Joint Bone Spine 82 (2015) 31–37

Available online at ScienceDirect www.sciencedirect.com

Elsevier Masson France EM|consulte www.em-consulte.com/en

Original article

Treatment response, drug survival and safety of anti-tumour necrosis factor α therapy in 193 patients with psoriatic arthritis: A twelve-year "real life" experience

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ARTICLE INFO

Article history:
Accepted 5 August 2014
Available online 11 October 2014

Keywords:
Psoriatic arthritis
Anti-TNFα
Drug survival
Switching
Methotrexate
Safety

ABSTRACT

Objective: To evaluate the performance of anti-TNFα therapy in psoriatic arthritis (PsA) in a routine care setting.
Methods: Inclusion criteria were patients with PsA who initiated anti-TNFα therapy between April 2001 and April 2013 with a follow-up of at least 6 months. For peripheral forms, treatment was considered to be effective for patients with a favourable expert opinion or > 30% clinical improvement of swollen and tender joint counts. For axial forms, efficacy criteria were: improvement of BASDAI by at least 2 points on a scale from 0 to 10 or 50% improvement (BASDAI 50) or expert opinion. Drug survival of first anti-TNFα therapy was also investigated.
Results: The study included 193 patients (107/86 M/F, mean age: 46.8 years, mean disease duration: 6.7 years, 171/22 peripheral/axial forms). Only 48 (25%) patients received concomitant DMARD therapy (65% were treated with methotrexate). The majority of patients started with first-line etanercept ($n = 102$), followed by adalimumab ($n = 46$), infliximab ($n = 44$) and golimumab ($n = 1$). At 3 months, 90% of patients had obtained an adequate response, 7% had discontinued due to lack of efficacy and 3% due to adverse events. Median drug survival was 2 years. One-year and 2-year drug survival rates were 77% and 67%, respectively. Seventy-nine (41%) patients switched to a second anti-TNFα and 29 to a third anti-TNFα; 82% of switchers responded to second-line therapy and 83% responded to third-line therapy.
Conclusion: High drug survival and high response rates were observed in these patients with PsA receiving their first anti-TNFα therapy in routine clinical practice.

1. Introduction

Psoriatic arthritis (PsA) is a form of spondyloarthritis. The therapeutic approach is essentially multidisciplinary and must take rheumatological as well as dermatological aspects into account [1–3]. Non-steroidal anti-inflammatory drugs (NSAIDs) and corticosteroids (systemic or intra-articular) have a place in the treatment of PsA together with cs-DMARDs (methotrexate, leflunomide, sulfasalazine) for the treatment of peripheral forms of the disease [1–3]. Following failure of cs-DMARDs or in predominantly axial forms, anti-TNFα therapy constitutes the reference biotherapy for the treatment of PsA [1–3]. The clinical and structural efficacy of anti-TNFα therapy was demonstrated during therapeutic trials and five anti-TNFα drugs are currently marketed in France for the treatment of PsA: etanercept (soluble receptor) [4–6], infliximab (chimeric monoclonal antibody) [7–10], adalimumab (humanised monoclonal antibody) [11], golimumab (humanised monoclonal antibody) [12,13] and certolizumab (pegylated monoclonal antibody) [14].

Clinical experience acquired from patient registries or so-called "real life" studies provides valuable information to assess routine management of PsA by anti-TNFα and can be used to validate the results obtained during therapeutic trials in populations of older patients with multiple comorbidities. Several national registries are available: DANBIO for Denmark [15,16], NOR-DMARD for Norway [17,18], BSR-BR for England [19], and SSATG for Sweden [20].

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http://dx.doi.org/10.1016/j.jbspin.2014.08.001
1297-319X/

However, the available data remain fairly limited, based on relatively short patient follow-up with sometimes contradictory results and conclusions, particularly concerning the value of switching anti-TNFα [16,17] and the relevance of concomitant treatment with methotrexate and an anti-TNFα at the time of initiation especially to achieve better drug survival [18,20].

The objective of this study was to evaluate the "real life" use of anti-TNFα therapy for the management of PsA in a large patient cohort with a maximum duration of follow-up of 10 years, with particular emphasis on efficacy, drug survival, safety and predictive factors of discontinuation of first-line anti-TNFα therapy.

2. Methods

2.1. Patients

This single centre, retrospective, observational study was conducted from April 2001 to April 2013. The charts of all patients with PsA treated with at least one anti-TNFα drug for more than 6 months were reviewed. Patient charts were retrieved from the health informatics department. Moll and Wright and/or CASPAR criteria were used to establish the diagnosis of PsA [21,22]. In doubtful cases, the final diagnosis was validated by the use of the new ASAS criteria for axial and peripheral spondyloarthritis [23,24]. The patients' demographic and clinical characteristics were collected according to a standardized procedure (age, gender, weight, smoking, excessive alcohol consumption, i.e. ≥ 2 units per day for women and ≥ 3 units for men, diabetes). A history of cardiovascular disease was investigated (composite criterion combining peripheral artery disease, coronary heart disease or stroke). Predominantly axial or peripheral forms were distinguished. The presence of psoriasis of the skin and/or nails was also investigated. The tender joint count (TJC) and swollen joint count (SJC), BASDAI, erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) at the time of initiation of first-line anti-TNFα therapy were recorded.

2.2. Treatments

The number and type of cs-DMARDs prescribed prior to initiation of first-line anti-TNFα therapy were recorded: methotrexate, leflunomide, sulfasalazine and other (ciclosporin, gold salts, tiopronin, hydroxychloroquine or azathioprine). Long-term systemic corticosteroid therapy (oral, for more than 3 months) prior to or at the time of initiation of first-line anti-TNFα therapy was also investigated. The anti-TNFα drugs used were etanercept (ETA, 25 mg twice weekly or 50 mg once weekly, available in France since 2003), infliximab (IFX, 3 to 5 mg/kg every 6 to 8 weeks, available since 2004), adalimumab (ADA, 40 mg every 14 days, available since 2005), and golimumab (GOL, 50 mg per month, available since 2011). These drugs are indicated in peripheral forms of PsA after failure of at least one cs-DMARD. The Summaries of Product Characteristics (SPC) of these biotherapies do not recommend systematic co-prescription of methotrexate. The *Société Française de Rhumatologie* (SFR) guidelines were used to validate initiation of anti-TNFα therapy [25]. The possible off-label prescription of other biotherapies for the treatment of PsA (abatacept, rituximab, ustekinumab or tocilizumab) was also studied.

2.3. Evaluation of efficacy and drug survival

Due to the retrospective nature of this study (inevitably comprising missing data) and the polymorphic features of PsA (difficulties of evaluation and diverse methods of evaluation of response to treatment), we expected that it would be difficult to achieve response criteria, such as ACR20/50/70 response, EULAR response, DAS28 or PsARC response (Psoriasis Arthritis Response Criteria) after 3 months of treatment [26]. We therefore pragmatically evaluated responding patients at 3 months according to ASAS [27] and SFR [25] guidelines: favourable expert opinion and/or > 30% improvement of TJC and SJC for predominantly peripheral forms and favourable expert opinion and/or BASDAI 50 (50% improvement of BASDAI) and/or at least 2-point improvement of the BASDAI on a scale from 0 to 10 for predominantly axial forms. The reasons for discontinuation of treatment at 3 months were also recorded: (I) development of adverse effects, (II) primary inefficacy, or (III) other (patient's personal decision, pregnancy, lost to follow-up).

We then evaluated the outcome at the end of the study of patients who continued treatment for more than 3 months according to continuation of treatment or discontinuation of treatment for (I) adverse effects, (II) escape (progressive loss of efficacy after a satisfactory initial response), or (III) other (patient's personal decision, pregnancy, lost to follow-up). The decision to discontinue first-line anti-TNFα therapy was based on the prescribing physician's opinion. Possible switching to another anti-TNFα drug was also studied. Evaluation of the response to treatment 3 months after switching and the subsequent outcome of patients was based on the same criteria as those defined above, together with recording of the reasons for discontinuation. The median duration of treatment and the one-year and two-year drug survival rates were analysed for each treatment sequence.

Drug survival rated for first-line anti-TNFα therapy was compared between the various anti-TNFα agents (ETA, IFX and ADA) and the value of initial prescription of a cs-DMARD was assessed. Finally, drug survival curves were compared between first-, second-, and third-line anti-TNFα.

2.4. Analysis of predictive factors of discontinuation of first-line anti-TNFα therapy

Predictive factors of discontinuation of first-line anti-TNFα therapy were also analysed, based on the following parameters: gender, age, weight, comorbidities (smoking, alcohol, diabetes, history of cardiovascular disease), TJC, SJC, history of the disease, co-prescription of a cs-DMARD, corticosteroids, ESR and CRP.

2.5. Statistical analysis

SAS (Statistical Analysis System) version 9.2 software was used for statistical analyses. Descriptive data analysis was initially performed. Qualitative data were expressed as frequency and percentage. Quantitative data were expressed as mean and standard deviation or median and range. Univariate analyses were then performed. A chi^2 test or Fisher's exact test was used to compare patients with continuation or discontinuation of first-line anti-TNFα therapy at the end of the study according to qualitative items. The normal distribution of quantitative data was first verified by a Shapiro–Wilk test to determine whether parametric or non-parametric tests should be used. A parametric Student *t*-test was used for comparison of quantitative data and a non-parametric Mann–Whitney *U* test (Rank test) was used to compare distributions. Multivariate logistic regression analysis was then performed. A stepwise model was used to identify items corresponding to predictive factors of discontinuation of first-line anti-TNFα therapy. Drug survival was analysed by means of Kaplan–Meier curves and Log-Rank test. Finally, for all results, a *P* value less than or equal to 5% was considered to be statistically significant.