



**HAL**  
open science

## Trough infliximab concentration may predict long-term maintenance of infliximab in ankylosing spondylitis

D Chu Miow Lin, D. Mulleman, N. Azzopardi, G Griffoul-Espitalier, P Valat, P Paintaud, P. Goupille

### ► To cite this version:

D Chu Miow Lin, D. Mulleman, N. Azzopardi, G Griffoul-Espitalier, P Valat, et al.. Trough infliximab concentration may predict long-term maintenance of infliximab in ankylosing spondylitis. *Scandinavian Journal of Rheumatology*, 2010, 39 (1), pp.97 - 98. 10.3109/03009740903177745 . hal-01769938

**HAL Id: hal-01769938**

**<https://hal.science/hal-01769938v1>**

Submitted on 11 May 2022

**HAL** is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

# Trough infliximab concentration may predict long-term maintenance of infliximab in ankylosing spondylitis

D Chu Miow Lin<sup>1\*</sup>, D Mulleman<sup>1,2,3\*</sup>, N Azzopardi<sup>1,2</sup>, I Griffoul-Espitalier<sup>1</sup>, J-P Valat<sup>1</sup>, G Paintaud<sup>1,2</sup>, P Goupille<sup>1,2,3</sup>

<sup>1</sup>Tours University Hospital, Tours, <sup>2</sup>François Rabelais University of Tours, CNRS UMR 6239, Tours, and <sup>3</sup>Inserm CIC 202, Tours, France

Infliximab is approved for refractory ankylosing spondylitis (AS) but 39% of patients experience no response to treatment after 24 weeks (1). de Vries et al reported that the clinical response was related to infliximab concentration, so exposure to infliximab may account for the variability in response (2). However, more recent data have not confirmed that responsiveness is associated with infliximab concentration (3).

We analysed the relationship between trough infliximab concentration and long-term maintenance of infliximab treatment in patients with AS routinely treated in our centre. Patients at initiation of treatment were excluded from the study. On the day of the infusion (baseline), infliximab concentration was measured by enzyme-linked immunosorbent assay as described previously (4), as was positivity for antibodies towards infliximab (ATI). Disease activity was assessed at each infusion, for 52 weeks, by the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI). Infliximab treatment was categorized by comparing infusion dose and dosing interval with those recorded at the baseline infusion. We considered infliximab dosage stable if both the dose (in mg/kg) and the interval ( $\pm 4$  days) were equivalent between baseline and subsequent infusions. Dose modification and discontinuation of infliximab were based on disease activity and tolerance. Patients were divided into two groups on the basis of their staying with the same or lower dosage (group A = infliximab success) or switching to another biopharmaceutical or requiring an increase in dosage (group B = infliximab failure). Infliximab maintenance in group A at the last follow-up was compared between categories of infliximab concentration at baseline according to median infliximab concentration by Kaplan–Meier curves and a log-rank test.

We analysed data for 22 patients with AS; the demographic, clinical, and biological characteristics are presented in Table 1. Patients with an infliximab

concentration above the median at baseline showed a low, although not statistically significant, risk of treatment failure ( $p = 0.14$ ). Three patients were positive for ATI at baseline with no detectable infliximab concentration. During follow-up, one patient switched to etanercept 12 weeks after baseline measurement, one discontinued treatment 30 weeks after baseline measurement, and one remained in group A at 56 weeks after baseline measurement.

Patients with high concentrations of infliximab at baseline showed sustained maintenance of infliximab treatment, although the results were not statistically significant, possibly because of better control of disease activity (Figure 1). In an open-label study (5) and a randomized controlled trial (1), patients with inadequate response to infliximab were found to benefit from dosage escalation. Systematic treatment was also found to produce a better response than an ‘on-demand’ regimen (6). Our study was based on a single measurement of serum infliximab concentration at baseline. A repeated measurement of infliximab concentration would have allowed us to confirm the status of the patients in terms of their exposure to infliximab, and to analyse the impact of exposure on treatment maintenance more precisely.

Positivity for ATI was shown to influence response to infliximab. The study by de Vries et al found that

Table 1. Characteristics of patients at baseline.

|  |                  |
|--|------------------|
| Age (years)                                  | 46.5 (29.0–72.0) |
| Sex (F/M)                                    | 12/10            |
| Positivity for HLA-B27                       | 14 (63.6%)       |
| Duration of infliximab treatment (months)    | 30.2 (8.3–52.3)  |
| Dose of infliximab infusion (mg/kg)          | 5.0 (4.2–7.8)    |
| Time elapsed since previous infusion (weeks) | 6.4 (5.1–17.4)   |
| BASDAI                                       | 3.3 (0.4–8.0)    |
| Infliximab concentration (mg/L)              | 6.4 (0.0–20.7)   |

F, female; M, male; HLA-B27, human leucocyte antigen B27; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index. Clinical and biological markers were measured just before baseline infliximab infusion. Continuous variables are reported as median (range).

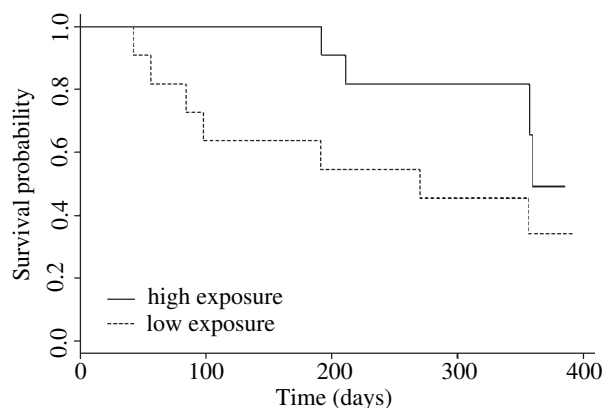


Figure 1. Probability of maintaining equivalent infliximab dosage or decreasing the dosage over time according to infliximab exposure at baseline. Straight line: patients with infliximab concentration above the median. Dotted line: patients with infliximab concentration below the median. Log rank test:  $p=0.14$ .

only one in 11 patients with positivity for ATI (9%) were responders to infliximab at 54 weeks as compared to 20 in 27 patients without ATI positivity (74%) (2). Positivity for ATI has an impact on infliximab pharmacokinetics and leads to reduced exposure to infliximab in AS (7). In the present study, only three patients showed ATI positivity; two discontinued treatment. Because detection of ATI is hampered by the persistence of infliximab in the circulation, we may have underestimated the number of patients with ATI positivity.

In conclusion, infliximab concentration in patients with AS seems to predict sustained efficacy of the same infliximab regimen continued throughout treatment.

### Acknowledgements

We thank M.-F. Coudray, F. Gouais, P. Pithaud, and R. Laurent for blood sampling, A.-C. Duveau for technical assistance in measuring infliximab concentrations, T. Lecomte and D. Ternant for statistical analysis advice, and C. Magdelaine-Beuzelin for

carrying out the measurement of antibodies towards infliximab serum concentrations.

### References

1. van der Heijde D, Dijkmans B, Geusens P, Sieper J, DeWoody K, Williamson P, et al. Efficacy and safety of infliximab in patients with ankylosing spondylitis: results of a randomized, placebo-controlled trial (ASSERT). *Arthritis Rheum* 2005;52: 582–91.
2. de Vries MK, Wolbink GJ, Stapel SO, de Vrieze H, van Denderen JC, Dijkmans BA, et al. Decreased clinical response to infliximab in ankylosing spondylitis is correlated with anti-infliximab formation. *Ann Rheum Dis* 2007;66: 1252–4.
3. Krzysiek R, Breban M, Ravaud P, Prejean MV, Wijdenes J, Roy C, et al. Circulating concentration of infliximab and response to treatment in ankylosing spondylitis: results from a randomized control study. *Arthritis Rheum* 2009;61:569–76.
4. Ternant D, Mulleman D, Degenne D, Willot S, Guillaumin JM, Watier H, et al. An enzyme-linked immunosorbent assay for therapeutic drug monitoring of infliximab. *Ther Drug Monit* 2006;28:169–74.
5. Collantes-Estevez E, Muñoz-Villanueva MC, Zarco P, Torre-Alonso JC, Gratacós J, González C, et al. Effectiveness of reducing infliximab dose interval in non-responder patients with refractory spondyloarthropathies. An open extension of a multicentre study. *Rheumatology (Oxford)* 2005;44: 1555–8.
6. Breban M, Ravaud P, Claudepierre P, Baron G, Henry YD, Hudry C, et al. Maintenance of infliximab treatment in ankylosing spondylitis: results of a one-year randomized controlled trial comparing systematic versus on-demand treatment. *Arthritis Rheum* 2008;58:88–97.
7. Xu Z, Seitz K, Fasanmade A, Ford J, Williamson P, Xu W, et al. Population pharmacokinetics of infliximab in patients with ankylosing spondylitis. *J Clin Pharmacol* 2008;48:681–95.

Denis Mulleman, Department of Rheumatology, Trousseau Hospital, 37044, Tours Cedex 9, France.  
E-mail: denis.mulleman@univ-tours.fr

\*Both authors contributed equally to this work.

Accepted 12 July 2009