

Infliximab Therapy for Patients With Active and Refractory Spondyloarthropathies at the Dose of 3 mg/kg

A 20-Month Open Treatment

E.P. Cherouvim, MD, E. Zintzaras, MSc, PhD,† K.A. Boki, MD,*
H.M. Moutsopoulos, MD, FACP, FRCP (Edin),* and M.N. Manoussakis, MD**

Background: Infliximab at the dose of 5 mg/kg per infusion has been shown effective for the treatment of active spondyloarthropathies. It is not clear if the 5 mg/kg is required in most patients.

Objective: To evaluate the long-term efficacy and safety of infliximab at the lower dose of 3 mg/kg in patients with active and refractory ankylosing spondylitis (AS) and psoriatic arthritis (PsA).

Methods: Thirty patients were enrolled in a 78-week, single-center, prospective, open-label pilot study, including 16 patients with severe and active AS and 14 patients with active and refractory PsA. Infliximab (3 mg/kg, in combination with a stable dose of methotrexate was administered intravenously at 0, 2 and 6 weeks, and q8 weeks thereafter (schedule-A) and the improvement of Bath Ankylosing Spondylitis Disease Activity Index (BASDAI; for AS patients) and Patient Global Assessment of Disease Activity (PDA; for PsA patients) was monitored at baseline and at every visit (primary variables). Patients who did not respond sufficiently at 14 weeks, as well as patients who relapsed at any time during follow-up, received infliximab every 4 weeks (treatment schedule-B). Three different statistical approaches (per-protocol, last observation carried forward and by intention-to-treat) were applied.

Results: Ten patients discontinued treatment for various reasons, including 3 (10.0%) because of allergic reactions. Twenty patients (66.7%, 9 with AS and 11 with PsA) had completed 78 weeks of treatment (schedule-A, 11 patients; schedule-B, 9 patients). Of these patients, 18 (90.0%) showed optimal response (improvement $\geq 50\%$), including 13 (65.0%) with improvement $\geq 70\%$. AS assessments in AS (ASAS) 50% was attained by 7/9 AS patients (77.8%). At 78 weeks of treatment, statistically significant improvement of indices of disease activity, function and quality of life was observed by all statistical approaches applied.

Conclusions: Infliximab at 3 mg/kg every 8 weeks or, if needed, every 4 weeks appears to be an effective and rather safe treatment of patients with active and refractory AS and PsA after 78 weeks of treatment.

Key Words: infliximab, spondyloarthropathy, ankylosing spondylitis, psoriatic arthritis, treatment

(*J Clin Rheumatol* 2004;10: 162–168)

The seronegative spondyloarthropathies, such as ankylosing spondylitis (AS) and psoriatic arthritis (PsA) represent a group of related disorders with common clinical, biologic, and genetic characteristics.^{1,2} To date, therapeutic options have been particularly limited for patients with AS, whereas disease-modifying agents lack efficacy in a substantial number of PsA patients.^{3–8}

During the recent years, the application of biologic agents that block TNF- α (tumor necrosis factor- α) in patients with AS and PsA have indicated significant therapeutic efficacy in several short-term controlled and uncontrolled trials.^{9–20} TNF- α has been thought to play an important role in the pathogenesis of AS and other forms of spondyloarthritis as suggested by the increased expression of this cytokine in joints and serum of spondyloarthritis patients^{21–26} as well as in the skin of PsA patients.²⁷ Among anti-TNF- α therapies, the chimeric monoclonal antibody infliximab represents the most extensively studied agent for patients with spondyloarthropathies.^{9,10,12–15,17–20} To date, all except one¹⁸ of the above clinical trials of infliximab have used a dose (5 mg/kg per infusion) that is higher than the one that is currently recommended for the treatment of rheumatoid arthritis (3 mg/kg per infusion). This approach may be associated with increased risk for serious infections and other adverse effects and possibly imposes unnecessary costs.²⁸ In this context, the objective of the present open-label pilot study was to assess the long-term efficacy and safety of infliximab at the dose of 3 mg/kg in patients with active and refractory to conventional

From the *Department of Pathophysiology, School of Medicine, National University of Athens; and †Biomathematics Unit, School of Medicine, University of Thessaly, Greece.

Reprints: M. N. Manoussakis, MD, Department of Pathophysiology, School of Medicine, National University of Athens, 75 Mikras Asias Str., 115 27 Athens, Greece. E-mail: menman@med.uoa.gr.

Copyright © 2004 by Lippincott Williams & Wilkins

ISSN: 1076-1608/04/1004-0162

DOI: 10.1097/01.rhu.0000135551.47780.ba

treatment spondyloarthropathies in a prospective open pilot study.

PATIENTS AND METHODS

Study Design

Thirty Greek patients who were referred from both university and private practice were enrolled in this 78-week, single-center, prospective, open-label, pilot study. Patients studied included 16 with AS (all men) and 14 with PsA (7 men and 7 women). All patients gave written informed consent. Patients with AS were diagnosed on the basis of the modified New York criteria²⁹ and were considered eligible for the study if they had the following clinical characteristics: significant pain lasting >3 months, a pain score of ≥ 4 on a 10 cm visual analogue scale on 2 successive occasions with at least 3 days in between and a Bath Ankylosing Spondylitis Disease Activity Index (BASDAI)³⁰ score of ≥ 3 .¹⁹ Eligible patients with PsA were those who had active arthritis defined by the presence of ≥ 3 swollen and tender joints. All the patients had an inadequate response to nonsteroidal antiinflammatory drugs (NSAIDs) and/or disease modifying antirheumatic drugs (DMARDs). Table 1 shows the baseline features of the 30 patients studied.

Infliximab was administered as currently recommended for refractory rheumatoid arthritis³¹ (ie, at the dose of 3 mg/kg per infusion at weeks 0, 2, and 6 [loading dose regimen] and subsequently pulsed every 8 weeks [treatment schedule-A]). Patients with relapsing or unresponsive disease to this treatment were admitted in treatment schedule-B, which consisted of shortened intervals between infusions (every 4 weeks), while maintaining the same dose (3 mg/kg). Patients with AS were allowed to continue NSAIDs, at a stable dose during the treatment period. Fourteen patients (3 with AS with peripheral joint involvement and 11 with PsA) were already receiving methotrexate prior the administration of infliximab (10–12.5 mg/wk) and maintained this dose throughout the study. Aiming to reduce the risk of severe allergic reactions due to the development of antibodies against infliximab,³¹ stable doses of methotrexate (10 mg/kg) were also administered to the remaining patients throughout the study.

According to protocol, any other DMARDs were discontinued at least 4 weeks prior to the initiation of the study, whereas prednisone was allowed at a dose of ≤ 7.5 mg/day with a stable dose for at least 1 month prior to entry. Topical therapies and oral retinoids for psoriasis were discontinued at least 2 weeks before the baseline evaluation. Isoniazid 300 mg/day was administered in 5 patients with positive PPD test (defined as an area of induration ≥ 8 mm in diameter) as prophylactic treatment of latent tuberculosis infection. A detailed clinical and laboratory assessment (including ESR and CRP) was performed at the screening visit, baseline and

TABLE 1. Baseline Characteristics of Patients with Ankylosing Spondylitis (AS) and Psoriatic Arthritis (PsA)

Patient Features	AS	PsA
No. patients	16	14
Age, median years (range)	38.0 (21–51)	36.5 (21–55)
Men/ Women	16/0	7/7
Disease duration, median years (range)	14 (1.5–29)	7.5 (2–21)
Duration of psoriasis, median years (range)	—	15 (9–40)
HLA-B27 positive (%)	12 (75.0)	3 (21.5)
Predominantly axial involvement	13	—
Predominantly peripheral involvement	—	9
Axial and peripheral joint involvement	3*	5
Prior history of uveitis [†]	4	2
ANA-positive (%)	1 (6.2)	4 (28.5)
Previous medications used:		
NSAIDs	16	14
Corticosteroids	6	7
Methotrexate	3	13
Cyclosporine	1	11
Sulfasalazine	8	2
Gold (i.m.)	1	6
D-penicillamine	1	2
Leflunomide	—	1

*All 3 AS patients with peripheral joint disease had involvement of the lower extremities (knees and ankles), whereas one patient had also symmetrical involvement of elbows and small joints of both hands.

[†]No patient had active anterior uveitis at study entry.

during each visit. A normal chest radiograph was mandatory prior to enrollment. ANA, anti-dsDNA, and RF determination were performed at the screening visit and at completion of 1 year of treatment (weeks 52 to 54).

Assessment of Efficacy and Outcome

Every patient had a detailed clinical examination by the same clinician at baseline and at each follow-up visit (prior to each infusion), that included the assessment of various disease parameters. In patients with AS, the evaluation included patient and doctor global assessment of disease activity (PDA and DDA, respectively), the assessment of total body and spinal pain, fatigue and morning stiffness, the BASDAI,³⁰ the Bath Ankylosing Spondylitis Functional Index (BASFI),³² the Bath Ankylosing Spondylitis Metrology Index; BASMI³³ (that included the modified Schober index, the measurements of tragus to wall distance, of cervical rotation, of lateral spinal flexion and of intermalleolar distance), the measurements of fingers-to-floor distance and chest expansion, tender and

swollen joint counts and the Health Assessment Questionnaire for Spondyloarthropathies (HAQ-S).³⁴ In addition, at the end of the study the ASAS 20%, 50% and 70% improvement criteria were estimated.³⁵ In patients with PsA the measurements included PDA, DDA, pain, morning stiffness, the assessment of peripheral arthritis (number of tender and swollen joints; 68 and 66 sites, respectively), of mobility impairment that was related to axial involvement (by the modified Schober test, the chest expansion and the cervical rotation measurements), and of psoriasis (by the Psoriasis Area and Severity Index, PASI³⁶), as well as the HAQ-S questionnaire. Finally, all patients studied had measurements of inflammatory indices of disease activity at baseline and at each visit, including erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP).

At any time point, the individual BASDAI or PDA values of patients with AS or PsA, respectively, were applied as primary variables for the evaluation of response to the treatment. At week 14 (prior to the fourth infusion) of treatment (schedule-A), patients with reduction of BASDAI or PDA scores of <40% of the baseline values were considered as treatment failure and were considered eligible for admission in treatment schedule-B. At any time, treatment failure was considered if the BASDAI score (for AS patients) or the PDA score (for PsA patients) had reached $\geq 60\%$ of the baseline value for at least 2 times in 3 consecutive visits. Patients with treatment failure at any time while on schedule-A were also eligible for admission in treatment schedule-B. Discontinuation of treatment was planned upon the occurrence of a significant adverse event (including the significant alteration in a laboratory parameter), patient's non-compliance to the visit schedule, as well as treatment failure while on schedule-B. At week 78, the disease status of patients was evaluated according to the improvement of primary variables (BASDAI or PDA scores, for AS and PsA patients, respectively) compared with baseline, as optimal response (improvement $\geq 50\%$), limited response (improve-

ment between 20% and 50%) and no response (improvement <20%). Patients who withdrew from the study at any time point were also evaluated for the primary variables after a period of 78 weeks.

Statistical Analysis

Three different statistical approaches were applied, including per-protocol analysis (PP), last observation carried forward analysis (LOCF; whereby the last measured time point was considered as the end point) and by intention-to-treat (ITT) analysis.³⁷ Nonparametric statistical methods were used because of the small sample size and the skewness of the data using Statistica software v.5. The comparison between end-point (PP, LOCF) and baseline for each variable was tested by the Wilcoxon matched pairs test. The ITT analysis using the Wilcoxon matched pairs test was performed only for the primary outcomes (BASDAI for AS and PDA for PsA). Statistical significance was defined as $P < 0.05$.

RESULTS

Evaluation of Initial Response at 14 Weeks of Treatment

Twenty-eight patients (15 with AS and 13 with PsA) had completed 14 weeks of treatment. Two patients (1 each with AS and PsA) had failed to adhere to the visit schedule (1 due to emigration and 1 who decided to be followed by a private practitioner, on weeks 2 and 6, respectively). As judged by at least 40% improvement of baseline BASDAI or PDA values (for AS and PsA patients, respectively), 22 patients (22/28, 78.6%, 12 with AS and 10 with PsA) manifested significant response to treatment (Table 2). Failure of treatment was noted in 6 patients (6/28, 21.4%), including 2 who did not respond at all (1 each with AS and PsA) and 4 patients (2 each with AS and PsA) who had experienced worsening of their disease status at week 14 after a short-term improvement. According to the protocol, 5 out of these 6

TABLE 2. Percent Improvement of BASDAI and PDA (In Patients With AS and PsA, Respectively) From Baseline Values at Various Time Points During Follow-up of Patients on Treatment Schedule-A

	% Improvement from baseline values			
	14 Weeks	30 Weeks	54 Weeks	78 Weeks
AS				
No. patients	12	6	6	4
% reduction of BASDAI, median (range)	66.5% (41.9% to 94.3%)	74.7% (50.0% to 94.3%)	76.2% (50.0% to 94.3%)	77.5% (51.6% to 86.9%)
PsA				
No. patients	10	7	7	7
% reduction of PDA, median (range)	75.7% (50.0% to 100%)	83.3% (62.5% to 100%)	77.8% (66.7% to 100%)	85.7% (0.0% to 100%)

nonresponders consented to receive the study drug as treatment schedule-B (ie, at shorter intervals, every 4 weeks) while maintaining the same dose (3 mg/kg of body weight). One nonresponder patient with AS had refused further treatment and withdrew from the study.

Follow-up of Initial Responders

Among the 22 patients who responded initially, 2 patients with AS refused further treatment (because of fear of adverse effects of the drug) and withdrew from the study (both at week 22). In addition, 7 patients had experienced relapse of their disease (7/22, 31.8%, 4 with AS and 3 with PsA, respectively) at a later time (AS patients; median time point of relapse: 22 weeks [range: 22 to 62 weeks], PsA patients; median time point of relapse: 34 weeks [range: 22 to 78 weeks]). Six out of these 7 patients consented to enroll in treatment schedule-B, whereas 1 patient with PsA objected to further treatment (at week 30) and withdrew from the study. During follow-up and despite optimal response to treatment, 2 patients with AS had to withdraw from treatment (on weeks 30 and 54, respectively) due to the development of serious allergic rash and as a safety measure prior to intended procreation, respectively. The remaining 11 patients (4 with AS and 7 with PsA) had remained on treatment schedule-A through week 78. The sequential analysis of primary disease parameters following 30, 54 and 78 weeks of such treatment had revealed marked and sustained improvement in the majority of patients (Table 2). One patient with PsA experienced significant worsening at week 78 (reverted to the baseline PDA value).

Administration of Infliximab as Treatment Schedule-B

As mentioned above, 11 patients in total (6 with AS and 5 with PsA, respectively, 5 nonresponding and 6 relapsed patients) were enrolled in treatment schedule-B. This treatment was initially efficacious for all the above patients. However, 2 patients (1 each with AS and PsA) had experienced adverse effects (fever with myalgias and urticaria,

respectively) that necessitated the discontinuation of treatment. In the 9 patients who remained in treatment, the sequential analysis of primary disease parameters following 20 and 44 weeks of treatment after the initiation of the new treatment had revealed significant reduction of disease activity indices (Table 3). All 9 patients had substantial recovery at 20 weeks; however, improvement sustained in 7 out of 9 patients at 44 weeks (3 with AS and all 4 patients with PsA). At week 44 after the initiation of treatment schedule-B, disease relapse was experienced by a patient with AS.

Overall Efficacy and Safety of Infliximab Therapy After 78 Weeks of Treatment

Overall, 10 patients withdrew from treatment of various reasons, whereas 20 patients (9 with AS and 11 with PsA) had completed 78 weeks of treatment. Optimal response was noted in 18 out of these 20 patients, including 16 patients with excellent response ($\geq 70\%$ improvement of primary variables compared with baseline; Table 4).

At 78 weeks of treatment, infliximab treatment was found effective for patients in every response criterion applied. Highly significant statistical differences were observed when changes from baseline were analyzed by all 3 statistical approaches applied (data not shown). Among patients with AS, ASAS 20%, 50% and 70% improvement criteria were attained by 8 of 9 (88.9%), 7 of 9 (77.8%) and 6 of 9 (66.7%) patients, respectively. In addition, at 78 weeks of treatment, a considerable proportion of patients with AS manifested 50% and 70% improvement of BASDAI (88.9% and 55.6% of patients, respectively), as well as of BASFI, BASMI, HAQ-S and abnormal CRP (data not shown). Complete remission of peripheral arthritis was observed in the 3 AS patients with peripheral joint involvement. The patients with PsA displayed even better responses of PDA (90.9% and 72.7% of patients, respectively), as well as of tender joint count, swollen joint count, HAQ-S, PASI and abnormal CRP (data not shown). In a female patient with PsA who had experienced exacerbation of psoriasis and arthritis, the administration of

TABLE 3. Percent Improvement of BASDAI and PDA (In Patients With AS and PsA, Respectively) From Baseline Values at Initiation, at 20, and 44 Weeks After the Initiation of Treatment Schedule-B

	% Improvement From Baseline Values		
	At Initiation	20 Weeks After	44 Weeks After
AS			
No. patients	6	5	5
% reduction of BASDAI, median (range)	-2.7% (-62.5% to 30.0%)	76.0% (54.5% to 96.0%)	65.0% (5.6% to 96.0%)
PsA			
No. patients	5	4	4
% reduction of PDA, median (range)	20.0% (0.0% to 37.5%)	75.5% (57.1% to 87.5%)	80.0% (71.4% to 87.5%)

TABLE 4. Overall Outcomes in Patients With Active and Refractory AS and PsA Studied [Number (%)] at the Completion of 78 Weeks of Treatment With Infliximab at Either Treatment Schedules

Outcomes	AS (n = 16)	PsA (n = 14)	Total (n = 30)
Withdrawal	7 (43.8%)	3 (21.4%)	10 (33.3%)
Patient noncompliance	5 (31.3%)	2 (14.3%)	7 (23.3%)
Adverse events	2 (12.5%)	1 (7.1)	3 (10.0%)
Response	8 (50.0%)	10 (71.4%)	18 (60.0%)
Optimal response	8 (50.0%)*	10 (71.4%) [†]	18 (60.0%) [‡]
Limited response	0 (0.0%)	0 (0.0%)	0 (0.0%)
No response	1 (6.3%)	1 (7.1%)	2 (6.7%)

The % improvement of BASDAI (for AS patients) and PDA (for PsA patients) compared to the baseline values is used for the definition of optimal response (improvement $\geq 50\%$), limited response (improvement between 20–50%) and no response (improvement $< 20\%$).

*Four patients each on schedule-A and schedule-B respectively.

[†]Six patients on schedule-A and 4 patients on schedule-B.

[‡]Excellent response (improvement $\geq 70\%$ of the respective variables) was observed in 13 out of the 18 optimally responded patients (72.2%), including 5 with AS and 8 with PsA.

infliximab at 4-week intervals had resulted in significant improvement of arthritis but only marginal improvement of psoriatic lesions. Another female patient with PsA and past history of anterior uveitis had experienced 5 episodes of acute anterior uveitis while on treatment with infliximab, despite the remission of arthritis.

The comparable analysis of various clinical and laboratory parameters at baseline (including CRP and ESR) between patients who showed sustained improvement while on treatment schedule-A and those who remained unresponsive or relapsed at any time while on infliximab treatment did not reveal any significant differences (data not shown).

Adverse Events

Several adverse events were observed that in most cases did not necessitate the discontinuation of treatment. These included infections, rashes, as well as a variety of nonspecific complaints during infliximab infusion (Table 5). In total, 31 infectious episodes were noted. Fourteen patients had an episode of a self-limited upper respiratory tract infection. Infectious episodes that required antibiotic treatment and resolved without complications were encountered in 4 patients, including purulent pharyngotonsillitis, tooth abscess, pyelonephritis/prostatitis, and cellulitis (that required admission to hospital), respectively. No malignancies were observed. ANA seroconversion was noticed in 4 patients at 1 year of treatment (titers ranging from 1/160 to 1/640) with no evidence of lupus-like symptomatology. No patient developed anti-dsDNA antibodies.

DISCUSSION

Similarly to previous published experience with other dosing regimens, our findings indicate that the use of infliximab at the dose of 3 mg/kg per infusion can lead to

TABLE 5. Adverse Events Recorded From Baseline to Week 78

	AS	PsA
Infections:		
Upper respiratory tract infections	10	11
Purulent pharyngo-tonsillitis	—	1
Genitourinary tract infection (pyelonephritis, prostatitis)	1	—
Skin infection	4	3
Tooth abscess	1	—
Skin:		
Injection-site reaction	2	1
Rash	2	1
Other:		
Nausea, dizziness or somnolence	7	10
Headache	3	4
Palpitations or fainting (during infusion)	3	1
Fever, chills, myalgias, arthralgias	1	—
Hypoglycemia	1	—

significant improvement of spondylarthritis in a considerable proportion of patients with active and refractory AS and PsA. Improvement involved all major disease parameters, including clinical and laboratory indices of disease activity, indices of functional impairment, and quality of life. In addition, shortening of intervals between infliximab infusions showed substantial efficacy in cases with relapsing or intractable disease. Although the small number of observations precludes the extraction of firm conclusions, our observational data indicate that patients who were admitted in treatment schedule-B due to disease relapse while on treatment schedule-A, had comparatively less improvement than those who

remained in schedule-A, a fact which likely suggests a more resistant subgroup of patients. Yet, the comparable efficacy between the dose increment and the shortening of intervals between infliximab infusions remains to be delineated. Most likely, the most effective dose and pulsing intervals of infliximab therapy need to be tailored to the individual patient. Nevertheless, as far as the induction of clinical response is concerned, recent data have advocated the shortening of pulse intervals, as this appears to result in larger increment in trough serum infliximab concentrations and the efficacy of the drug thereof.³⁸ In addition, the adaptable protocol that we had presently employed (infusion every 8 weeks and selective administration every 4 weeks in patients with relapsing or refractory disease) appears less costly than the fixed administration of infliximab (5 mg/kg every 8 weeks). In this study, a total number of 308 pulses of infliximab have been administered (including 193 pulses every 8 weeks and 115 pulses every 4 weeks, ie, total: 924 mg/total patient-kg). Assuming that the administration of 5 mg/kg infliximab every 8 weeks is efficient for all patients (no relapsing or refractory patients) and is associated with a withdrawal rate that is similar to the dose of 3 mg/kg, a total number of 204 pulses (every 8 weeks) would be needed for the treatment of the present cohort of patients (ie, total: 1020 mg/total patient-kg). This indicates that if the 5 mg/kg pulsing protocol were to be adopted, at least a 10.4% higher total amount of infliximab would be required.

Apart from the efficacy of the 3 mg/kg dose, we had monitored systematically the pattern of response and the safety features of such treatment over a rather extensive period of time. The efficacy of the long-term treatment with infliximab was found comparable to that reported previously by shorter-term trials^{9,10,12-15,17-20} regarding early time points and had become even more impressive at 78 weeks. Although fast and remarkable response to treatment with 3 mg/kg infliximab was the rule, a significant number of patients had experienced relapse that usually occurred between weeks 22 and 38 of treatment and necessitated the modification of dosing schedule. Nevertheless, after that critical period, the risk of a relapse appears quite low for patients who remain on treatment, and sustained improvement is the usual outcome. Finally, the long-term infliximab therapy was found rather safe. Allergic reactions that required the discontinuation of treatment were very few and represented the most alarming adverse event, whereas no cases of serious chronic infections, such as tuberculosis, were observed. This likely owes to the prophylactic administration of isoniazid as latent infection treatment and the close monitoring of our patients. Nevertheless, comparative double-blind controlled studies are needed to address whether the administration of infliximab at 3 mg/kg per infusion is associated with lower frequency of infection³⁹ in patients with spondyloarthropathies. Interestingly, a PsA patient (with past history but without

active anterior uveitis at study entry) suffered recurrent episodes of acute anterior uveitis during treatment with infliximab, despite the remission of arthritis. In fact, in patients with inflammatory eye disease and associated arthritis, joint disease may benefit more than eye disease,⁴⁰ and patients receiving a TNF inhibitor may even develop inflammatory eye disease for the first time.^{40,41}

In conclusion, infliximab at a dose of 3 mg/kg per infusion appears to represent an effective and rather safe treatment of patients with active and refractory spondyloarthropathies. Further parallel studies are necessary to specify the optimal conditions of infliximab administration in patients with spondyloarthropathies, including dosing, intervals and the pulsing protocol, the long-term safety, as well as the capacity of the drug to prevent the radiographic progression and structural damages observed.

REFERENCES

1. Khan MA. Spondyloarthropathies. *Rheum Dis Clin North Am.* 1992;18:1-282.
2. Arnett FC. The seronegative spondyloarthropathies. *Bull Rheum Dis.* 1987;37:1-12.
3. Ferraz MB, Tugwell P, Goldsmith CH, et al. Meta-analysis of sulfasalazine and ankylosing spondylitis. *J Rheumatol.* 1990;17:1482-1486.
4. Creemers MCW, Franssen MJAM, van der Putte LBA, et al. Methotrexate in severe ankylosing spondylitis: an open study. *J Rheumatol.* 1995;22:1104-1107.
5. Espinoza LR, Zakraoui L, Espinoza CG, et al. Psoriatic arthritis: clinical response and side effects to methotrexate therapy. *J Rheumatol.* 1992;12:872-877.
6. Steinsson K, Jonsdottir I, Valdimarsson H. Cyclosporin-A in psoriatic arthritis: an open study. *Ann Rheum Dis.* 1990;49:603-606.
7. Mazzanti G, Coloni L, Desabbata G, et al. Methotrexate and cyclosporin combined therapy in severe psoriatic arthritis: a pilot study. *Acta Derm Venereol Suppl (Stockm).* 1994;186:116-117.
8. Farr M, Kittas GD, Waterhouse L, et al. Sulphasalazine in psoriatic arthritis: a double blind, placebo-controlled study. *Br J Rheumatol.* 1990;29:46-49.
9. Brandt J, Haibel H, Cornely D, et al. Successful treatment of active ankylosing spondylitis with the anti-TNF- α monoclonal antibody infliximab. *Arthritis Rheum.* 2000;43:1346-1352.
10. Van den Bosch, Kruithof E, Baeten D, et al. Effects of a loading dose regimen of 3 infusions of chimeric monoclonal antibody to TNF- α (infliximab) in spondyloarthropathy: an open pilot study. *Ann Rheum Dis.* 2000;59:428-433.
11. Mease PJ, Goffe BS, Metz J, et al. Etanercept in the treatment of psoriatic arthritis and psoriasis: a randomised trial. *Lancet.* 2000;356:385-390.
12. Stone M, Salonen D, Lax M, et al. Clinical and imaging correlates of response to treatment with infliximab in patients with ankylosing spondylitis. *J Rheumatol.* 2001;28:1605-1614.
13. Brandt J, Haibel H, Sieper J, et al. Infliximab treatment of severe ankylosing spondylitis: one-year follow-up (letter). *Arthritis Rheum.* 2001;44:2936-2937.
14. Van den Bosch F, Kruithof E, Baeten D, et al. Randomized double-blind comparison of chimeric monoclonal antibody to tumor necrosis factor- α (Infliximab) versus placebo in active spondyloarthropathy. *Arthritis Rheum.* 2002;46:755-765.
15. Braun J, Brandt J, Listing J, et al. Treatment of active ankylosing spondylitis with infliximab: a randomized controlled multicentre trial. *Lancet.* 2002;359:1187-1193.
16. Gorman J, Sack K, Davis J. Treatment of ankylosing spondylitis by inhibition of tumor necrosis factor- α . *N Engl J Med.* 2002;346:1349-1356.

17. Kruithof E, Van den Bosch F, Baeten D, et al. Repeated infusions of infliximab, a chimeric anti-TNF α monoclonal antibody, in patients with active spondyloarthritis: one year follow up. *Ann Rheum Dis*. 2002; 61:207–212.
18. Maksymowych W, Jhangri G, Lambert R, et al. Infliximab in ankylosing spondylitis: a prospective observational inception cohort analysis of efficacy and safety. *J Rheumatol*. 2002;29:959–965.
19. Breban M, Vignon E, Claudepierre P, et al. Efficacy of infliximab in refractory ankylosing spondylitis: results of a six-month open-label study. *Rheumatology*. 2002;41:1280–1285.
20. Antoni C, Dechant C, Hanns-Martin Lorenz P, et al. Open-label study of infliximab treatment for psoriatic arthritis: clinical and magnetic resonance imaging measurements of reduction of inflammation. *Arthritis Care Res*. 2002;47:506–512.
21. Braun J, Bollow M, Neure L, et al. Use of immunohistologic and in situ hybridization techniques in the examination of sacroiliac joint biopsy specimens from patients with ankylosing spondylitis. *Arthritis Rheum*. 1995;38:499–505.
22. Grom AA, Murray KJ, Luyrink L, et al. Patterns of expression of TNF- α , TNF- β , and their receptors in synovia of patients with juvenile rheumatoid arthritis and juvenile spondyloarthritis. *Arthritis Rheum*. 1996;39:1703–1710.
23. Ritchlin C, Haas-Smith SA, Hicks D, et al. Patterns of cytokine production in psoriatic synovium. *J Rheumatol*. 1998;25:1544–1552.
24. Partsch G, Steiner G, Leeb BF, et al. Highly increased levels of TNF- α and other proinflammatory cytokines in psoriatic arthritis synovial fluid. *J Rheumatol*. 1997;24:518–523.
25. Gratacos J, Collado A, Filella X, et al. Serum cytokines (IL-6, TNF- α , IL-1 β , IFN- γ) in ankylosing spondylitis: a close correlation between serum IL-6 and disease activity and severity. *Br J Rheumatol*. 1994;33: 927–931.
26. Toussiot E, Lafforgue P, Boucraut J, et al. Serum levels of IL-1 β , TNF- α , soluble IL-2 receptor and soluble CD8 in seronegative spondyloarthropathies. *Rheumatol Int*. 1994;13:175–180.
27. Ettehadi P, Greaves MW, Wallach D, et al. Elevated TNF- α biological activity in psoriatic skin lesions. *Clin Exp Immunol*. 1994;96:146–151.
28. Russell AS, Orozco JH, Maksymowych WP. The dosage of infliximab in the treatment of ankylosing spondylitis: dollars and sense. *Clin Exp Rheumatol*. 2002;28(suppl):S135–136.
29. Van der Linden S, Valkenburg HA, Cats A. Evaluation of diagnostic criteria for ankylosing spondylitis: a proposal for modification of the New York criteria. *Arthritis Rheum*. 1984;27:361–368.
30. Garrett S, Jenkinson T, Kennedy LG, et al. A new approach to defining disease status in ankylosing spondylitis: the Bath Ankylosing Spondylitis Disease Activity Index. *J Rheumatol*. 1994;21:2286–2291.
31. Emery P, Reginster JY, Appelboom T, et al. WHO Collaborating Centre consensus meeting on anti-cytokine therapy in rheumatoid arthritis. *Rheumatology (Oxford)*. 2001;40:699–702.
32. Calin A, Garrett S, Whitelock H, et al. A new approach to defining functional ability in ankylosing spondylitis: the development of the Bath Ankylosing Spondylitis Functional Index. *J Rheumatol*. 1994;21:2281–2285.
33. Jenkinson TR, Mallorie PA, Whitelock HC, et al. Defining spinal mobility in ankylosing spondylitis: the Bath Ankylosing Spondylitis Metrology Index. *J Rheumatol*. 1994;21:1694–1698.
34. Daltroy L, Larson M, Roberts N, et al. A modification of the Health Assessment Questionnaire for the Spondyloarthropathies. *J Rheumatol*. 1990;17:946–950.
35. Van Tubergen A, van der Heijde D, Anderson J, et al. Comparison of statistically derived ASAS improvement criteria for ankylosing spondylitis with clinically relevant improvement according to an expert panel. *Ann Rheum Dis*. 2003;62:215–221.
36. Fredrickson T, Peterson U. Severe psoriasis-oral therapy with a new retinoid. *Dermatologica*. 1978;157:238–244.
37. Pocock SJ. *Clinical Trials*. Chichester, England: Wiley; 1990.
38. St. Clair EW, Wagner CL, Fasanmade AA, et al. The relationship of serum infliximab concentrations to clinical improvement in rheumatoid arthritis. *Arthritis Rheum*. 2002;46:1451–1459.
39. Keane J, Gershon S, Wise RP, et al. Tuberculosis associated with infliximab, a tumor necrosis factor- α neutralizing agent. *N Engl J Med*. 2001;345:1098–1104.
40. Smith J, Levinson R, Holland G, et al. Differential efficacy of tumor necrosis inhibition in the management of inflammatory eye disease and associated rheumatic disease. *Arthritis Rheum*. 2001;45:252–257.
41. Kaipainen-Seppänen O, Leino M. Recurrent uveitis in a patient with juvenile spondyloarthritis associated with tumor necrosis factor- α inhibitors. *Ann Rheum Dis*. 2003;62:88–89.