Repeated infusions of low-dose infliximab plus methotrexate in psoriatic arthritis: Immediate benefits are not maintained after discontinuation of infliximab

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Abstract

Objective

To assess the long-term efficacy and tolerability of a therapy consisting of infliximab at low dosage plus methotrexate in patients with psoriatic arthritis (PsA). As a second objective, we assessed whether the improvement obtained after 54 weeks of infliximab could be maintained with methotrexate alone.

Methods

A group of 26 patients with peripheral PsA resistant to various DMARDs were treated with infliximab + methotrexate for 54 weeks.

Results

The clinical response after the induction period was constant and progressive, with a high percentage of patients achieving an ACR50 response. The ESR and CRP values also declined continuously and gradually, but only CRP returned to normal values. During the follow-up period after 54 weeks, infliximab was stopped and the improvement obtained lasted for 2-6 months. The secondary end point was not achieved, and an extension period was designed. Results at 78 weeks are presented.

Conclusions

Open questions for treating patients with infliximab and methotrexate are the schedule and the length of the administration and how to preserve the improvement obtained after the drug discontinuation.

Key words

Rheumatoid arthritis, psoriatic arthritis, anti-TNFα.

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Introduction

Psoriatic arthritis (PsA) can cause, like rheumatoid arthritis (RA), a progressive functional inhability (1). In these subsets of patients the efficacy of various disease-modifying antirheumatic drugs (DMARDs) has been evaluated, methotrexate (MTX) being the most widely employed (2-4), either alone or in combination with other DMARDs (5). However, very often the administration of these drugs must be discontinued because of side effects or lack of response. Therefore, an alternative approach for the treatment of these patients is mandatory.

In RA patients unresponsive to traditional DMARDs, a monoclonal antibody (infliximab) directed against tumor necrosis factor (TNF-α) that plays a pivotal role in the pathogenesis of RA, has been effectively employed (6).

Several findings demonstrate that TNF-α is also involved in the pathophysiology of PsA (7), and then indicate that there is a rationale for administering this drug in treatment resistant PsA. Trials with infliximab administered with or without other DMARDs at different dosages and intervals between subsequent treatments have been reported (Table I) demonstrating that repeated infusions of infliximab every 8 weeks combined with MTX seem to be a good choice. Opening questions are either the choise of infliximab dosage or how long biologic agents must be administered and how long improvement lasts after discontinuation of infliximab.

In this paper we assessed the efficacy and safety of blocking TNF-α up to 54 weeks with every 8 weeks repeated infusions of infliximab at low dose combined with MTX in resistant peripheral PsA. Another purpose was to establish whether a period of 54 weeks was sufficient for a carryover effect of infliximab, i.e. for maintaining a sustained effect by discontinuing infliximab and going on with MTX alone.

Patients and methods

We performed a 54-week single center prospective open-label compassionate use study to evaluate two end points. The first one was the efficacy (defined as percentage of patients achieving a good clinical response) and the safety of a one year combined therapy with infliximab at low dosage (3 mg/Kg) and MTX in patients with traditional treatment resistant PsA. The second end point was the efficacy of a "step down strategy", i.e. to maintain a good clinical response, obtained after one year of combined therapy, continuing with methotrexate in monotherapy.

At a screening visit (Fig. 1) patients who fulfilled the European criteria diagnosis of PsA (14) were considered eligible if they had an active peripheral

Table I. Clinical studies concerning infliximab evaluation in PsA

Study	Dosage, schedule (duration,weeks)	n
Open pilot study (Van den Bosch 2000)	5 mg/Kg, Loading, (12) *	9
Double blind placebo controlled study (Van den Bosch 2002)	5 mg/Kg, Loading, (12) *	9
Open label study (Kruithof, Van den Bosch 2002)	5 mg/Kg, Loading, 5 mg/Kg q 14 wks (54) *	9
Open label study (Antoni 2002)	5 mg/Kg, Loading, 3 mg/Kg q 8 wks (54) **	10
Open label study (Provenzano 2003)	5 mg/Kg, Loading, 5 mg/Kg q 8 wks (30) ***	12
Open label study (Salvarani 2003)	3 mg/Kg, Loading 3 mg/Kg q 8 wks (30) ***	12

Loading = 0, 2, 6 weeks; n = number of patients;
*Monotherapy; **combination therapy with various DMARDs; ***combination therapy with methotrexate.

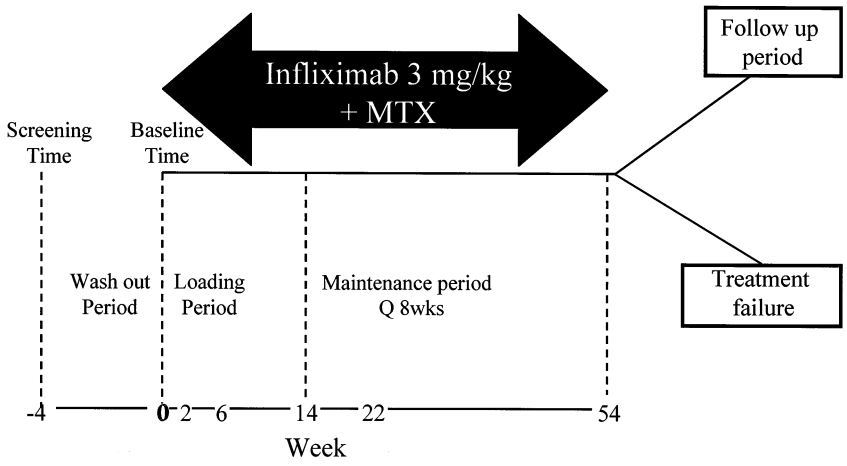

Fig. 1. Study design.

Table II. Clinical and laboratory parameters evaluated at the screening time and at each visit. Indicated are the variables on which the ACR, PsARC and DAS criteria are based.

	Screening time	Visit time	ACR	PsARC	DAS (44 joints)
Number of swollen joints (66)	*	*	*	*	*
Number of tender joints (68)	*	*	*	*	
Morning stiffness	*	*			
ESR and CRP	*	*	*		*
Ritchie's Index		*			*
VAS PzGA		*	*	*	*
VAS PhGA		*	*	*	
VAS Pain		*	*		
HAQ		*	*		

VAS PzGA: Visual analogue scale for the global evaluation of disease activity by the patient (0-100)
VAS PhGA: Visual analogue scale for the global evaluation of disease activity by the physician (0-100)
VAS Pain: (0-100)
HAQ: Health Assessment Questionnaire
Disease activity was defined at the screening time by the following criteria: presence of ≥ 3 swollen joints (66 joints), ≥ 3 tender joints (68 joints), and at least two of the following: morning stiffness of at least 45 min, erythrocyte sedimentation rate (ESR) > 20 mm/h or C-reactive protein (CRP) > 1 mg/dl.
Exclusion criteria were age < 18, a disease duration < 1 year, patients with childbearing potential who refused adequate contraception or with a prior history of pregnancy, patients with a positive history of infection (either chronic or recent and severe) or neoplasms, and patients with signs or symptoms suggestive of axial involvement. Patients were screened to identify those with previous tubercolosis.

disease unresponsive to traditional DMARDs and symptomatic therapy (nonsteroidal anti-inflammatory drugs and prednisone ≤ 10 mg/day) from at least three months. After obtaining an informed consent, in the wash out period patients were allowed to continue only symptomatic therapy at a stable dose. After one month, at the baseline time, an infliximab-MTX parallel association was added if disease was still active. Infliximab was administered every eight weeks (maintenance period) after a loading period. MTX was administered at the dose of 10-15 mg/week based on the tolerability of the patient. No folates were administered in order to avoid a diminished efficacy of MTX. Schedule of administration and doses were kept stable throughout the study period. After 54 weeks infliximab was discontinued and patients who were good responders (ie who satisfied ACR50 criteria) continued with MTX in monotherapy and symptomatic drugs at an unchanged dosage (follow up period). Patients who reached the ACR20 criteria were considered a treatment failure (bad responders) and discontinued treatment.

Disease activity was evaluated at the screening time (Table II). At each visit a complete evaluation was performed (see visit time, Table II) (15) and the American College of Rheumatology (ACR) criteria (17), the Psoriatic Arthritis Response Criteria (PsARC) (18) and the Disease Activity Score (DAS) were used to evaluate disease activity (DAS > 3.7) (19) and response to treatment (Table II). At each visit, prior of the infusion, routine laboratory tests were performed. At the baseline and at the week 54 urinalysis was performed and positivity for antinuclear antibodies (ANAs) and antibodies to double-stranded DNA (anti-dsDNA antibodies) was determined. Statistical significance of the change from baseline (intragroup analysis) was measured using the Wilcoxon signed rank test.

Results

Table III shows the demographic, clinic and laboratory data of the 26 patients (15 females, 11 males) at the screening time. Disease activity at the baseline (26 patients) was very high (DAS mean values 4.9±1.3, data not shown).

Response to treatment, a sign of clinical improvement evaluated using ACR, PsARC and DAS criteria, was satisfying and data at 14, 22 and 54 weeks are shown in Figure 2. At the time of the three observations the percentages of patients satisfying ACR20, 50 and 70 criteria were high. Comparable results reguarding response to treatment were obtained applying PsARC and DAS criteria.

For the primary end point, it was found that 80% (12 of 15 patients) achieved a good clinical response.

Among the first 5 patients who completed 54 weeks (Fig. 3, right side), one patient discontinued because of lack of response (i.e., did not achieve an ACR 20 response). The remaining 4 patients were good responders and entered in the follow up period, continuing only with MTX. The improvement lasted for a short period (from 2 to 6 months) in all but one (11 months) before a relapse occurred in all the patients. Therefore we retained that a period of 54 weeks

Table III. Demographic, clinical and laboratory data at the screening time and at any scheduled time during the study.

	Mean Mean (range)	Screening (n=26)	Baseline (n=26)	Week 14 (n=26)	Week 22 (n=24)	Week 54 (n=15)	Week 78 (n=9)
Sex (F/M)	15/11						
Age	52.3 (22-81)						
Disease duration (years)	6.5 (1-24)						
Previous DMARDs used	2 (1-4)						
Number of swollen joints (66)		13.8 (3-41)	13.8 (3-41)	1.84 (0-26) ***	2.6 (0-38) ***	0.4 (0-7) ***	0.7 (0-7) **
Number of tender joints (68)		24.7 (3-45)	24.7 (3-45)	6.76 (3-45) ***	7.4 (0-39) ***	2.8 (0-19) ***	2.6 (0-23) **
Length of morning stiffness (min)		111.9 (45-360)	111.9 (45-360)	14.8 (45-360) ***	47.5 (0-240) ***	24.6 (0-240) **	3.3 (0-30) **
Pain evaluation by the patient (VAS)			73.1 (9-100)	22.2 (0-85) ***	44.6 (0-100) ***	26.8 (0-100) **	10.6 (0-80) **
Global evaluation by the patient (VAS)			76.3 (22-100)	23.1 (0-92) ***	45.3 (0-100) ***	28.4 (0-100) ***	11.1 (0-100) **
Global evaluation by the physician (VAS)			76.0 (25-100)	20.1 (25-100) ***	27.2 (0-100) ***	15.5 (0-59) ***	13.8 (0-71) **
HAQ			1.24 (0.2-2.8)	0.4 (0-2.2) ***	0.5 (0-2.2) ***	0.4 (0-0.9) ***	0.2 (0-1.5) **
Ritchie's index			18.5 (3-44)	3.4 (0-20) ***	6.4 (0-34) ***	2.6 (0-18) ***	2.6 (0-22) **
ESR (mm/hr)	38.3 (2-90)		38.3 (2-90)	23.3 (2-90) **	26.1 (3-90) **	20.5 (2-79) **	31.3 (2-100) *
CRP (mg/dl)	2 (0.2-7.1)		2 (0.2-7.1)	1.8 (0.2-7.1) **	1.2 (0.2-10.2) **	0.8 (0.2-5.6) *	0.7 (0.2-3.3) *

*< 0.05; **< 0.01; *** < 0.001.
DMARDs previously employed (mean 2, range 1-4) included MTX (100% of patients), cyclosporine (53%), sulphasalazine (48%), MTX and cyclosporine (36%). All patients were taking NSAIDs and prednisone (≤ 10 mg/day).

was not sufficient to maintain a sustained effect after discontinuation of infliximab.

The secondary end point was not achieved and the originally study design was interrupted.

An extension period was then designed, i.e. to continue up two years the treatment period before discontinuation of infliximab, but only in the patients who were good responders at week 54. At this time treatment was discontinued either in non-responders or in bad responders. Among other 10 patients who completed the 54 weeks (Fig. 3, left side), 2 dropped out (one due to a lack of response and one due to a poor response) and 8 prolonged the treatment because of a good response. Data at 78 weeks (Fig. 2) show that all the 8 patients satisfied criteria of improvement. The study is ongoing at the moment.

Table III shows the raw clinic and laboratory data throughout the study, comprising the extension period. A statistically significant improvement compared with baseline was observed for all the variables evaluated either by the patient or by the physician at any visit. Moreover, a statistically significant decrease was noted for the laboratory variables (i.e. ESR and CRP levels).

Figure 4 shows the values of some variables evaluated from the patient (PzGA and HAQ) and from the physician (PhGA and Ritchie's index) and the values of ESR and CRP. A good correspondence was found between patient and physician evaluation and a significant improvement of HAQ (> 0.3 at week 54 and 78 from baseline) was observed. Interestingly, while CRP values gradually returned to normal levels, ESR levels decreased when compared with baseline values, but did not return to normal levels. Sometime mild disease flares occurred during the study (see week 22) with recurrence of symptoms and an increase of ESR and CRP, however not comparable with baseline values. During relapses no change of therapy was admitted, and re-treatment was efficacious to obtain improvement.

A severe infusion reaction was observed in 4 patients, during the fourth infusion (2 patients) and the fifth infusion (2 patients), who suspended the therapy (Fig. 3). Three patients dropped out at 54 weeks (2 were non-responders, one was a poor responder) (Fig 3). Mild infusion reactions and infections occurred in two and three patients respectively. None of our patients became positive for ANA and anti-dsDNA at week 54.

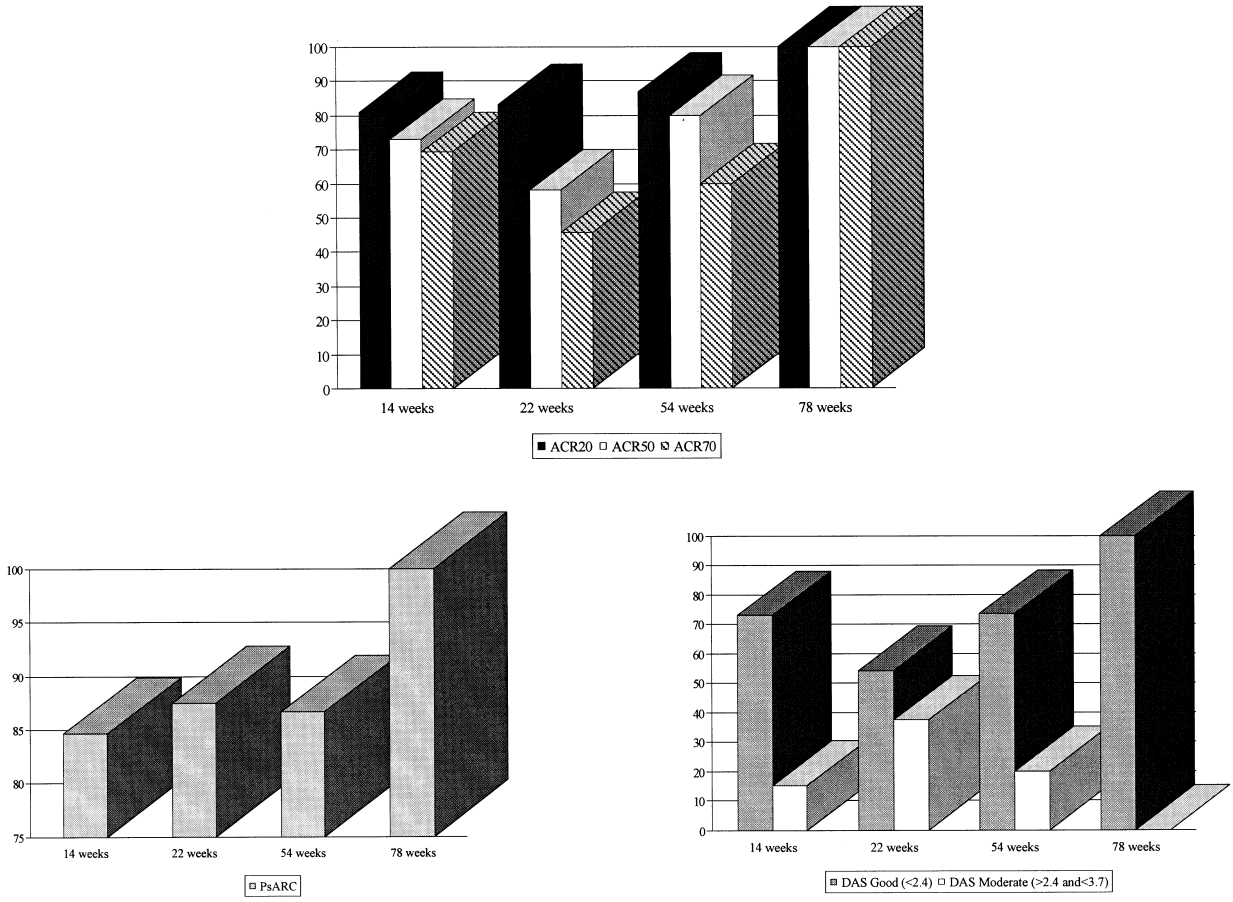

Fig. 2. Evaluation of signs and symptoms at each visit.

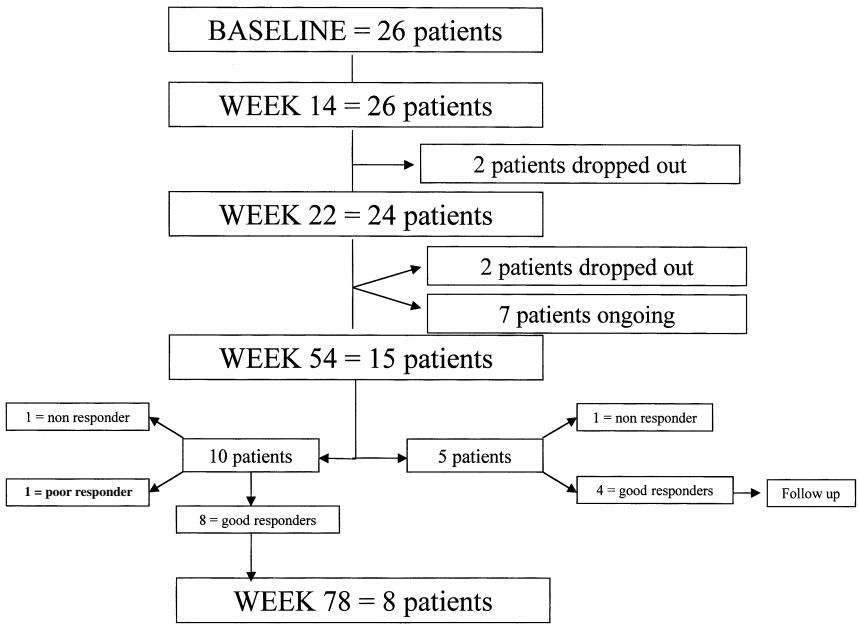

Fig. 3. Evolution of the study.

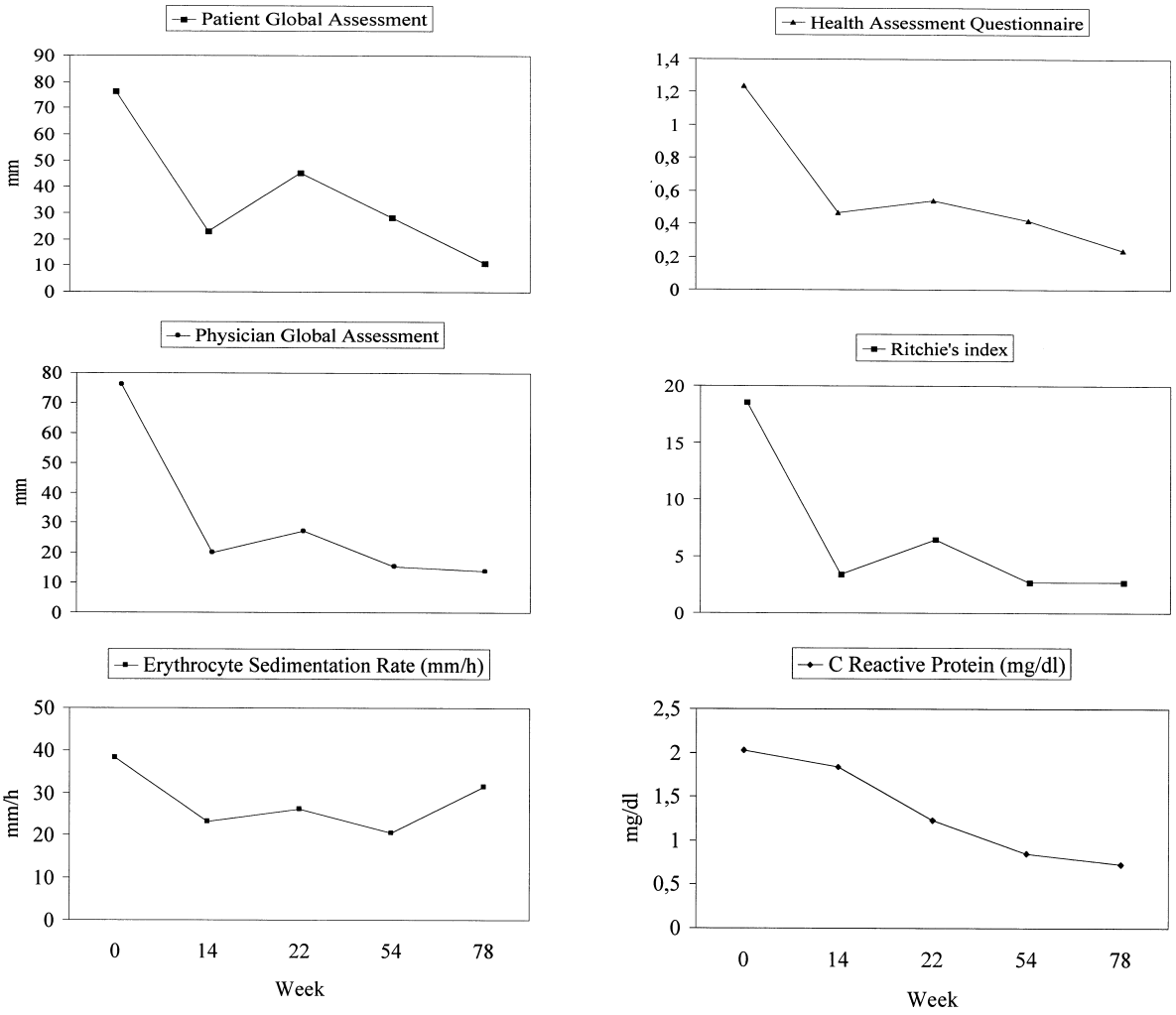

Fig. 4. Patient, physician and laboratory assessment during the study.

Discussion

This open label study demonstrates a sustained effect of infliximab at low dose (3 mg/kg every 8 weeks) combined with MTX in a long term treatment (up to week 78) of patients with resistant PsA. On the other end, this study demonstrates that improvement obtained after one year of treatment is sustained for a short term after infliximab discontinuation.

Efficacy of infliximab has been evaluated in six European trials published as a paper, all but one with an open label design, concerning a small number of patients suffering of PsA with peripheral and/or axial involvement. The only study to date evaluating a large number of patients is a randomised trial, the Infliximab Multinational Psoriatic Arthritis Controlled Trial (IMPACT), published in an abstract form (20).

Firstly, efficacy of monotherapy with infliximab at high dose (5 mg/kg) was demonstrated (8), (9) up to one year of treatment with repeated infusions every 14 weeks) (10). A disease relapse was reported, with the moment of recurrence between 10 and 14 weeks after re-treatment. In authors opinion these results indicated that a maintenance regimen of 5 mg/kg infliximab every 14 weeks could not control the inflammatory disease activity continuously. Therefore, adjustment of the maintenance regimen was required, but it was not clear whether this could be achieved by increasing the dose or shortening the interval between doses.

Better results were obtained by maintaining a high dose and modifying the therapeutic regimen (12).

Therefore, secondly it was demonstrated that a combination therapy and a shorter re-treatment of high dosage of infliximab was more effective.

Subsequently, positive results were obtained by administering MTX combined with infliximab q 8 weeks at low dosage (3 mg/kg at the loading period and at the re-treatment) (13).

Therefore, thirdly it was demonstrated that combination therapy and a short re-treatment with a low dosage of infliximab was effective.

Repeated infusions of infliximab at low dosage q 8 weeks associated with MTX was the therapeutic regimen of our study, distinguished for the presence of a peripheral disease in all the patients and for a longer study period (up to 78 weeks). The efficacy of this regimen in PsA was confirmed and a sustained effect was observed in the long term. The most common adverse events (> 10% of patients) were mild upper respirato-

ry infections, nausea, headache, pharingytis, sinusitis. Serious infusion reactions were observed in 15% of the patients. Recently, in an open label study of 16 patients with refractory PsA treated with infliximab, toxicity and rate of treatment termination was high but the explanation could be that characteristic of their cohort is different either from other groups or from the our (21).

Discontinuation of infliximab because of a therapeutic success was evaluated before our paper by Antoni who reported on the treatment with a loading dose of 5 mg/kg followed by the lower dose of 3 mg/kg of 10 patients with polyarticular PsA (14). Remission, defined as the absence of any active joint inflammation and/or serologic activity, was observed in 4 patients (one without DMARDs associated to infliximab, 3 with combined therapy infliximab plus methotrexate) and infliximab was discontinued. Remission lasted respectively for 7 months, 4 months, 5 months, 11 months at the time of the final evaluation (i.e., at week 54). There are no data on the clinical course of the disease after this final evaluation.

In our study clinical remission was not observed with the fixed regimen of 3 mg/kg. A good clinical response was obtained but after discontinuation of infliximab the improvement obtained lasted for few months, when recurrence of symptoms occurred in all the patients. Our data on the clinical course of the disease after discontinuation of infliximab seem indicate that a longer treatment period before discontinuing infliximab could be more effective for maintaining a good clinical response.

In conclusion, the association infliximab at low dosage (3 mg/kg) with MTX is effective in the long term (78 weeks) treatment of PsA. All the efficacy parameters evaluated as primary end point were achieved. The secondary end point failed to be achieved, because improvement obtained during the treatment period lasted only for a few weeks. Therefore, we need more informations in order to establish the length of the treatment with anti-TNF and how to preserve the improvement obtained after the drug discontinuation.

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