

## Dose-creep of Infliximab During Psoriasis Treatment: An Observational Study

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Infliximab (Remicade<sup>®</sup>) is a chimeric monoclonal antibody that binds to the proinflammatory cytokine, tumour necrosis factor- $\alpha$  (TNF- $\alpha$ ), and neutralizes its biologic activity. Data generated from randomized controlled trials document the efficacy and safety of infliximab for short-term treatment (up to 1 year) (1, 2). The efficacy of infliximab also seems to be maintained for longer periods of time, as we documented in a 5-year observational study (3). Infliximab showed the highest patient retention rate among the three anti-TNF- $\alpha$  agents included in the analysis (the others being etanercept and adalimumab) and the most frequent cause of treatment termination was loss of clinical efficacy. This result contrasted with the review of the data from the clinical trials (4), in which drug survival was highest for etanercept, followed by adalimumab and infliximab.

One of the explanations of the significantly higher patient retention to infliximab in our data-set could be the flexibility in the adjustment of the dose and the intervals between drug infusions. Infliximab is the only TNF- $\alpha$  antagonist that is dosed by weight, and international expert opinion encourages optimization of the treatment by either decreasing the intervals between infusions (e.g. from every 8 weeks to every 6 weeks) or increasing the dose of drug administered (5). In this retrospective study, we were able to confirm the hypothesis that the mean dose of infliximab is often adjusted upwards during the course of therapy and many patients require the dosage to exceed the recommended 5 mg/kg every 8 weeks.

### PATIENTS AND METHODS

We performed a retrospective analysis on patients in our clinic, at Bispebjerg University Hospital, Copenhagen, with moderate to severe psoriasis who were treated with infliximab from June 2003 to November 2010. Six patients received more than one treatment course with infliximab, amounting to 92 treatment courses. The median age of the patients was 41.5 years (range 19–75 years), 51% were men, median weight was 87.4 kg (range 47–160 kg). The median duration of psoriasis was 16 years (range 3–57 years). Forty-two patients (49.4%) had psoriasis arthritis and 61 patients (71.8%) were anti-TNF- $\alpha$  naïve, 21 patients (24.7%) had received one anti-TNF- $\alpha$  agent and three patients (3.5%) had received two anti-TNF- $\alpha$  agents. Mean Psoriasis Area Severity Index (PASI) at baseline was 14.9 (SD 8.2). Concomitant or intervening systemic therapy with methotrexate was introduced or maintained in 47 patients (55.3%). The inclusion criteria were similar for the phase trials and for clinical practice (the rule of 10s (6)) according to the Danish national guidelines for biological treatment (<http://www.dds.nu>) (3). Data were retrieved from the medical records and from the Danish nationwide clinical database Dermbio (3).

Statistical analysis was carried out using Microsoft Excel, Graph Pad Prism version 5.00 for Mac (Graph PAD Software, San Diego, CA, USA) and SPSS 18 statistical package (SPSS 18 Inc., Chicago, IL, USA) for the Cox regression analysis.  $p$ -values  $<0.05$  were considered significant.

### RESULTS

Eighty-five patients were treated with infliximab for at least one consecutive period.

At the time of analysis 47 patients (55.3%) were still on infliximab after the mean of 17.3 months of treatment (SD 19.1, maximum duration 80.1 months). Of the 10 patients who received infliximab before the market authorization for psoriasis in 2005, four were still on the drug in November 2010. Among the patients who discontinued the therapy, 40% discontinued due to loss of efficacy (12% of patients after the dose had been increased), 40% due to adverse effects, and in 9% due to lack of compliance or the patient's wish. The adverse events were mainly immediate infusion reaction, serum sickness ( $n=1$ ), increased transaminases ( $n=1$ ) and a case of both pustulosis palmo-plantaris and alopecia areata (which resolved after discontinuation of infliximab). Three serious adverse events (SAE) occurred, none of them fatal. Two of the SAE occurred in female patients, a ruptured abdominal aortic-aneurysm, and severe vertigo that resolved spontaneously. The third case was a male patient with neurological symptoms, paraesthesia in the lower extremities that resolved on cessation of infliximab. Other adverse events were eight allergic/intolerance reactions for infliximab and 11 cases of mild infections, which did not require hospitalization.

Fig. 1A shows patient retention rates over time. As previously reported (3), the major negative predictors of drug survival were female sex (odds ratio (OR) 0.258, 95% confidence interval (CI) 0.099–0.0672,  $p<0.006$ ) and prior exposure to TNF- $\alpha$  (OR 0.072 (0.011–0.467),  $p=0.006$ ), but not other covariates such as the age, baseline PASI, presence of psoriasis arthritis or comorbidities, weight, or concomitant methotrexate.

In 24 treatment series (26.1% of the 87 treatment series with complete data for the analysis) the dosage was increased over the recommended initial dose of 5 mg/kg (loading infusions at week 0, 2, 6, maintenance infusions every 8 weeks) either by the change in dose-interval ( $n=28$ ) and/or change in the dose ( $n=9$ ). The probability of the dose/interval increase over time (Fig. 1B) was not influenced by any of the analysed

covariates (previous TNF- $\alpha$  treatments, baseline PASI, concomitant methotrexate, presence of co-morbidities or psoriasis arthritis, patient's weight, age and gender). With dose and interval adjustments taken into account, our patients were treated with the mean dose of infliximab of 4.82 mg/kg/month (Fig. 1C). There was only a weak relationship between the mean monthly dose of infliximab and patient weight, which only attained statistical significance in the case of patients who had not been exposed to other anti-TNF $\alpha$  agents before the treatment with infliximab (Fig. 1D).

## DISCUSSION

Biologic treatment provided a new paradigm in the treatment of psoriasis. Instead of rotational use of different drugs with different mode of action, the biologic agents are used continuously until the loss of efficacy or due to side-effects (5). Unfortunately, the currently available results from randomized clinical trials are relatively short-term (approximately 1–1.5 years) and do not provide the much-wanted clinical information on long-term efficacy and safety.

We have published registry data from the national Danish psoriasis database, Dermbio, documenting dif-

ferences between different anti-TNF- $\alpha$  agents in their long-term use for psoriasis (3). The major determinants of the ability of the drug to retain the patient in therapy were the patient's gender and the history of failure of another TNF blocker. This study revealed that infliximab was superior to etanercept and adalimumab in terms of patient retention. The reasons for this could be the possibility of a more flexible dosage and adjustment of treatment intervals than in the case of the subcutaneous anti-TNF- $\alpha$  agents. Since the information on the dosage of infliximab is not available from the national Dermbio database, we undertook this study on the real-life use of infliximab from our institution.

We confirmed that patient's gender and the previous use of anti-TNF- $\alpha$  agents were the only significant determinants of the chances of continuing treatment (patient retention ratio). In combination therapy with methotrexate the clearance of infliximab is reduced (7); however, in our study we did not reveal any influence of concomitant methotrexate on the probability of the dose/interval increase or on drug-survival. The general level of patient retention was somewhat lower than reported from Dermbio material (50% at 4 years). This is probably due to the fact that many of our patients were high-need patients with resistant psoriasis, and that in

the early days of infliximab, treatment was terminated prematurely due to the lack of experience with side-effects. The dose or frequency of infliximab administration was modified in a third of all patients, resulting in a larger than expected mean monthly dose. The recommended monthly dose is 2.9 mg/kg/month if the patient is treated with 5 mg/kg infusions every 8 weeks. In our cohort the dose was 65% higher and equalled 4.82 mg/kg. Thus, dose increase is often necessary to maintain the effect of infliximab. In a similar line, Chaudhari et al. (8) demonstrated a higher efficacy for the dosage of 10 mg/kg compared with 5 mg/kg. Another reason for the apparent overdosing may be the clinical practice where the total infusion dose is rounded up to utilize the whole content of the vial. From the data in Fig. 1B it seems that this dose adjustment takes place within the first year of treatment and remains stable thereafter.

The current data may have importance for the calculation of the cost of treatment with infliximab. If our cohort can be considered representative, one could estimate the mean consumption of the drug to be 360 mg/patient/month, with only a weak influence of patient's weight. This mean dose produces a 4-year patient retention rate of a minimum of 50%.

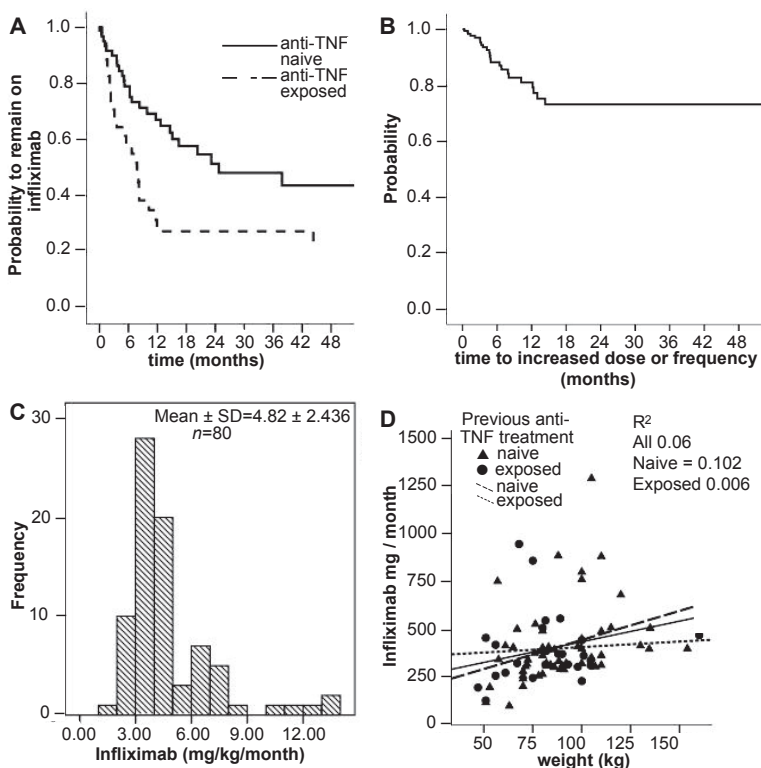


Fig. 1. Long-term treatment with infliximab in 85 patients (92 treatment series). (A) Drug survival rates separated according to the previous exposure to an anti-TNF- $\alpha$  agent. (B) Probability of remaining on the same (or lower) dose of infliximab during treatment series. (C) Distribution of mean infliximab doses across the treatment series. (D) Relationship between patient's weight and the mean dose of infliximab expressed in mg/month of treatment. The correlation is significant in case of the anti-TNF- $\alpha$  naïve patients ( $p=0.03$ , triangles, dashed line). The solid regression line is drawn for the whole data-set.

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