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Maintenance of remission and monotherapy status over 66 months in patients with psoriatic arthritis receiving etanercept

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ABSTRACT

Objective. *To determine if patients with psoriatic arthritis (PsA) who achieved remission within 6 months with etanercept (ETN) treatment (with or without methotrexate) were able to maintain remission over 66 months. Monotherapy status over the study duration was also monitored.*

Methods. *This was a post hoc analysis of PROVE (NCT00938015), a multicentre, observational study into the long-term adherence of ETN performed in rheumatology clinics in Belgium. To be included in PROVE, patients had active PsA and were either already receiving ETN treatment or had recently been prescribed it. Patients who achieved remission (defined as zero joints with synovitis) after 6 months of ETN treatment were monitored for maintenance of remission at each subsequent visit. In addition, patients on ETN monotherapy at Month 6 were observed.*

Results. *303 patients participated and 156 (51.5%) patients completed 66 months of ETN treatment. The mean (standard deviation [SD]) disease duration was 7.5 (7.4) years and the majority had polyarticular-type PsA (87.1%). Overall, 142 patients achieved remission after 6 months of ETN treatment. Among the 83 patients who were in remission at Month 6 and remained in the study until the end, 72 (86.7%) were still in remission at Month 66. After 6 months, 66 patients were receiving ETN monotherapy and the majority continued with it until Month 66 (n=22/26; 84.6%).*

Conclusion. *Within this patient population, remission was achieved quickly and was sustained in the long-term. Of those patients who were receiving monotherapy, most continued with this treatment strategy for the duration of the study.*

Introduction

Psoriatic arthritis (PsA) is a chronic, inflammatory arthritis, often associated with the skin disease psoriasis (1). Joint disease in PsA can lead to irreversible bone damage, interfering with the patient's physical functioning and their quality of life over time (2).

Recent treatment guidelines for patients with PsA have proposed that remission should be the primary treatment target (3). Once remission is achieved, they recommend that its status is monitored and treatment is adapted to ensure it is sustained. Therefore, it is important that patients receive an effective treatment that they will adhere to in the long term. The first line of treatment is often a traditional disease-modifying anti-rheumatic drug (DMARD), most commonly methotrexate (MTX). Patients who have failed ≥1 DMARD or have a poor prognosis are recommended to initiate tumour necrosis factor (TNF) inhibitor therapy (4). TNF inhibitors are often taken in combination with MTX in order to increase efficacy, reduce the risk of immunogenicity and ultimately improve drug survival (5). However, due to the lack of immunogenicity of etanercept (ETN) compared with other types of TNF inhibitors, combination MTX may not be necessary and evidence has shown its effectiveness in patients with PsA does not offer a significant advantage over monotherapy (6-8).

The PROVE study was designed to determine the long-term adherence to the TNF inhibitor, etanercept (ETN), in patients with PsA (9). Patients prescribed ETN (with or without concomitant MTX) were followed at regular intervals for 66 months. Although PROVE showed high proportions of patients in remission with ETN over the course of the study, it is unclear if patients achieving remission quickly can maintain this state for a longer period. In addition, published data on the long-term adherence to ETN monotherapy is limited.

The objective of this post hoc analysis was to discover if patients who achieved remission within the first 6 months of treatment remained in remission for the duration of the study. Additionally, we aimed to identify the patients who were receiving ETN monotherapy at Month 6 and remained on this regimen until Month 66.

Methods

Patients and study design

The PROVE study was a long-term prospective observational study performed in Belgium over a 66-month period.

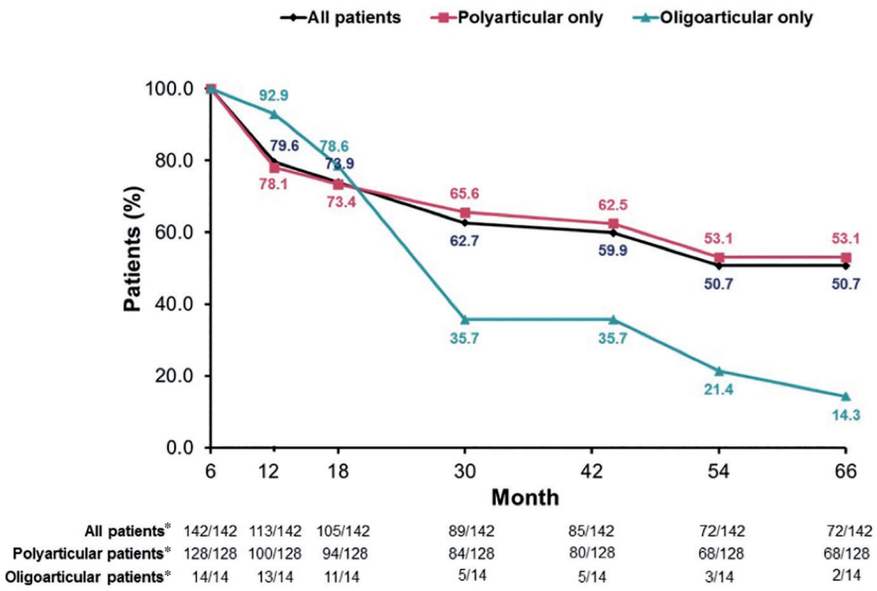

Fig. 1. Patients with PsA maintaining remission with ETN treatment over 66 months.
* 142 patients in remission at 6 months

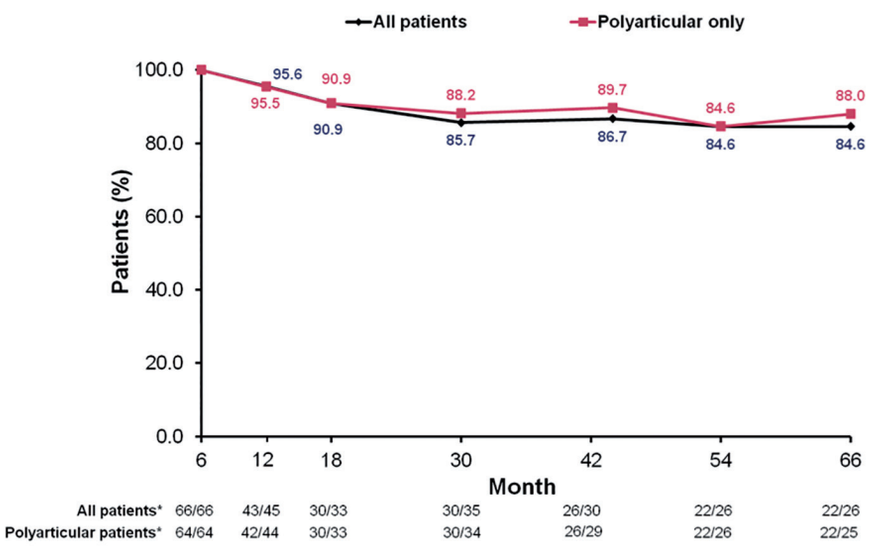

Fig. 2. Patients with PsA maintaining ETN monotherapy over 66 months.
* 66 patients on monotherapy at 6 months

The patient population and study design are described in more detail elsewhere (9). Briefly, patients were required to be ≥18 years old, and were either already receiving ETN treatment or had recently been prescribed it (with or without concomitant MTX therapy), and fulfilled Belgian reimbursement criteria for either polyarticular- or oligoarticular-type PsA. All patients provided written informed consent. Patients were required to attend eight visits: at baseline (occurred within 4 weeks of starting ETN treatment), and at Months 6, 12, 18, 30, 42, 54 and 66. Patients missing a visit were not excluded from attending future visits.

Assessments

Patient adherence was monitored over 66 months. Patients were withdrawn from the study if any of the following occurred: lack of patient compliance with the protocol; withdrawal of consent; investigators decision; or sponsor decision. Remission status (defined as zero joints with synovitis) was determined at each visit. Patients who achieved remission by Month 6 were monitored for maintenance of remission at each subsequent visit. Similarly, numbers of patients on ETN monotherapy at Month 6 were identified and the proportions of patients who maintained monotherapy at each visit were calculated.

Statistical analysis

The statistical software used was IBM SPSS Statistics (v. 21.0). A number of baseline variables were analysed for prediction of remission at last observation carried forward (LOCF) using a multivariate logistic regression. These included age, gender, disease duration, number of joints affected at baseline and disease type (polyarticular or oligoarticular). The same baseline variables were also used to predict monotherapy status at LOCF.

Results

Patient population

A total of 303 patients were enrolled in the study and the mean study time was 4.0 (SD, 1.9) years. Most of the patients had polyarticular PsA (87.1%) and the mean (SD) disease duration was 7.5 (7.4) years. The study was completed by 156 (51.5%) patients. Overall, 145 patients withdrew and two patients were eliminated due to the absence of follow-up information after the baseline visit. Causes of withdrawal varied over time and have been reported in detail previously (9). The most common reasons for withdrawal overall were non-response (35.9%), patient lost to follow-up (20.7%), reasons unrelated to ETN (20.0%), and non-serious AE (13.1%). Baseline demographics, disease characteristics, adherence rates, and safety data are reported elsewhere (9). Concomitant treatment with MTX was received by 173 patients (57.1%) and oral corticosteroids were received by 79 patients (26.1%) for some or all of the study duration.

Maintenance of remission

By Month 6, 142 patients had achieved remission (Fig. 1). A proportion of these patients relapsed by Month 12 and remission rates based on defining withdrawals as non-responders

were 113/142 (79.6%) at Month 12 and 72/142 (50.1%) at Month 66 (although discontinuation was not necessarily due to lack of drug efficacy).Of patients remaining in the study 113/135 (83.7%) were still in remission at Month 12, and 72/83 (86.7%) at Month 66. The proportions of patients in the polyarticular group and maintaining remission followed a similar pattern to the overall population. Patients with oligoarticular-type PsA did not maintain remission as well as the others: the proportions dropped to 62.5% by Month 30 and 66.7% at Month 66.

Baseline predictors of remission

A total of 101 patients achieved remission at LOCF. Gender was predictive of remission at LOCF (p=0.044), and the probability of remission was lower in males than females (odds ratio [OR] 0.60; 95% confidence interval [CI] 0.37, 0.99).

Maintenance of ETN monotherapy

At baseline of the PROVE study, the majority of patients were receiving ETN + MTX. After 6 months, 66 patients were receiving ETN monotherapy (Fig. 2). Overall and for the polyarticular group, the proportion of patients receiving ETN monotherapy remained relatively constant over the 66 months. However, only 26 of the original 66 patients were still continuing the study. Two patients with oligoarticular PsA were receiving ETN monotherapy but both of these patients switched to combination therapy during the course of the study.

Baseline predictors of ETN monotherapy status

A total of 161 patients were receiving ETN and a concomitant therapy at LOCF and 106 patients were receiving ETN monotherapy at LOCF. Gender (p=0.002) and disease type (polyarticular- or oligoarticular-type PsA; p=0.018) were significantly predictive of monotherapy status at LOCF. The probability of monotherapy was higher in male patients (OR=2.26; 95% CI 1.33, 3.82) and in patients with polyarticular PsA (OR=3.17; 95% CI 1.22, 8.24).

Discussion

When choosing a treatment for a chronic disease such as PsA, long-term adherence is an important aspect, as is the ability to achieve remission quickly and without relapsing. In the PROVE study, the level of adherence was high with 51.5% of patients remaining for the study duration and the mean study time was 4.0 (SD, 1.9) years. Remission here was simply defined by absence of tender and swollen joints. We have shown in Belgian clinical practice that the majority (72/83; 86.7%) of patients who achieved remission after just 6 months were able to sustain it in the long-term. As most of the study patients had polyarticular-type PsA, it was not surprising that there were no great differences in the levels of remission between these patients and the overall population. The numbers of patients with oligoarticular PsA in remission reduced substantially over the course of the study, however, the sample size for this subpopulation was too low to draw any firm conclusions from this. The association of female gender with remission was unexpected and in contrast to previous studies in which patients achieving remission were more likely to be male (16, 19).

Anti-drug antibodies against the monoclonal antibody form of biologics, such as infliximab and adalimumab, can significantly reduce their effectiveness over time (10, 11). Using MTX in combination with a TNF inhibitor may decrease immunogenicity and thereby maintain efficacy (5, 10). However, ETN is thought to be less immunogenic than the monoclonal antibody forms of TNF inhibitors, so concomitant MTX may not be needed (10, 12, 13). Although most of the PROVE patients were receiving combination ETN plus MTX, the majority of those who were receiving monotherapy at the start of the study remained on it for the duration.

This study had some limitations. It was designed to measure long-term adherence to ETN and not necessarily to determine maintenance of remission or monotherapy. We used zero joints with synovitis as a surrogate measure of clinical remission but remission in PsA has not yet been clearly defined in the literature, although a variety of potential definitions have been published which used multiple measures, including laboratory markers (14-16).

In conclusion, and consistent with other recent studies (17-18), data confirm that it is possible for patients with PsA to achieve remission quickly, effectively, and maintain it in the long-term. In addition, the majority of patients receiving ETN monotherapy stay on it and do not switch to combination therapy.

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References

1. GLADMAN DD, ANTONI C, MEASE P *et al*.: Psoriatic arthritis: epidemiology, clinical features, course, and outcome. *Ann Rheum Dis* 2005; 64 (Suppl. 2): ii14-7.
2. HUSTED JA, GLADMAN DD, FAREWELL VT *et al*.: Health-related quality of life of patients with psoriatic arthritis: a comparison with patients with rheumatoid arthritis. *Arthritis Rheum* 2001; 45: 151-8.
3. SMOLEN JS, BRAUN J, DOUGADOS M *et al*.: Treating spondyloarthritis, including ankylosing spondylitis and psoriatic arthritis, to target: recommendations of an international task force. *Ann Rheum Dis* 2013; 73: 6-16.
4. RITCHLIN CT, KAVANAUGH A, GLADMAN DD *et al*.: Treatment recommendations for psoriatic arthritis. *Ann Rheum Dis* 2009; 68: 1387-94.
5. JANI M, BARTON A, WARREN RB *et al*.: The role of DMARDs in reducing the immunogenicity of TNF inhibitors in chronic inflammatory diseases. *Rheumatology* (Oxford) 2014; 53: 213-22.
6. DALY M, ALIKHAN A, ARMSTRONG AW: Combination systemic therapies in psoriatic arthritis. *J Dermatolog Treat* 2011; 22: 276-84.
7. FAGERLI KM, LIE E, VAN DER HEIJDE D *et al*.: The role of methotrexate co-medication in TNF-inhibitor treatment in patients with psoriatic arthritis: results from 440 patients included in the NOR-DMARD study. *Ann Rheum Dis* 2014; 73: 132-7.
8. KRISTENSEN LE, GULFE A, SAXNE T *et al*.: Efficacy and tolerability of anti-tumour necrosis factor therapy in psoriatic arthritis patients: results from the South Swedish Arthritis Treatment Group register. *Ann Rheum Dis* 2008; 67: 364-9.
9. DE VLAM K, BOONE C: Treatment adherence, efficacy and safety of etanercept in patients with active psoriatic arthritis and peripheral involvement in Belgium for 66 months

(PROVE study). *Clin Exp Rheumatol* 2015; 33: 624-31.
10. ZISAPEL M, ZISMAN D, MADAR-BALAKIRSKI N *et al*.: Prevalence of TNF-alpha blocker immunogenicity in psoriatic arthritis. *J Rheumatol* 2015; 42: 73-8.
11. WOLBINK GJ, AARDEN LA, DIJKMANS BA: Dealing with immunogenicity of biologicals: assessment and clinical relevance. *Curr Opin Rheumatol* 2009; 21: 211-5.
12. ANDERSON PJ: Tumor necrosis factor inhibitors: clinical implications of their different immunogenicity profiles. *Semin Arthritis Rheum* 2005; 34: 19-22.
13. DORE RK, MATHEWS S, SCHECHTMAN J *et al*.: The immunogenicity, safety, and efficacy of etanercept liquid administered once weekly in patients with rheumatoid arthritis. *Clin Exp Rheumatol* 2007; 25: 40-6.
14. SABER TP, FEARON U, VEALE DJ: Is remission a more realistic goal in psoriatic arthritis? *Ther Adv Musculoskelet Dis* 2011; 3: 3-7.
15. CAPERON A, HELLIWELL PS: Remission in psoriatic arthritis. *J Rheumatol* 2012; 89 (Suppl.): 19-21.
16. GLADMAN DD, HING EN, SCHENTAG CT *et al*.: Remission in psoriatic arthritis. *J Rheumatol* 2001; 28: 1045-8.
17. LÓPEZ-GONZÁLEZ R, LEÓN L, LOZA E *et al*.: Adherence to biologic therapies and associated factors in rheumatoid arthritis, spondyloarthritis and psoriatic arthritis: a systematic literature review. *Clin Exp Rheumatol* 2015; 33: 559-69.
18. KIRKHAM B, DE VLAM K, LI W *et al*.: Early treatment of psoriatic arthritis is associated with improved patient-reported outcomes: findings from the etanercept PRESTA trial. *Clin Exp Rheumatol* 2015; 33: 11-9.
19. SABER TP, NG CT, RENARD G *et al*.: Remission in psoriatic arthritis: is it possible how it can be predicted? *Arthriris Res Ther* 2010; 12: R94.