

# Sustained maintenance of clinical remission after adalimumab dose reduction in patients with early psoriatic arthritis: a long-term follow-up study

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**Purpose:** The primary purpose of this study was to evaluate the proportion of psoriatic arthritis (PsA) patients maintaining clinical remission after adalimumab (ADA) dose reduction compared with patients with rheumatoid arthritis. Secondary purposes include evaluating the proportion of PsA patients who achieve remission, the duration of remission after ADA dose reduction, time to relapse, psoriasis course, and the frequency of adverse events at the end of follow-up.

**Methods:** This was a single-center, prospective, follow-up, case-control study of 76 consecutive patients (35 females, 41 males; mean age  $46 \pm 10.2$  years) who met the classification criteria for psoriatic arthritis and required anti-tumor necrosis factor therapy according to Group for Research and Assessment of Psoriasis and Psoriatic Arthritis recommendations. The 76 patients were compared with 55 patients (40 females, 15 males; mean age  $50 \pm 11.6$  years) who satisfied the American College of Rheumatology criteria for rheumatoid arthritis and received the same treatment. Case patients and controls were recruited from January 2008 to December 2010. At baseline, PsA patients and controls received 40 mg of ADA every other week, usually with methotrexate (10 to 20 mg/weekly). In the presence of clinical remission, ADA dose was reduced to 40 mg every 4 weeks in both groups.

**Results:** Fifty-three of the 76 (69.7%) PsA patients and 17 of the 55 (30.9%) rheumatoid arthritis ( $P < 0.019$ ) controls achieved remission after a mean time of  $5.1 \pm 1.2$  and  $6.3 \pm 1.6$  months, respectively ( $P =$  nonsignificant). After halving the dose of ADA, 47 of the 53 (88.6%) PsA patients and three of the 17 (17.6%) controls maintained remission ( $P = 0.016$ ) over a mean follow-up period of  $28.9 \pm 8.4$  and  $24.2 \pm 6.4$  months, respectively. No significant changes in Psoriatic Arthritis Severity Index scores were observed. The mean time to relapse was  $8.3 \pm 3.4$  months in six case patients and  $7.2 \pm 4.2$  in 14 controls ( $P =$  not significant). No serious adverse events occurred in either group.

**Conclusion:** Clinical remission is possible in a high percentage of patients with early PsA receiving ADA. Such remission is maintained in a high proportion of subjects after ADA dose halving, with relevant advantages in terms of patient compliance, drug-exposure risk, and economic burden.

**Keywords:** psoriatic arthritis, anti-TNF, adalimumab, remission, dose reduction

## Introduction

Psoriatic arthritis (PsA) has long been considered a benign disease, although several follow-up studies have demonstrated an aggressive course with development of joint erosions and deformities in up to 70% of cases.<sup>1</sup> PsA is characterized by three main patterns of articular involvement: peripheral oligo-polyarthritis without axial involvement, isolated psoriatic spondylitis, and concurrent involvement of peripheral and axial articular structures.<sup>2</sup>

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Recently, the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis<sup>3</sup> and an Italian experts committee<sup>4</sup> developed treatment recommendations based on a literature review. Anti-tumor necrosis factor (TNF)  $\alpha$  agents are recommended for the treatment of peripheral PsA that is resistant to traditional disease modifying anti-rheumatic drugs, for PsA spondylitis that fails to respond to nonsteroidal anti-inflammatory drugs (NSAIDs), and for patients with dactylitis and enthesitis who do not improve with NSAIDs and local corticosteroid injections.

Owing to the evidence of efficacy provided by randomized clinical trials,<sup>5–8</sup> four anti-TNF $\alpha$  agents – etanercept (Enbrel<sup>®</sup>, Immunex Corporation [a wholly owned subsidiary of Amgen, Inc], Seattle, WA), adalimumab (ADA) (Humira<sup>®</sup>, Abbott Laboratories, Abbott Park, IL), infliximab (Remicade<sup>®</sup>, Centocor, Malvern, PA), and golimumab (Simponi<sup>®</sup>, Centocor Ortho Biotech Inc and Schering-Plough Corporation, PA) – are currently licensed in Italy for the treatment of resistant PsA.

A fully humanized monoclonal anti-TNF $\alpha$  antibody that is usually administered subcutaneously at a dose of 40 mg every other week (eow), ADA was licensed for the treatment of PsA by the Italian Regulatory Authorities in 2005. Evidence regarding the effectiveness of ADA in controlling the signs and symptoms of PsA and in slowing/arresting the radiographic damage of its different clinical patterns was provided by the Adalimumab Effectiveness in Psoriatic Arthritis Trial<sup>7</sup> and its long-term extension phase reports.<sup>9,10</sup> At week 24 of this trial,<sup>7</sup> 57% of the ADA group were American Rheumatism Association (ACR) 20 responders compared with 15% of the placebo group ( $P < 0.001$ ); the ACR 50 and ACR 70 response rates were significantly higher in the ADA-treated patients. None of the previously mentioned ADA studies<sup>7,9,10</sup> focused on the frequency of clinical remission of PsA.

Similar to other biologics, ADA represents an expensive therapy with a heavy economic burden for the health care systems of all countries. Consequently, we believe that every ethical strategy effective at reducing cost with no worsening of patient quality of life would be of great value.

In this view, we designed a prospective, follow-up, case-control study to evaluate the proportion of early PsA patients treated with ADA who maintain clinical remission after drug dose reduction.

## Patients and methods

### Study design

This was a prospective, follow-up, case-control study.

### Case patients

Case patients were consecutive new outpatients fulfilling the classification criteria for psoriatic arthritis<sup>11</sup> with a disease duration of less than 24 months who required anti-TNF $\alpha$  therapy according to the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis recommendations<sup>3</sup> and who received ADA. Patients were observed between January 2008 and December 2010 at the Rheumatology Division of the Hospital of Prato, Italy. PsA patterns and clinical manifestations were defined as previously reported.<sup>2,13–15</sup>

### Controls

Control patients were consecutive new outpatients meeting the 1987 revised criteria of the ACR for the classification of rheumatoid arthritis (RA)<sup>12</sup> who were treated with ADA. Patients were observed over the same period as the case patients.

### Primary goal

The primary goal of the study was to evaluate the proportion of PsA patients maintaining clinical remission after ADA dose reduction compared with patients with RA.

### Secondary goals

The secondary goals of the study were to evaluate the proportion of PsA patients who achieve clinical remission, the duration of remission after ADA dose reduction, time to relapse, skin disease changes, and the frequency of adverse events.

### Exclusion criteria

Patients with contraindications to the use of traditional disease modifying anti-rheumatic drugs and anti-TNF $\alpha$  drugs were excluded from the study.

### Disease remission

To define clinical remission in PsA patients, we used the previously reported criteria<sup>16</sup> based on the absence of fatigue and pain (score  $\leq 10$  by visual-analogue scale 1 to 100 mm), peripheral and axial articular symptoms (including tendons and entheses), extra-articular features, and normality of acute-phase reactants. Patients with PsA spondylitis with a Bath Ankylosing Spondylitis Disease Activity Index score  $\leq 4$ <sup>17</sup> in the absence of articular, tenosynovial, and enthesal manifestations and normality of acute-phase reactants were considered in remission. Remission in controls with RA was defined by a disease activity score  $\leq 2.6$ .<sup>18</sup>

Patients of both groups treated with ADA alone or with methotrexate (MTX) were considered in clinical remission if satisfying the previously described criteria and without taking any additional drugs, including NSAIDs and CS for at least two consecutive visits.

## Relapse

Patients and controls were considered as relapsing in the case of the recurrence of any articular or extra-articular clinical manifestations occurring independently on the acute-phase reactants values.

## Treatment regimen

ADA was prescribed at the dose of 40 mg subcutaneous injections eow, usually with MTX at the dose of 10/weekly, both in case patients and in controls. MTX dose escalation to 20 mg/weekly was allowed in cases of unsatisfactory clinical response. In case of MTX intolerance, ADA was given alone.

In PsA patients and controls achieving and maintaining clinical remission for at least 6 months, ADA dose was reduced to 40 mg/monthly and patients were followed up over time. MTX was continued at stable doses. In case of relapse, patients returned to ADA 40 mg/eow.

## Outcome measures

At baseline and at every follow-up visit, all PsA patients and controls were evaluated for the remission criteria as the primary outcome measure.

Secondary outcome measures were disease activity scores, number of tender and swollen joints, number of painful entheses, number of digits showing dactylitis, inflammatory spinal pain, erythrocyte sedimentation rate and C-reactive protein, and Psoriatic Arthritis Severity Index.<sup>19</sup>

## Follow-up

Each patient received follow-up by the same rheumatologist who had done the first visit; follow-up visits were scheduled at baseline and every 3 months. Control visit intervals were shortened in the case of urgent clinical problems, and all patients were instructed to call the center in presence of worsening of previous arthritis, additional joint involvement, extra-articular manifestations onset, and adverse events.

At each visit, patients had a complete physical examination including all previously listed outcome measures. Moreover, routine blood examinations including erythrocyte sedimentation rate, C-reactive protein, rheumatoid factor, complete blood cell count with differential count, renal and

liver function tests, and antinuclear antibodies were carried out. All clinical and laboratory data were recorded in an electronic patient chart.

## Adverse events

All patients were monitored for clinical and laboratory evidence of adverse events, which were classified as mild (transient and easily tolerated), moderate (subject discomfort with interruption of usual activities), or severe (incapacitating or life threatening). The date of last visit constituted the end of the follow-up period, which was extended to December 2011.

The local ethics committee reviewed and approved the study protocols. Before entering the trial, each patient was informed of the nature, duration, and purpose of the study, as well as of all the potential benefits and drawbacks that could be expected. All participants gave written informed consent.

## Statistical analysis

Descriptive statistics and statistical differences were calculated using SPSS statistical package version 11 for Windows (SPSS Inc, Chicago, IL).

Wilcoxon's matched pairs signed-rank test was used to measure the changes from baseline; *t*-test for continuous variables and chi-square test for nominal variables were used to calculate the differences between the study patients and controls. *P* values <0.05 were considered significant.

## Results

Over the 3-year study period, 76 PsA patients and 55 RA controls requiring anti-TNF therapy were treated with ADA. The baseline demographic and clinical characteristics of PsA cohorts and controls are summarized in Table 1. As shown in Table 2, of the 76 PsA patients, 53 (69.7%) achieved clinical remission compared with 17 (30.9%) out of 55 controls with RA (*P* < 0.001). Remission was recorded in 14 of the 49 (28.5%) rheumatoid factor positive patients and in three of six (50%) rheumatoid factor negative RA patients, with no significant statistical difference (*P* = 0.753). The mean time to achieve the remission was 5.1 ± 1.2 months for PsA patients and 6.3 ± 1.6 months for controls (*P* = not significant). The remission rates in peripheral, axial, and mixed PsA were 71.1%, 71.4%, and 66.6%, respectively.

After ADA dose reduction, 47 of the 53 (88.6%) PsA patients and three of the 17 (17.6%) RA controls maintained remission (*P* = 0.016). Psoriatic Arthritis Severity Index score dropped from 8.7 ± 5.9 at baseline to 3.1 ± 1.8 at remission

**Table 1** Baseline demographic, clinical characteristics, and treatment of 76 case patients and 55 controls observed over a 3-year period

	Psoriatic arthritis	Rheumatoid arthritis	P value
Patient N	76	55	NS
Females (N/%)	35 (46%)	40 (73%)	0.004
Males (N/%)	41 (54%)	15 (27%)	
Age (years)	46 ± 10.2	50 ± 11.6	NS
Disease duration (months)	12 ± 8.3	16 ± 9.6	NS
Rheumatoid factor positive (N/%)	0	48 (89%)	
Psoriatic arthritis pattern			
Peripheral	45 (59%)		
Axial	7 (9%)		
Mixed	24 (31.5%)		
Fatigue (VAS 0–100 mm)	58 ± 14.3	62 ± 14.9	NS
Pain (VAS 1–100)	66 ± 13.4	69 ± 10.8	NS
Articular morning stiffness (minutes)	120 ± 46.2	132 ± 55.3	NS
Tender joint count (N)	11 ± 4.1	12 ± 3.5	NS
Swollen joint count (N)	5 ± 2.1	7 ± 3.3	NS
Erythrocyte sedimentation rate (mm/h)	40 ± 15.2	46 ± 19.1	NS
C-reactive protein (mg/dL)	4.4 ± 1.9	4.9 ± 2.2	NS
Patients with dactylitis (N/%)	10 (13%)	0 (0%)	0.014
Patients with enthesitis/tenosynovitis (N/%)	22 (29%)	3 (5%)	0.002
Patients with extra-articular features (N/%)	8 (12%)	5 (9%)	NS
Disease activity score	5.21 ± 0.87	5.48 ± 0.34	NS
Bath Ankylosing Spondylitis Disease Activity Index	6.1 ± 1.1		
Psoriatic Arthritis Severity Index score	8.7 ± 5.9		
Methotrexate (N/%)	64 (84%)	47 (85%)	NS

**Notes:** Bath Ankylosing Spondylitis Disease Activity Index was calculated in patients with axial and mixed pattern PsA (31 patients). Except where otherwise indicated, data are expressed as mean ± SD.

**Abbreviations:** N, number; NS, not significant; SD, standard deviation; VAS, visual analog scale.

( $P < 0.001$ ) and did not change significantly after ADA dose halving, with the mean value at the end of the follow-up period being  $3.9 \pm 2.6$  ( $P = 0.086$ ). Disease relapse was recorded in six PsA patients – three (9.3%) with peripheral PsA, one (20%) with axial, and two (12.5%) with mixed PsA patterns – with a mean time to recur of 8.3 months. As dictated by the protocol, ADA dose was increased to 40 mg/eow in these patients, who then achieved remission again after a mean interval of  $5.1 \pm 2.4$  months.

Regarding drug tolerability and safety, mild injection site reactions were recorded in 11 (20.7%) patients, urinary infections in three (5.6%), upper airways infections

**Table 2** Frequency of remission in psoriatic arthritis (PsA) patients and rheumatoid arthritis (RA) controls receiving adalimumab (ADA), time to remission, and duration of remission after ADA dose reduction

	Psoriatic arthritis 76 patients	Rheumatoid arthritis 55 patients	P value
Overall remission (N/%)	53 (69.7%)	17 (30.9%)	0.019
Combined methotrexate (N/%)	46 (86.7%)	16/17 (94.1%)	NS
Remission by PsA pattern			
• Peripheral	32 (71.1%)		
• Axial	5 (71.4%)		
• Mixed	16 (66.6%)		
Time to remission (months/ mean ± SD)	5.1 ± 1.2	6.3 ± 1.6	NS
PsA remission after ADA dose reduction (N/%)	47 (88.6%)	3 (17.6%)	0.016
Relapse by PsA pattern (N/%)			
• Peripheral	3 (9.3%)		
• Axial	1 (20%)		
• Mixed	2 (12.5%)		
Time to relapse (months/ mean ± SD)	8.3 ± 3.4	7.2 ± 4.2	NS
Duration of follow-up (months/mean ± SD)	28.9 ± 8.4	24.2 ± 6.4	NS

**Abbreviations:** ADA, adalimumab; PsA, Psoriatic arthritis; N, number; NS, not significant; SD, standard deviation.

in 12 (22.6%), and slightly elevated liver enzymes in three (5.6%), with no severe adverse events requiring ADA interruption. Antinuclear antibodies positivity was observed in five (9.4%) PsA patients and in six (10.9%) controls with RA during the entire follow-up period, which was not statistically significant. No patients developed signs or symptoms of lupus-like syndromes.

## Discussion

While no remission criteria have been standardized for PsA, data from several clinical series<sup>20–22</sup> and from the British Society for Rheumatology Biologics Register<sup>23</sup> reported a frequency of clinical remission ranging from 17.6% to 58%, with the highest rate observed in patients treated with anti-TNF $\alpha$  agents. This wide range may be partly explained by the absence of validated criteria for remission in PsA, which has led to the use of different sets for remission assessment, as well as the different methods of selecting patients. In a previous study,<sup>16</sup> we evaluated the frequency and duration of clinical remission in patients with early peripheral PsA requiring second-line drugs, adopting a restrictive set of criteria based on the absence of systemic manifestations, peripheral and axial articular symptoms (including tendons and entheses), extra-articular features, and normality of acute-phase reactants. The overall frequency of remission was 24.1%, with a remission

rate of 60.5% in patients taking anti-TNF $\alpha$  agents. In this study, a consistent percentage of subjects with PsA, treated with either traditional disease modifying anti-rheumatic drugs or anti-TNF, did not relapse over a prolonged time (mean  $12 \pm 2$  months) after therapy interruption, thus suggesting an intermittent therapeutic strategy as a possible option for PsA patients achieving remission.

Since the recruitment period in the above-mentioned study preceded the approval of ADA for the treatment of PsA, none of the patients received this drug. However, the effectiveness of ADA for PsA therapy has been demonstrated in different clinical trials,<sup>7,9,10,24–28</sup> with approximately 60% of patients achieving a good clinical response. In addition, a recent study of 152 PsA patients with long-standing disease (median 8 years) treated with ADA demonstrated a 58% remission rate, with a significant difference with respect to the 48% rate recorded in patients with RA.<sup>22</sup>

Given the evidence of the efficacy of ADA (and of all anti-TNF agents in general terms) in the treatment of PsA, another important issue is the economic impact of this therapy, which has an estimated cost of around €14,000/patient/year. Consequently, every effort to reduce this economic burden is desirable on the condition that patient outcome and quality of life does not worsen. As we observed in a previous clinical series,<sup>16</sup> in PsA patients achieving remission, therapy withdrawal may be a possible strategy for reducing drug-exposure risk and lowering the economic burden on public health care systems. This therapeutic approach has also been attempted in patients with RA. In a Japanese study, 52 (30.2%) of the 172 RA patients treated with combined infliximab and MTX achieved remission. In nine of these patients, infliximab was discontinued with no recurrences over a mean follow-up period of 14.2 months.<sup>29</sup>

In this context, we designed the present case-control study to evaluate the efficacy of ADA dose reduction in PsA patients achieving clinical remission. Over a 3-year period, according to the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis recommendations,<sup>3</sup> we treated 76 patients with active early PsA and 55 RA patients with ADA. Confirming the results of other authors,<sup>22</sup> in our study, a significantly higher percentage of PsA patients compared with those with RA achieved clinical remission (69.7% vs 30.9%;  $P = 0.019$ ). After ADA dose reduction to 40 mg every 4 weeks, 47 of the 53 (88.6%) PsA patients maintained remission over a mean follow-up period of  $28.9 \pm 8.4$  months compared with three of the 17 (17.6%) RA patients ( $P < 0.001$ ); no significant worsening of skin manifestations were found.

To the best of our knowledge, this is the first study on PsA patients that demonstrates the sustained efficacy of ADA in maintaining remission after halving the dose. A similar therapeutic strategy has been previously attempted both in RA and in ankylosing spondylitis patients. In an open-label study of 21 RA patients, infliximab dose titration using disease activity score improvement allowed for the reduction of 67% of the total amount of the drug with maintenance of clinical response.<sup>30</sup> The sustained efficacy after halving the dose of etanercept in patients with ankylosing spondylitis has been reported in two studies. In the first, 18 patients receiving etanercept at a dose of 25 mg/weekly were still in remission after 6 months,<sup>31</sup> and in the second, 16 patients maintained remission after etanercept tailoring over a mean follow-up period of  $26.1 \pm 21$  months.<sup>32</sup>

The successful ADA dose halving in our PsA patients suggests two main considerations. First, none of the patients included into the present study experienced ADA-related adverse events, allowing us to speculate that dose reduction may be hypothetically associated with a long-term lower incidence of drug-related adverse events and toxicity. Second, ADA dose halving permitted a marked cost-saving effect, with an estimated savings of more than €700,000 (cost of ADA standard dose therapy/patient/month: €1166; ADA halving dose: €583 /month; multiplied by 47 patients over a mean follow-up period of 28 months).

To conclude, our results indicate that clinical remission is possible in a high percentage of patients with early PsA receiving ADA, with a significant difference with respect to those with RA. Moreover, different from patients with RA, after ADA dose reduction, a high proportion of PsA patients (88.6%) maintained remission over a long-term follow-up period. Sustained disease remission after ADA dose halving suggests the application of this therapeutic strategy in clinical practice with important advantages in terms of drug-exposure risk and cost savings.

## Disclosure

The authors have no conflicts of interest to declare.

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