Persistence of low disease activity after tumour necrosis factor inhibitor (TNFi) discontinuation in patients with psoriatic arthritis

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ABSTRACT

Objective: To determine the duration of clinical benefit among patients with psoriatic arthritis (PsA) discontinuing tumour necrosis factor inhibitor (TNFi) therapy while in low disease activity (LDA), and to identify patient characteristics associated with prolonged clinical benefit.

Methods: We performed an observational cohort study assessing patients with PsA from the Consortium of Rheumatology Researchers of North America (CORRONA) registry who had discontinued TNFi after achieving LDA, defined as clinical disease activity index (CDAI) score ≤10 and physician’s global assessment (PGA) of skin psoriasis ≤20/100. Kaplan–Meier method was used to estimate the duration of clinical benefit.

Results: Of the 5945 patients with PsA in CORRONA, 302 patients had discontinued TNFi (n=325) while in LDA and had follow-up data available. At time of discontinuation, mean PsA duration was 9.8 years, mean CDAI was 3.9, and mean duration of TNFi use was 1.5 years; 52.6% of patients had discontinued their first TNFi. Median time to loss of benefit was 29.2 months. 179 (55.1%) patients had persistent benefit at their previous clinic visit. An increased risk of losing clinical benefit was seen among patients with higher disease activity at discontinuation (CDAI≥3.2 vs <3.2; HR 1.43 (p=0.03)) and among smokers (HR 1.74 (p=0.027)).

Conclusions: Patients with PsA who achieve LDA may maintain clinical benefit after discontinuation of TNFi therapy.

INTRODUCTION

Psoriatic arthritis (PsA) is a chronic inflammatory disease with heterogeneous clinical manifestations. Tumour necrosis factor inhibitors (TNFi) effectively treat all domains of disease activity in PsA.1 Aggressive treatment strategies, particularly involving the use of TNFi, have revolutionised the treatment of PsA resulting in low disease activity (LDA) and remission becoming viable treatment goals.2 3 Indeed, intensive treatment strategies in early disease have been shown to result in better clinical outcomes in PsA.4

Owing to factors such as economic burden, concern for drug toxicity, and patient preferences, there has been increasing interest in the possibility that TNFi treatment may be reduced or discontinued in patients achieving remission or LDA, with maintenance of clinical benefits. There is some evidence for discontinuation of biological therapies in rheumatoid arthritis (RA) with persistent clinical benefit.5 6 Whether TNFi can be withdrawn in PsA with sustained clinical benefit remains unknown.

The objectives of this study were to determine the duration of sustained clinical benefit among patients with PsA who had discontinued TNFi while in LDA, and also to identify patient characteristics and disease-related factors that may be associated with prolonged clinical benefit after TNFi discontinuation.
Statistical analyses

Descriptive statistics are presented as means±SD for continuous variables, and frequency and percentages for categorical variables. p Values <0.05 were considered statistically significant. Kaplan-Meier method was used to estimate the median time to loss of clinical benefit. Both univariable and multivariable Cox proportional hazard analyses were used to evaluate characteristics associated with duration of clinical benefit. Factors that were significant at the 20% level (p value <0.20) in the univariable analysis were further evaluated in the multivariable model.

RESULTS

Of the 5945 patients with PsA in the CORRONA database, there were 325 discontinuations of TNFi therapy while in LDA in 302 patients who had follow-up data available. The mean age was 52.6±13.1 years, 51.9% were women, and mean body mass index (BMI) was 30.1±6.5 (table 1). At discontinuation, the mean duration of PsA was 9.8±8.1 years, mean CDAI was 3.9±2.8, mean modified disease activity score (mDAS) was 2.4±0.6, and PGA of skin psoriasis was 6.7±6.1%.

Among the patients assessed, 52.6% of patients had discontinued their first TNFi and 31.1% had discontinued their second TNFi. The mean duration of TNFi use prior to discontinuation was 1.5±1.6 years. Concomitant medications at the time of TNFi discontinuation were recorded: 53.5% of patients were treated with TNFi monotherapy, 42.2% were on background methotrexate (MTX); and 5.2% took concomitant low-dose prednisone.

After withdrawal of TNFi treatment, 146 (44.9%) patients lost clinical benefit due to: increased CDAI (31.5%); worsening skin disease (15.8%); non-biological DMARD initiation or dose escalation (32.2%); TNFi initiation or restart (6.8%); or prednisone initiation or dose escalation (9.6%) (table 2). Kaplan–Meier survival estimate of median time to loss of clinical benefit was 29.2 months (figure 1). At last clinic visit, 179 (55.1%) patients had persistent clinical benefit off TNFi therapy.

Patients with higher disease activity at the time of TNFi discontinuation had increased risk of losing clinical benefit HR: CDAI ≥3.2 versus <3.2, HR 1.43 (p=0.032); moderate versus low mDAS, HR 1.65 (p=0.017); patient global assessment >5 versus ≤5, HR 1.7 (p=0.007) (table 3). Current smokers had

Table 1 Population characteristics at time of TNFi discontinuation (N=325)

| Characteristic            | Mean±SD       |
|---------------------------|---------------|
| Age (years)               | 52.6±13.1     |
| Female                    | 168 (51.9%)   |
| BMI (kg/m²)               |               |
| Normal                    | 61 (19.1%)    |
| Overweight                | 113 (34.8%)   |
| Obese                     | 150 (46.1%)   |
| Duration of PsA (years)   | 9.8±8.1       |
| Duration of TNFi (years)  | 1.5±1.6       |
| Tender joint count (mean±SD) | 0.66±1.13   |
| Swollen joint count (mean±SD) | 0.38±0.83   |
| Patient global assessment (mean±SD) | 20.2±19.0 |
| Physician global assessment (mean±SD) | 8.6±8.6     |
| CDAI (mean±SD)            | 3.9±2.8       |
| mHAQ (mean±SD)            | 0.20±0.32     |
| mDAS (mean±SD)            | 2.4±0.6       |
| TNFi use                  |               |
| 1st TNFi                  | 171 (52.6%)   |
| 2nd TNFi                  | 101 (31.3%)   |
| 3rd TNFi                  | 46 (14.2%)    |
| 4th TNFi                  | 7 (2.1%)      |
| TNFi monotherapy          | 174 (53.5%)   |
| TNFi+MTX                  | 137 (42.4%)   |
| TNFi+prednisone           | 24 (7.4%)     |

BMI, body mass index; CDAI, clinical disease activity index; mDAS, modified disease activity score; mHAQ, modified health assessment questionnaire; PsA, psoriatic arthritis; TNFi, tumour necrosis factor inhibitor.
significantly higher risk for loss of clinical benefit (smokers versus non-smokers), HR 1.78 (p=0.027) in univariable and multivariable analysis. In the multivariable model, current smoking was associated with higher risk of losing clinical benefit HR 1.76, 95% CI (1.13 to 2.27) while CDAI >3.2 versus <3.2 also appeared to convey increased risk for loss of clinical benefit HR 1.42 (0.99 to 2.03). Age and gender did not alter this risk in the multivariable model. The number of prior TNFi used and overweight or obese status did not significantly affect loss of clinical benefit in our cohort.

**DISCUSSION**

Advances in highly effective therapies have led to improved clinical outcomes in PsA, making LDA and remission achievable goals. Since TNFi are associated with both a high financial burden and an increased risk of potentially life-threatening adverse events, the need for maintenance therapy with these biological agents has been challenged. As a result, there is increasing interest into whether TNFi could be reduced or discontinued while maintaining clinical benefit in patients with PsA who have achieved good clinical outcomes on these medications.

There is a paucity of data looking at tapering strategies—through either dose reduction or drug discontinuation—for TNFi in PsA, and the results are not straightforward. In a single-centre, prospective study of the 76 patients with PsA treated with adalimumab,
In summary, patients with PsA who achieve LDA on treatment may maintain persistent clinical benefit after the discontinuation of TNFi. Patients with higher disease activity at the time of discontinuation and smokers may have less success at stopping TNFi therapy. Whether biological therapy can be reduced or discontinued in the long term requires further study in controlled withdrawal trials.

**Funding** This study was funded by Corrona, LLC.

**Competing interests** None declared.

**Ethics approval** IRB.

**Provenance and peer review** Not commissioned; externally peer reviewed.

**Data sharing statement** No additional data are available.

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