

SHORT COMMUNICATION

Down-titration of Adalimumab and Etanercept in Psoriatic Patients: A Multicentre Observational Study

Stefano Piaserico¹, Paolo Gisondi², Clara De Simone³, Elena Marinello¹, Andrea Conti⁴, Paolo Amerio⁵ and Andrea Peserico¹¹Dermatology Unit, Department of Medicine, University of Padua, Via Cesare Battisti 206, IT-35128 Padua, ²Section of Dermatology and Venereology, Department of Medicine, University of Verona, Verona, ³Dermatology Unit, Catholic University of the Sacred Heart, Rome, ⁴Dermatology Unit, Department of Head and Neck Surgery, University of Modena, Modena, and ⁵Dermatologic Unit, Department of Oncology and Neuroscience, University G. D'Annunzio, Chieti, Italy. E-mail: stefano.piaserico@unipd.it

Accepted Aug 11, 2015; Epub ahead of print Aug 13, 2015

Several studies have demonstrated that tumour necrosis factor (TNF)- α inhibitors are associated with a rapid, sustained clinical response and an improvement in health-related quality of life (QOL) in patients with psoriasis. Etanercept or adalimumab achieve a 75% reduction in the Psoriasis Area and Severity Index score (PASI 75) in, respectively, 49% and 70% of cases after 12 weeks of treatment (1, 2).

A possible dose-dependent higher risk of malignancies and rare severe adverse events has been described with TNF- α inhibitors (3, 4). Optimal dosing is therefore important both to reduce the risks of adverse effects and to increase cost-effectiveness.

Mostly uncontrolled emerging data indicate that dose reduction of TNF- α inhibitors can be achieved in a relevant proportion of patients with rheumatoid arthritis without losing clinical efficacy (5–7). No data about down de-escalation of these drugs are as yet available with regard to psoriatic patients.

The aim of the present study is to assess the proportion of patients with psoriasis treated with etanercept or adalimumab in whom dose reduction is reached without loss of clinical efficacy.

PATIENTS AND METHODS

Patients with severe psoriasis being treated at 5 Italian referral centres (Chieti, Modena, Padova, Roma, Verona) were included in this retrospective cohort study. Other inclusion criteria were: remission of psoriasis (PASI=0) and stable continuous treatment with etanercept 50 mg weekly or adalimumab 40 mg every other week for at least 12 months. No other inclusion or exclusion criteria were used.

At baseline, the dose interval was increased from 7 to 10 days in the patients being treated with etanercept and from 14 to 21 days for those being treated with adalimumab. Disease flare-up (relapse) was defined as a $\geq 50\%$ loss of PASI improvement with respect to the score at baseline. In the event of a flare, dosing intervals were returned to the original, conventional ones. Each patient was assessed for a minimum follow-up time of 12 months. The study's primary endpoint was defined as the proportion of patients being studied showing a flare of disease activity.

Statistical analysis

Comparisons between the 2 groups were examined using the unpaired *t*-test or non-parametric Mann–Whitney (for skewed data).

The proportion of patients who relapsed after dose reduction of therapy was analysed using the Kaplan–Meier method. Determinants of drug survival were analysed using univariate Cox-regression analysis. Those that differed between the 2 groups with a *p*-value lower than 0.05 were entered into a multivariate Cox-regression model.

The local ethics committee was consulted, but approval was not required because PASI-guided dose adaptation in the centres participating in the study was performed as part of usual care.

RESULTS

A total of 85 patients (55 (65%) males, 30 (35%) females; mean age 51 ± 13.6 years) were included in the study. Patients' mean psoriasis duration was 21.7 ± 10.8 years (range 2–63.9 years), mean baseline C-reactive protein (CRP) was 1 ± 2.6 mg/l, mean baseline body mass index (BMI) was 26.4 ± 3.5 kg/m². Twenty-eight of the patients (33%) smoked or had a history of smoking. No statistical differences were found in these variables between the patients treated with etanercept ($n = 54$) and those receiving adalimumab ($n = 31$).

As shown in Fig. 1, the cumulative relapse risk in the etanercept and adalimumab-treated patients was 14% and 0%, 31% and 12%, and 39% and 20% after, respectively, 3, 6 and 12 months ($p = 0.03$ with log-rank test). The mean time to relapse was 39.3 months (CI 95% 33.7–44.8) and 48 months (CI 95% 43–52.7), respectively, in the etanercept and adalimumab groups.

All the patients who experienced a relapse were treated with the original, conventional drug dosing intervals and showed a rapid response.

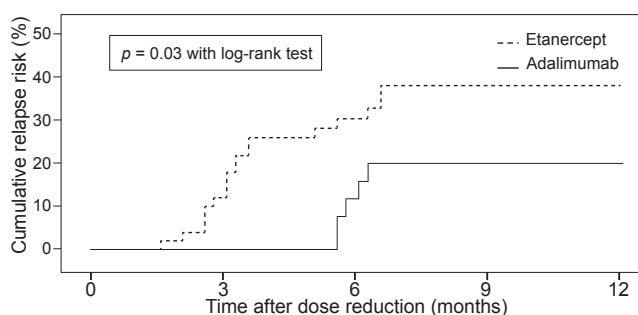


Fig. 1. Cumulative relapse risk in patients treated with low-dose etanercept ($n = 54$) and adalimumab ($n = 31$). Survival difference between the 2 groups is shown.

Predictive relapse factors

The variables linked to an increased risk of relapse in patients treated with etanercept were: age younger than 52 years (hazard rate (HR) 2.6, $p=0.04$), disease duration longer than 20 years (HR 3.7, $p=0.007$), PASI before TNF- α inhibitors treatment higher than 15 (HR 3.4, $p=0.01$) and baseline CRP higher than 1 mg/l (HR 3.7, $p=0.006$). No variables predicted an increased risk of relapse in the patients treated with adalimumab.

Cox-regression multivariate analysis using a forward stepwise model showed that PASI before TNF- α inhibitors treatment higher than 15 (HR 2.9, 95% CI 1.2–7.2; $p=0.018$), disease duration longer than 20 years (HR 2.8, 95% CI 1.2–6.6; $p=0.019$) and use of etanercept (HR 3.6, 95% CI 1.4–9.9M; $p=0.01$) were independently associated with relapse risk.

DISCUSSION

Our study showed that adalimumab and, to a lesser extent, etanercept, could be down-titrated using longer dosing intervals in the great majority of stable psoriatic patients without signs of disease relapse. This may be explained by the fact that patients' serum concentrations after dose reduction could be still above the minimal effective drug level.

It should also be remembered that amidst the patients who seemingly respond to TNF- α inhibitor treatment, some of these would, in any case, have experienced spontaneous improvement even without treatment (4).

Down-titration may, nevertheless, have some undesirable effects, such as an increase in disease activity. In our cohort, the cumulative relapse risk was higher for patients treated with etanercept compared with those treated with adalimumab, increasing from 14% and 0% to 39% and 20% after 3 and 12 months, respectively ($p=0.03$ with log-rank test).

In addition, since TNF- α inhibitor treatment seems to be associated with a reduced incidence of cardiovascular events in psoriasis patients (8), lowering TNF- α inhibitor dosage might abolish this effect.

Another possible down-side of TNF- α inhibitor down-titration could be anti-drug antibody formation (9).

Our study showed that patients with higher disease activity at the time therapy was commenced and/or longer disease duration had higher relapse risks when the interval between drug administrations was extended. As these patients have a more severe disease activity, they presumably need a more intensive treatment regimen as far as dose or interval is concerned.

Further studies are necessary to determine when monitoring of drug blood levels should be carried out to help optimize treatment outcome. Future research will help to determine what predictive values these levels have in terms of achieving successful dose reductions.

The limitations of this study include its retrospective, non-interventional nature. All patients studied were treated in a standard fashion according to the guidelines of the Italian Health Care Service and at the discretion of the physicians and patients.

In conclusion, our study indicates that conventional maintenance doses of adalimumab and, to a lesser extent, etanercept, can be lowered in the majority of stabilized psoriasis patients without compromising their disease control.

The authors declare no conflicts of interest.

REFERENCES

1. Papp KA, Tying S, Lahfa M, Prinz J, Griffiths CE, Nakanishi AM, et al. A global phase III randomized controlled trial of etanercept in psoriasis: safety, efficacy, and effect of dose reduction. *Br J Dermatol* 2005; 152: 1304–1312.
2. Menter A, Tying SK, Gordon K, Kimball AB, Leonardi CL, Langley RG, et al. Adalimumab therapy for moderate to severe psoriasis: a randomized, controlled phase III trial. *J Am Acad Dermatol* 2008; 58: 106–115.
3. Bongartz T, Sutton AJ, Sweeting MJ, Buchan I, Matteson EL, Montori V. Anti-TNF antibody therapy in rheumatoid arthritis and the risk of serious infections and malignancies: systematic review and meta-analysis of rare harmful effects in randomised controlled trials. *JAMA* 2006; 295: 2275–2285.
4. Leombruno JP, Einarson TR, Keystone EC. The safety of anti-tumour necrosis factor treatments in rheumatoid arthritis: meta and exposure-adjusted pooled analyses of serious adverse events. *Ann Rheum Dis* 2009; 68: 1136–1145.
5. den Broeder AA, van der Maas A, van den Bemt BJ. Dose de-escalation strategies and role of therapeutic drug monitoring of biologics in RA. *Rheumatology* 2010; 49: 1801–1803.
6. Smolen JS, Nash P, Durez P, Hall S, Ilivanova E, Irazoque-Palazuelos F, et al. Maintenance, reduction, or withdrawal of etanercept after treatment with etanercept and methotrexate in patients with moderate rheumatoid arthritis (PRESERVE): a randomised controlled trial. *Lancet* 2013; 381: 918–929.
7. Fautrel B, Pham T, Tubach F, Alfaite T, Morel J, Dernis E, et al. Tapering TNF-blockers in established rheumatoid arthritis patients in DAS28 remission: results of a step-down strategy randomized controlled trial. *ACR* 2012, 64(s12): L7.
8. Wu JJ, Poon KY, Channal JC, Shen AY. Association between tumor necrosis factor inhibitor therapy and myocardial infarction risk in patients with psoriasis. *Arch Dermatol* 2012; 148: 1244–1250.
9. De Simone C, Amerio P, Amoruso G, Bardazzi F, Campanati A, Conti A, et al. Immunogenicity of anti-TNF α therapy in psoriasis: a clinical issue? *Expert Opin Biol Ther* 2013; 13: 1673–1682.