The Use of Infliximab in Academic Rheumatology Practice: an Audit of Early Clinical Experience

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ABSTRACT. ***Objective***. To audit a first clinical experience of treating rheumatic disease patients with infliximab in the setting of an academic tertiary care rheumatology practice.

Methods. The infusion history of patients referred to the McGill University Health Centre during the first 18 month period of a special access program for treatment with infliximab, a tumor necrosis factor-α antibody, was audited for disease characteristics, dosing schedule for infliximab, concomitant treatments, response rate, and side effect profile.

Results. Forty-one patients received a total of 300 infusions of infliximab over a period of 9 ± 5 months (mean ± standard deviation). Rheumatic disease indications were rheumatoid arthritis in 30, spondyloarthropathy in 6, psoriatic arthritis in 2, juvenile onset polyarthritis in 2, and scleroderma in one. Disease duration was 17 ± 11 years. Concomitant treatment with steroids and methotrexate was present in 68% and 54%, respectively. Infliximab treatment was continued beyond 5 infusions or 22 weeks in 63%. Of the 26 patients continuing treatment, adjustment to dosing and/or interval schedule of infusions was made in 58%. The clinical response rate was moderately to greatly improved in 96%. Severe side effects considered directly related to the treatment were observed in 6 (15%) patients; less severe side effects, which did not preclude continuation of treatment but frequently required medical intervention, were noted in 93%.

Conclusion. Infliximab is a valuable treatment for patients with resistant rheumatic diseases in the short term. Both the serious, and the frequent, more benign complication rate observed in this group of patients should alert physicians to be vigilant in the routine care of patients treated with infliximab. (J Rheumatol 2002;29:2525–30)

Key Indexing Terms:
INFLIXIMAB AUDIT OF CLINICAL PRACTICE ANAPHYLAXIS
VASCULITIS HISTOPLASMOSIS

The introduction of strategies targeting specific pathophysiologic processes with biologic agents has heralded a new era in the management of rheumatoid arthritis (RA)[1-3]. Infliximab, a monoclonal antibody to tumor necrosis factor-α (TNF-α), and etanercept, a genetically engineered soluble TNF-α receptor fusion protein, have shown an outstanding influence on inflammatory disease in general, and RA in particular[2,4]. Smaller studies of these treatments in other rheumatic diseases also indicate good efficacy[5-8]. There is enthusiasm similar to that of the 1950s with the advent of corticosteroids for the treatment of RA[9]. As a result of clinical experience and recognition of longterm side effects, initial enthusiasm for corticosteroids was tempered[10]. Clinical experience and careful postmarketing surveillance for any new treatment intervention is thus essential to determine the position that it will hold in the treatment of rheumatic diseases.

We describe our initial clinical experience with the use of infliximab, outside the setting of a randomized clinical trial (RCT). Our audit presents information on indications, dosing schedules, concomitant medications, clinical response rates, and the side effect profile in the first 41 patients who received 300 infusions of infliximab during the study period.

MATERIALS AND METHODS

Our analysis includes all patients referred to the Rheumatology Clinic of the McGill University Health Centre at the Montreal General Hospital for treatment with infliximab between June 2000 and January 2002. Schering Canada graciously provided the medication as part of a special access program for treating patients with therapy resistant rheumatic disease. The program was approved by the hospital internal review board and all patients gave written informed consent.

Patients were evaluated at baseline and on each subsequent visit, which was at the time of the scheduled infusion, by means of a predetermined protocol. Patients were initially treated as per current recommendations of: an initial infusion given at first visit; the second infusion at week 2, third infusion at week 6, and fourth and subsequent infusions at either 8-weekly or 6-weekly intervals. At the initial visit, demographic as well as disease related information was recorded. Disease related information included: diagnosis; duration of disease since diagnosis; history of joint surgery; joint count for pain and tenderness, and for swelling for patients with RA[11];

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Submitted March 15, 2002, revision accepted June 11, 2002.

previous/current medications were recorded as nonsteroidal antiinflammatory drugs (NSAID), steroids, and/or disease modifying antirheumatic drugs (DMARD).

Baseline and followup measurements at each infusion included complete blood count (CBC), liver function tests, erythrocyte sedimentation rate (ESR) by the Wintrobe method, C-reactive protein (CRP), and antinuclear antibody (ANA). If the ANA was positive, serologic testing for the presence of anti-dsDNA was performed. All patients had a skin test with purified protein derivative (PPD) as well as a chest radiograph at baseline. The frequency and dosage of infusions were initiated as described, and thereafter adjusted according to physician discretion[2].

Response to treatment was judged by a composite of the following: global patient and physician assessment of disease status, pain severity, and fatigue. All were assessed by means of a 4 category Likert scale: unchanged, slightly improved, moderately improved, and greatly improved. After the fourth infusion a clinical decision regarding continued treatment with infliximab as well as dosing and treatment intervals was made. Adjustments to other treatments for rheumatic disease were made at each treatment visit according to physician discretion. If after initial favorable response the effect waned over the weeks approaching the time of next infusion, the interval between infusions was reduced to a 6-weekly interval. If, however, the response was judged to be suboptimal, then the dosage of the next infusion was increased. If treatment was discontinued, the reason for the discontinuation was recorded. At each visit a report of any adverse events was also recorded.

Between-group and within-group statistical analysis was by simple descriptive statistics and chi-square and Fisher's exact tests. Statistical significance was set at $p < 0.05$.

RESULTS

Patients. Forty-one patients with various rheumatic diseases were given a total of 300 infusions of infliximab with a mean duration (± SD) of 9.7 (± 4.7) months of followup, and a mean number of 7.3 (range 2–13) infusions per patient. Patient demographic and disease related information is shown in Table 1.

Table 1. Demographic and disease related information for 41 patients with rheumatic diseases treated with infliximab. Values are expressed as number of patients (%) or mean ± SD.

Age, yrs	51.9 ± 14.05
Female, n (%)	35 (85)
Rheumatic disease, n (%)	
Rheumatoid arthritis	30 (73)
Spondyloarthritis	6 (15)
Juvenile rheumatoid arthritis	2 (5)
Psoriatic arthritis (peripheral)	2 (5)
Scleroderma	1 (2)
RA and spondyloarthritis	2 (5)
Duration of disease, yrs	17.2 ± 10.9
Joint surgery	20 (49)
Joint count (in 27 with RA)	
Joint pain	20.6 (11.9)
Joint swelling	20. 9 (9.7)
Current treatments	
NSAID	36 (88)
Steroids	28 (68)
DMARD	33 (80)
DMARD, 2 or more	14 (34)
Methotrexate	22 (54)
Hydroxychloroquine	14 (34)
Myochrysine	2 (5)
Salazopyrine	2 (5)
Azathioprine	4 (10)
Cyclosporine	2 (5)
D-penicillamine	1 (2)

Two patients had a diagnosis of both RA and spondyloarthropathy (SpA), with the predominant manifestation of disease being symmetrical peripheral synovitis of both small and large joints; they were thus classified as RA. Joint counts are reported for 27 of the 30 patients with RA. Three RA patients had such severe destructive joint disease, as well as joint replacements to small and large joints, that a meaningful joint count could not be performed.

Specific information regarding patients with RA: disease duration: 17.4 ± 10.8 years, number of previous DMARD: 4.5 ± 1.2, and mean MTX dose in the 15 patients taking this agent: 17 ± 7 mg.

All RA, juvenile rheumatoid arthritis, and psoriatic arthritis (PsA) patients had previously been treated with at least 3 DMARD, including MTX, but at the time of introduction of infliximab, 8 patients were not currently taking DMARD due either to lack of efficacy or toxicity. The 6 SpA patients had failed treatment with MTX and/or salazopyrine. The single patient with scleroderma had failed to respond to high dose steroids, D-penicillamine, and cyclophosphamide. Twenty-two of the 33 patients taking DMARD were receiving MTX. Two-thirds of the patients were currently using oral steroids. No patient had radiographic changes consistent with prior infection with tuberculosis. The PPD was positive in one Asian patient without a preceding history of tuberculosis; she was treated with isoniazide.

Outcome. Twenty-six (63%) patients received at least 5 infusions of infliximab with anticipated continuation of treatment. There were no significant demographic or disease related differences between patients who continued or those who discontinued treatment. The reasons for discontinuation of infliximab in 15 patients (11 RA, 2 SpA, 1 PsA, 1 scleroderma) were lack of effect in 7, severe side effects attributable to treatment in 6, death in the one patient with scleroderma, and request to withdraw for personal reasons in one patient.

Modifications to the dosage or to infusion interval for infliximab were made in 20 (50%) of all patients receiving treatment. Details of treatment adjustments are shown in Table 2. Eighteen patients experienced a loss of effect of infliximab after initial favorable response, and treatment was discontinued in spite of dosage/interval adjustments in 3 for this reason. This loss of effect was observed prior to the fifth infusion in 8 and after the fifth infusion in 10. The dose of infliximab was increased in 18 patients, with a final dose of 5 mg/kg in 16 and 7 mg/kg in 2. The infusion interval time after the third infusion was reduced from 8 weeks to 6 weeks in 12 patients. Fifteen (58%) of the 26

Table 2. Treatment characteristics for infliximab in 41 patients with rheumatic disease treated with infliximab. Values are expressed as number of patients (%).

Dosage/interval changes	20 (50)
Increased dose	18 (44)
Reduced interval	12 (29)
Both increased dose and reduced interval	10 (24)
Continued treatment with adjustment	15 (37)
Continued treatment with no adjustment	11 (27)
Discontinued	15 (37)
Side effects	6 (15)
Lack of efficacy	7 (17)
Other reasons	2 (5)

Table 3. Adverse event profile in 41 patients with rheumatic disease treated with infliximab. Values are expressed as number of patients (%).

Less severe	37 (90)
Upper respiratory symptoms	17 (41)
Itching/rash	15 (37)
Infection requiring antibiotics	12 (29)
Gastrointestinal, nausea, bloating, diarrhea	10 (24)
Flu-like symptoms	8 (20)
Central nervous system (dizziness, headaches)	9 (22)
Mucosal ulcers	9 (22)
Herpes zoster	2 (5)
Severe	7 (17)
Anaphylaxis	3 (7)
Vasculitis	2 (5)
GI bleed	1 (2)
Infection, histoplasmosis	1 (2)

patients who continued treatment did so with a dosage or interval adjustment for infliximab. Ten patients finally continued treatment with infliximab with both the higher dose and a reduced time interval of infusions. In the 26 (63%) patients who had more than 5 infusions and continued treatment, the response rate following the first infusion was reported to be moderately to much improved for patient global assessment in 77%, physician global assessment in 61%, pain in 69%, and fatigue in 50%; and similarly, at the time of the last infusion, response rates were recorded to be moderately to much improved in 96%, 96%, 96%, and 73%, respectively.

Medication adjustments for the 26 patients continuing treatment were as follows: 9 of 14 originally treated with steroids either reduced or discontinued steroid treatment, and DMARD treatment was reduced in 10. This constituted a reduction in the dose of MTX in 7, and discontinuation of hydroxychloroquine in 5. For the 26 patients in whom treatment was continued, significant changes for CRP were seen from baseline to fifth infusion: 28.2 ± 25.8 vs 14.5 ± 21.4 ($p = 0.0432$), but there was a nonsignificant trend in the reduction of ESR: 38.4 ± 15 vs 31.9 ± 15.6 mm/h. The ANA became positive in 4 patients who had previously tested negative, none of whom tested positive for dsDNA. Two patients who had initially tested positive for ANA subsequently tested positive for dsDNA. No patient developed features of systemic lupus erythematosus. The only abnormality of CBC and liver function tests was observed in the patient with histoplasmosis infection, who developed transient thrombocytopenia and elevated transaminase levels during the active phase of infection (see below).

Side effects. The side effect profile is shown in Table 3. Six patients experienced severe side effects that were clinically attributable to treatment with infliximab and required discontinuation of treatment. An additional patient had a gastrointestinal bleed that was more likely attributable to treatment with both steroids and NSAID.

Vasculitis, presenting as a diffuse macular papular rash of the trunk and limbs, and biopsy proven as leukocytoclastic vasculitis in one, occurred in 2 patients with RA, both after the second infusion. Neither had previously experienced vasculitic complications related to RA or to medication. Both patients had severe RA, were currently taking steroids, and had each previously been treated with 5 different DMARD. One was currently receiving intramuscular gold and the other was not receiving any DMARD. The vasculitis was confined to the skin in both and gradually resolved over a period of 3 months. Both patients had been weakly positive for ANA prior to initiation of infliximab treatment and neither developed any additional immunological abnormalities.

Three patients, all with RA, had acute anaphylactic reaction at the time of the second, fifth, and eighth infusions, respectively. These reactions were characterized by acute facial and chest wall flushing, chest pain, and hypotension (with a systolic blood pressure drop of between 30 and 40 mm Hg, and diastolic drop of between 10 and 40 mm Hg) within minutes of initiating the infusion. All 3 patients were currently receiving steroid treatment for RA, and all were taking DMARD (MTX in one, gold in one, and a combination of hydroxychloroquine and sulfasalazine in one). All patients responded promptly to discontinuation of the infusion and treatment with intravenous antihistamines and steroids. Adrenaline was not administered, as the first 2 patients who presented with acute reaction had severe crushing chest pain suggestive of myocardial ischemia. These 2 patients were also given nitroglycerine sublingual spray and an intravenous opioid analgesic. There was, however, no evidence of myocardial ischemia by normal electrocardiogram and creatine kinase level in 2 of the 3 patients with prolonged chest pain. Two of the 3 patients had experienced mild skin reaction after the penultimate infusion.

The patient diagnosed with histoplasmosis was a 28-year-old woman with a diagnosis of SpA unresponsive to treatments. Following the second infusion of infliximab she experienced increasing fatigue with subsequent diffuse body

pain, fever, and chest pain. Chest radiograph showed hilar and mediastinal adenopathy that had been absent at the initiation of infliximab treatment (histoplasmosis was diagnosed on mediastinal node biopsy). On discontinuation of infliximab, MTX, and steroids, her symptoms of fever, and chest pain gradually subsided, but she has experienced recurrence of spondylitic symptoms. She had recently moved into a house in which pet birds had flown freely and her infection was thought to be recent as opposed to reactivation of a previous infection.

Less severe side effects were recorded in 37 patients, with a total of 128 specific events. Nonspecific upper respiratory tract symptoms and allergic type skin reactions were the most commonly recorded adverse events. Allergic type reactions, characterized by rash and itching, were seen in one-third of patients but seldom required treatment. Premedication with antihistamines was required in 5 patients, 3 of whom also required steroids. Bacterial infections requiring treatment with antibiotics, but not requiring hospital admission, were observed in 12 patients and included sinusitis, pneumonia, and urinary tract infections. No patient elected to discontinue infliximab because of less severe side effects.

DISCUSSION

RCT settings differ considerably from real-life clinical practice[12,13]. Our report reflects the latter in the use of infliximab for the treatment of rheumatic disorders. Although the special access program was directed primarily at patients with RA, off-label usage is significant, as was observed in one-quarter of our patient cohort. It is notable that our patients represent those at the extreme end of the spectrum for disease severity, with long duration of disease, failed previous multiple DMARD therapy, a high rate of steroid treatment, and joint surgeries. Thus a large proportion of patients in this study received treatment with infliximab in a way not consistent with regulatory approval, i.e., they had diseases other than RA, and received infliximab in the absence of MTX treatment. The patients in our study had more severe disease than patients with RA reported in TNF inhibition RCT[2,4]. SpA was present in one-fifth of the group, emphasizing the difficulty in treating this condition. Additionally, the 2 adult patients with JRA represent a disease category that is seldom eligible for inclusion in studies examining treatments for inflammatory arthritis. The single patient with scleroderma was treated with infliximab in an attempt to control rapidly progressive interstitial lung disease that had been unresponsive to aggressive treatment. She died of respiratory insufficiency after 3 infusions of infliximab, with no indication that infliximab had favorably influenced pulmonary disease.

Whether the outcomes achieved within the time constraints of RCT are sustained or whether the side effect profile remains stable can only be judged after post-marketing surveillance and systematic audit. Patient participants in clinical trials are highly selected and often do not completely represent the spectrum of patient phenotype. Many of our findings are similar to those recently reported for etanercept in clinical practice[14]. The freedom for physician decision regarding manipulation of treatments is closer to real-life practice than the more rigid RCT. We observed impressive clinical response in almost all patients continuing treatment, but note that dosage adjustment for infliximab was needed in more that half of patients continuing treatment. This remarkable response resulted in a reduction in concomitant DMARD and/or steroid treatment in patients who had been mostly steroid dependent and also MTX resistant.

While infliximab is seen as a major advance for patients with severe arthritic diseases, there is little reported experience in open-label clinical practice, and the longterm consequences of continued treatment are unknown. The rate of adverse events, both less and more severe, was high in our patients. Fifteen percent of patients experienced a severe adverse event that was clinically attributed to treatment. We observed acute anaphylactoid-like reactions that required immediate medical intervention, as well as more prolonged illnesses identified as vasculitis in 2 and histoplasmosis in one. It is also noteworthy that we observed anaphylaxis-like reactions as late as the fifth and eighth infusions in 2 different patients, suggesting that patients may gradually develop a sensitization to the non-human antigenic component of infliximab. Although 2 of the 3 patients with anaphylaxis-like reactions had experienced mild transient rash after the previous infusion, similar rashes were reported by one-third of the total cohort, and for this reason we did not anticipate the severe reactions. Additionally, all 3 patients with anaphylactoid reactions and the 2 with vasculitis were receiving steroid treatment for their disease. Four of the 5 patients presenting with hypersensitivity type reactions were not receiving MTX or other immunosuppressive. However, we are unable to say whether immunosuppressive treatment, or MTX in particular, might have prevented these events.

Overall, our observations strongly support the recommendation of the European Agency for the Evaluation of Medicinal Products (EMEA) that infliximab "should be administered under the supervision and monitoring of physicians experienced in the diagnosis and treatment of rheumatoid arthritis..."[15]. We would add that infliximab should be administered in a secure setting, staffed by experienced medical staff, and with full resuscitation facilities available in the event of acute reaction. As adjustments to arthritic treatments, including infliximab dosing and scheduling, were made at the time of the infusion, we believe that the close followup received by our patients represented best medical care.

Minor side effects were commonly reported by almost all patients in this group. The most commonly reported side effects were upper respiratory tract symptoms and mild rash

and itching beginning within 24 h of infusion and usually resolving in a few days without need for treatment. Infections requiring antibiotic treatments were observed in over one-quarter of patients, with none requiring hospitalization. We are unable to comment whether these observed adverse events were truly more common as a result of treatment with infliximab, or whether both patients and medical staff were more vigilant regarding complaint of symptoms. Our findings suggestive of an increased rate of infection and adverse events are similar to those in a recent observational study of the use of etanercept in academic practice[14].

Meaningful and objectively documented clinical improvement was noted early in the treatment period. Indeed, up to three-quarters of patients reported good to excellent clinical response after first infusion. It is also possible that we have observed a considerable placebo response for a number of reasons: (1) Patients had high expectations of response to treatment with a novel and expensive agent; (2) patients were being treated in groups of 3 to 4 at a time in an infusion clinic and it was noticeable that friendships developed that were likely therapeutic; (3) since the infusion was mostly a nontraumatic experience without immediate unpleasant side effects, patients happily anticipated the clinic visit; (4) patients had the opportunity to interact with nursing and medical staff away from the busy clinic environment and perceived that their care was special; and (5) anti-TNF treatment may have a still undocumented but real euphoric effect.

In keeping with a recent consensus statement regarding use of TNF blocking agents, we used a combination of clinical judgment and clinically applicable response criteria to guide treatment in our patients[16]. Although the American College of Rheumatology response criteria, ACR 20%, 50%, and 70%, are considered the gold standard for response in clinical trials in RA[17], the use of such a time and personnel intensive measure, while important in the context of clinical trials, is unlikely to be used by the majority of clinicians in normal clinical practice. A survey of Australian rheumatologists showed they seldom use health status measures commonly used in clinical research when following patients longitudinally[18]. Additionally, an important component of response criteria for RA is the joint count, which, in the context of longstanding destructive and deforming joint disease and multiple joint surgeries, is difficult to perform accurately and therefore may be flawed and of limited clinical significance. In one study examining accuracy and sensitivity to change of 14 measures in RA, the joint count showed relatively poor responsiveness to change, with the conclusion that this measure, although the mainstay of clinical assessment in RA, may not be an optimal endpoint in clinical trials[19]. As well, thickened synovium that has been present for many years may also never fully recede, even in the context of considerable clinical improvement.

We believe most rheumatologists assess treatment outcome based on clinical consensus achieved between physician and patient by means of simple and easy to perform measures, as was done in our study. More efficient but simple instruments remain to be standardized and validated in the economic context of a busy clinical practice.

Our findings represent a unique opportunity to examine clinician prescribing practices and management of a new biologic agent. We believe our experience represents best clinical practice for patients with severe rheumatic disease and contributes to the understanding of the use, as well as the complications, of infliximab.

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