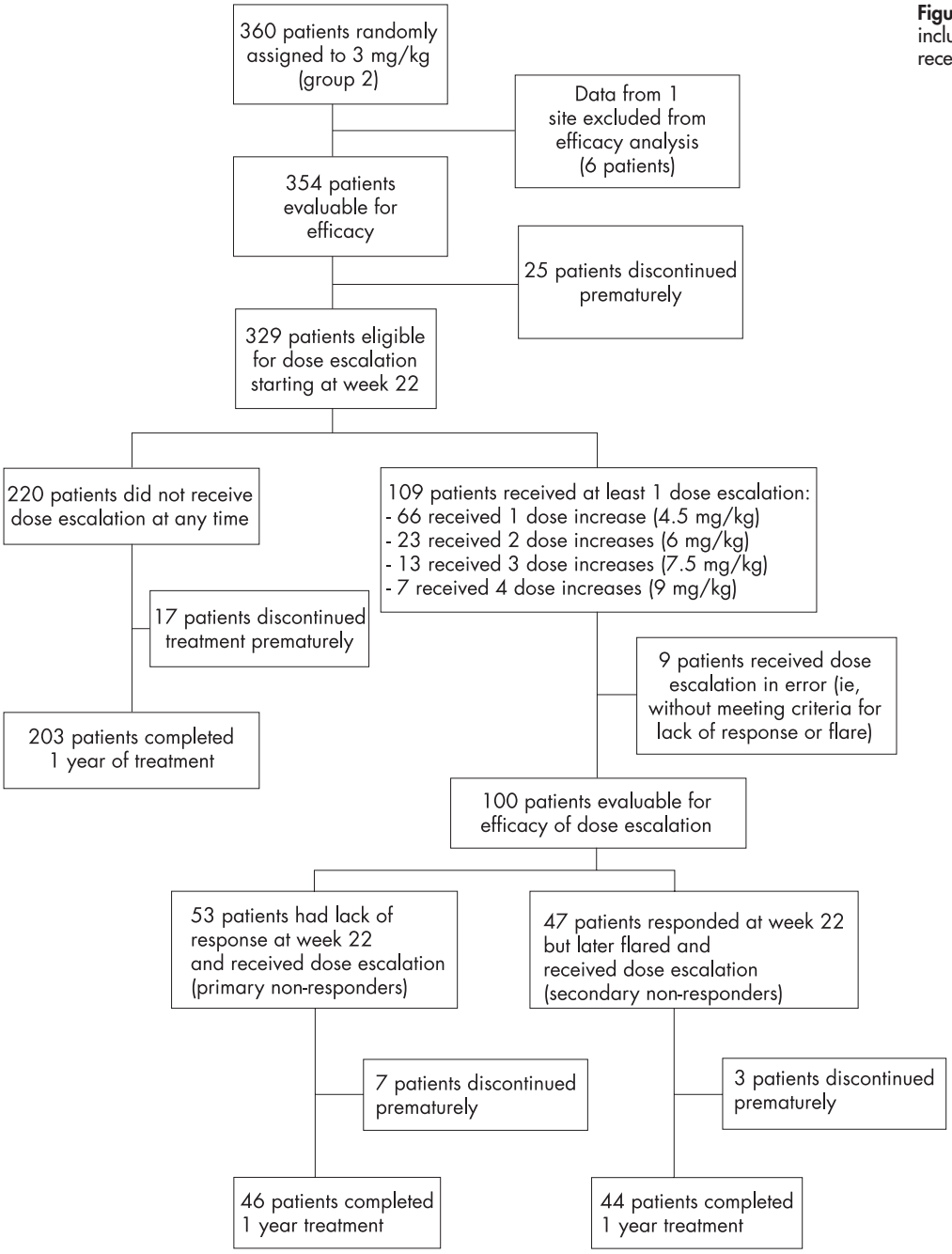

Figure 1 Disposition of patients in group 2, including the number of patients who received dose escalations.

22 were considered to be "primary non-responders". Patients who responded at week 22 but later flared were considered to be "secondary non-responders". Similar criteria have been used by others.[16] All patients received concomitant MTX (up to 25 mg/week) throughout the study.

Beginning at week 22, at each visit (weeks 22, 30, 38 and 46) the numbers of tender and swollen joints for each patient were entered into a telephone interactive voice response system (IVRS). The IVRS automatically calculated the total TJC and SJC and determined whether the patient met the criteria for lack of response or flare. The site pharmacist was automatically notified of the dose to be given. Patients, investigators and study personnel (except for the site pharmacist) were unaware of the treatment group allocation and the number and timing of dose increases the patient received.

Clinical response to infliximab treatment up to week 22 was measured using the American College of Rheumatology 20% response criteria (ACR 20).[17] However, the ACR 20 was not used to determine whether a patient required dose escalation or to determine response in patients who received dose escalations.

Serum infliximab levels and antibodies to infliximab were determined by using previously described methods.[18] Pre- and postinfusion blood samples were collected for infliximab concentration determination at weeks 0, 2, 6, 14, 22, 26, 30, 38, 46, 48, 50 and 54. Preinfusion blood samples were collected for antibody to infliximab testing at weeks 0, 48, 50, 54 and 66. Because the presence of infliximab in the serum sample can interfere with the antibody detection assay, patients were considered to have an inconclusive antibody status if they tested negative for antibodies to infliximab but had detectable concentrations of infliximab in their serum.[19]

Statistical methods

Patient data were included in the dose escalation analysis for pharmacokinetics and efficacy if they received dose escalations according to the protocol. Data for patients who received at

Table 1 Baseline characteristics of patients who were eligible for dose escalation

Assessment*	No dose escalation (n = 220)	Received dose escalation (n = 109)†	Primary non-responders‡ (n = 53)§	Secondary non-responders¶ (n = 47)§	Dose escalated to 9 mg/kg (n = 7)
Women, No (%)	170 (77.3)	92 (84.4)	46 (86.8)	40 (85.1)	6 (85.7)
Age (years)	54.0 (44.0, 62.0)	53.0 (47.0, 59.0)	52.0 (47.0, 64.0)	54.0 (45.0, 59.0)	57.0 (44.0, 66.0)
Weight (kg)	69.3 (60.1, 81.0)	72.0 (61.4, 83.0)	69.0 (61.0, 78.0)	75.0 (63.0, 86.0)	74.5 (59.3, 77.7)
Disease duration (years)	8.2 (3.5, 14.5)	8.2 (3.1, 16.5)	9.4 (5.2, 17.9)	7.3 (2.5, 14.3)	12.1 (1.8, 23.9)
Swollen joint count	16.0 (11.0, 22.0)	13.0 (9.0, 17.0)	14.0 (9.0, 22.0)	13.0 (9.0, 16.0)	12.0 (9.0, 17.0)
Tender joint count	23.0 (16.5, 31.0)	21.0 (14.0, 28.0)	25.0 (16.0, 33.0)	19.0 (13.0, 25.0)	23.0 (11.0, 31.0)
HAQ (0–3)	1.5 (1.0, 1.9)	1.6 (1.0, 2.0)	1.9 (1.1, 2.1)	1.5 (1.0, 1.9)	1.1 (0.9, 2.4)
Corticosteroids at baseline, No (%)	133 (60.5)	65 (59.6)	29 (54.7)	32 (68.1)	4 (57.1)
Extra-articular manifestations (%)	89 (40.5)	38 (34.9)	20 (37.7)	15 (31.9)	3 (42.9)
CRP (mg/l)	17 (7, 32)	16 (7, 33)	14 (7, 28)	16 (7, 30)	7 (4, 12)
Methotrexate (mg/week)	15.0 (10.0, 17.5)	15.0 (10.0, 15.0)	15.0 (10.0, 15.0)	15.0 (10.0, 17.5)	15.0 (10.0, 25.0)

CRP, C reactive protein; HAQ, Health Assessment Questionnaire
*All values are medians (interquartile range) unless otherwise specified.
†All patients who received at least one dose escalation are included.
‡A primary non-responder was a patient who did not respond at week 22.
§Patients who received dose escalations incorrectly are not included.
¶A secondary non-responder was a patient who responded at week 22 but later flared.

least one infusion of the study drug were included in the safety analysis and were categorised in the treatment group that most closely corresponded to the infliximab dosage actually received. Analyses suitable for categorical data (ie, χ^2) were used to compare the proportion of patients responding and the rates of adverse events. All statistical tests were two-sided and were performed at the $\alpha = 0.05$ level.

RESULTS

Patient population, baseline characteristics and patient disposition

A total of 360 patients were assigned to group 2 at the beginning of the START study, and 329 patients were eligible for dose escalation(s) starting at week 22 (fig 1). Of these, 220 patients (66.9%) did not receive a dose escalation at any time, while 100 patients were evaluable for the efficacy of dose escalation.

The baseline characteristics of patients in group 2 who received dose escalation(s) were generally similar to those of patients who did not receive a dose escalation (table 1). Patients who responded at week 22 but later flared had a lower median baseline TJC, SJC, disease duration and Health Assessment Questionnaire score than those who did not respond at week 22, but the differences were minimal. The median baseline C reactive protein (CRP) for the seven patients who received four dose escalations (7 mg/l) was nearly normal and well below the median baseline CRP for group 2 as a whole. These seven patients also had a greater median disease duration at baseline (12.1 years) than group 2 as a whole (8.2 years).

Initial efficacy of infliximab in group 2

As reported previously, 26% of patients in group 1 (placebo plus MTX), 58% of patients in group 2 (3 mg/kg plus MTX) and 61% of patients in group 3 (10 mg/kg plus MTX) achieved an ACR 20 response at week 22.[15]

In group 2, the proportion of ACR 20 responders increased from 36.0% at week 2 to 49% at week 6 and 55.0% at week 14. However, there was little change in the proportion of ACR 20 responders between weeks 14 and 22 (58.0%).

Efficacy of dose escalation: all patients

In table 2, patients are grouped according to the total number of dose escalations they received. Responders to the dose escalation regimen were patients who showed a 20% or more improvement from baseline in the total number of tender or swollen joints 8 weeks after the last dose escalation. The majority (80/100 (80%)) of patients responded to the dose escalation regimen. Seven of the 20 patients who did not respond to dose escalation received the maximum number of four dose escalations allowed by the protocol. The remaining 13 patients could not receive further dose escalation, as their last dose escalation was at week 46 (n = 8) when the last study

Table 2 Summary of responders by the number of dose escalations for patients who received dose escalations according to the protocol*

Patients and responders	Received dose escalation*	Primary non-responders*‡	Secondary non-responders* §
Patients whose dose was escalated correctly	100	53	47
Patients with one dose escalation	59	23	36
Responders, No (%)†	51 (86.4)	21 (91.3)	30 (83.3)
Patients with two dose escalations	21	13	8
Responders, No (%)†	17 (81.0)	11 (84.6)	6 (75.0)
Patients with three dose escalations	13	10	3
Responders, No (%)†	12 (92.3)	9 (90.0)	3 (100.0)
Patients with four dose escalations	7	7	0
Responders, No (%)†	0 (0.0)	0 (0.0)	NA

NA, not applicable.
*Patients who received dose escalations without meeting the criteria for lack of response or flare were not included.
†Responders were defined as patients who achieved at least 20% improvement in the number of tender and swollen joints from baseline at 8 weeks after the last dose escalation.
‡A primary non-responder was a patient who did not respond at week 22.
§A secondary non-responder was a patient who responded at week 22 but later flared.

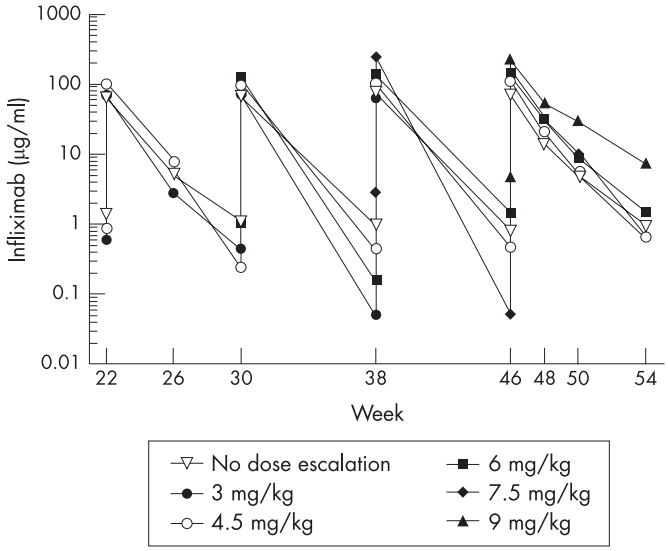

Figure 2 Mean pre- and postinfusion serum infliximab concentrations for patients in group 2. Open triangles represent values for patients who received 3 mg/kg without receiving dose escalation(s). Closed circles represent values for patients who received 3 mg/kg but later received dose escalation(s). Open circles, closed squares, closed diamonds and closed triangles represent values for patients who were receiving 4.5 mg/kg, 6 mg/kg, 7.5 mg/kg and 9 mg/kg, respectively.

treatment was administered, or they had to discontinue the study drug prematurely owing to adverse events (n = 4) or lack of efficacy (n = 1). A summary of the improvement in tender and swollen joints in patients who received or did not receive dose escalation is provided as supplementary material 1 (available at http://ard.bmjjournals.com/supplemental).

Efficacy of dose escalation: subsets of patients with lack of response or flare

Forty-one of 53 primary non-responders (77%) responded to dose escalation(s). Five of the 12 non-responding patients from this group could not receive subsequent dose escalation as their last dose increase was at week 46 or they discontinued the study drug prematurely owing to lack of efficacy or adverse events. The other seven patients received all four dose escalations according to the study design and never responded.

Of the 47 secondary non-responders, 39 (83%) responded to dose escalation. Of the remaining eight patients, one discontinued study treatment prematurely because of an adverse event, and seven received their last dose escalation at week 46. The study design only allowed a maximum number of three dose escalations for secondary non-responders (at weeks 30, 38 and 46). Thus, the subset of primary non-responders was eligible to receive up to four dose escalations, whereas secondary non-responders could receive a maximum of three dose escalations.

None of the seven patients who received all four of the possible dose escalations responded at any time during the study.

Pharmacokinetics

Figure 2 shows the mean pre- (trough) and postinfusion (peak) serum infliximab concentrations from week 22 to 54. Patients receiving 3 mg/kg with no dose escalation (open triangles) maintained a constant trough serum infliximab concentration over time (approximately 1–2 μg/ml). Patients who met the criteria for dose escalation generally showed lower trough infliximab concentrations than those who did not require dose escalation.

Table 3 Summary of adverse events from week 22 through week 54 for patients in group 2

Category	Patients without dose escalation	Patients with dose escalation
Patients in study at week 22	220	109
Average duration of follow-up (weeks)	31.9	31.7
Average exposure (weeks)	31.0	30.6
Patients with one or more adverse event	160 (72.7)	77 (70.6)
Patients who discontinued study agent because of one or more adverse event	7 (3.2)	6 (5.5)
Patients with one or more serious adverse event	19 (8.6)	14 (12.8)
Patients with one or more infection	80 (36.4)	39 (35.8)
Patients with one or more serious infection	5 (2.3)	2 (1.8)

Results are shown as No (%) unless stated otherwise.

Antibodies to infliximab

A total of 320 patients in group 2 had serum samples that were suitable for analysis of antibodies to infliximab, including 105 patients who received dose escalation(s) and 215 patients who did not receive dose escalation. A higher percentage of patients who received dose escalation(s) were positive for antibodies to infliximab (28.6%) compared with patients who did not receive any dose escalations (19.5%); however, the difference was not significant (p = 0.087). Only one of the seven patients who received all four possible dose escalations was found to be positive for antibodies to infliximab. A summary of the proportion of responders by antibody status and the number of dose escalations received is provided in supplementary materials 2 (available at http://ard.bmjjournals.com/supplemental).

Safety of dose escalation

As reported previously,[15] dose escalation(s) appeared to be well tolerated (table 3). Patients with and without dose escalation(s) had similar rates of adverse events, serious adverse events, infections and serious infections. The mean duration of follow-up and the mean exposure were also similar. Six patients (5.5%) who received dose escalations discontinued treatment prematurely because of adverse events, compared with seven patients (3.2%) who did not receive dose escalations.

DISCUSSION

In this study, we evaluated a predefined, infliximab dosing regimen in which patients were eligible to receive dose increases if they did not respond to treatment or if they initially responded but later flared in a double-blinded fashion. The predefined criteria for dose escalation were used to ensure uniformity in the administration of dose escalations according to changes in the total TJC and SJC. About two-thirds of patients did not require any dose escalation and continued to receive 3 mg/kg infliximab throughout the 1-year study. Of the patients who did require dose escalation(s), nearly 80% achieved or regained response using the criteria based on 20% improvement in the TJC and SJC. These data, however, should be viewed with caution as not all patients who met the criteria for response in this study may have had clinically meaningful improvement.

The decision to increase the dose was made beginning at week 22. However, the proportion of patients with an ACR 20 response at week 22 was not substantially higher than that at week 14, suggesting that patients could be evaluated for dose escalation as early as 3 to 4 months. Primary and secondary non-responders had similar response rates after dose escalation

(77% vs 83% response, respectively); thus, both categories of patients responded well to dose escalation. There were no distinguishing baseline clinical characteristics for the patients who required dose escalation.

The results of a previous study of infliximab and MTX in patients with RA indicate that infliximab trough serum concentrations of ⩾1.0 μg/ml are needed to maximise the potential for response.[13] In our study, low (<1.0 μg/ml) preinfusion (trough) serum infliximab levels were generally associated with the need for dose escalation. Although some non-responding patients seemed to clear infliximab more rapidly than others, increasing the dose of infliximab restored trough concentrations to levels sufficient for clinical response.

Infliximab concentrations of patients whose dose was increased were still generally lower than the concentrations seen for patients receiving 3 mg/kg who did not require dose escalation(s). It is noteworthy that there was no associated increase in the rate of adverse events for the patients receiving an escalated dose, which might be expected because the trough infliximab concentrations were generally not higher than those found in patients who did not receive dose escalation.

Patients who required dose escalation also had a slightly increased incidence of antibodies to infliximab (28.6%) compared with those who did not require dose escalation (19.5%); however, the difference was not statistically significant. An increased incidence of antibodies to infliximab in patients who required dose escalation was also reported in a smaller study (47% vs 29% for patients who did not require dose escalation).[20] However, antibodies were not detected in the majority of patients who required dose escalation in either the previous study or in our study.

Although, patients who were positive for antibodies to infliximab had a slightly lower response to treatment than patients who were antibody negative or those who had an inconclusive antibody status, there was a positive relationship between dose and clinical response even among patients who had antibodies to infliximab. Therefore, increased doses of infliximab may, at least to some degree, offset a reduction in clinical response for patients with antibodies to infliximab.

In a recent study of patients who received infliximab for Crohn's disease,[14] only detectable trough serum concentrations were a significant positive predictor of complete clinical remission among a variety of clinical and demographic variables, including antibody status. In the START study, trough median serum concentrations were low in patients who required dose escalation while the incidence of antibodies to infliximab was not statistically significantly increased. These results suggest that low trough serum concentrations may be a more important cause of lack of response or flare than antibodies to infliximab.

Seven patients received the maximum number of dose escalations allowed by the protocol (four dose increases to a total dose of 9 mg/kg). None of these seven patients met the criteria for response at any time during the study, even though their preinfusion (trough) infliximab serum concentrations at week 22 were well above 1 μg/ml. Only one of the seven patients was found to be positive for antibodies to infliximab, suggesting that antibodies were not the primary cause of the lack of response.

Although the numbers are small, the baseline characteristics for these seven patients suggest that inflammation was not a major part of their disease. Most of the patients had advanced disease (median disease duration 12.1 years). Possibly, these patients had secondary degenerative changes in their joints that contributed substantially to their symptoms. The median baseline CRP value (7 mg/l) was nearly normal and well below the median value for group 2 as a whole (24 mg/l). If these patients had signs and symptoms that were predominantly the result of secondary degenerative changes rather than active inflammation, it is not surprising that they did not respond to anti-tumour necrosis factor α (TNFα) treatment despite receiving the highest dose and having sufficient serum infliximab concentrations. It is also possible that these patients have a subtype of RA that is not primarily mediated by TNFα.

As reported previously,[15] an important finding of the START trial was that patients who received the unapproved induction regimen of 10 mg/kg infliximab in combination with MTX followed by maintenance doses of 10 mg/kg every 8 weeks had an increased risk of serious infections. The results of the current analysis show that most patients who received the induction regimen of 3 mg/kg followed by dose increases after week 22 (a regimen that is currently approved according to the product labelling in the United States)[4] had clinical benefit without an increased risk of adverse events, including serious infections, when compared with patients who did not receive dose increases. However, this comparison is limited because the sample size was small and patients were not randomly assigned to receive dose escalation(s).

In this trial, TJC and SJC data were entered into an IVRS, which automatically calculated response or flare. Therefore, we assessed clinical response using joint count data only, rather than the typical response criteria such as ACR 20 and the Disease Activity Score. Joint counts have been shown to correlate with disease status, changes in the disease activity, progression of disease and mortality.[21–24] Composite assessment criteria, such as ACR 20 and the Disease Activity Score, require acute phase reactant data, which were not available at the time of the patient visit when the need for dose escalation was determined. Acute phase reactant data could not have been used for determining the need for dose escalation while maintaining the blind. A recent study has shown that acute phase reactant data add little information to clinical assessments of disease activity.[25] The authors recommended using the Clinical Disease Activity Index, which includes patient and evaluator global assessments in addition to TJC and SJC. However, this tool was neither validated nor available when our study was designed.

The START study was also limited by the 1-year study duration. Patients who received a dose escalation at week 46 and did not respond at the following visit (week 54) could not receive further dose increases because the study ended. Some of these patients might have responded if the study had continued for longer than 1 year. In an extended study, patients would have been given the opportunity to receive additional dose increases or allowed more time to demonstrate a response.

In conclusion, some patients who did not respond to the initial dose of 3 mg/kg infliximab, or those who initially responded but subsequently flared, benefited from increased doses of infliximab without an increased risk of serious adverse events, including serious infections.

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