Early monitoring of infliximab serum trough levels predicts long-term therapy failure in patients with axial spondyloarthritis

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Objective: To evaluate whether serum infliximab trough levels (ITL) during the early stages of treatment are predictive of long-term clinical failure in patients with axial spondyloarthritis (axSpA).

Methods: Longitudinal observational study involving 81 patients with axSpA monitored during infliximab therapy. Serum ITL were measured before starting infliximab treatment and at weeks 2 (W2), W6 and W12 of treatment. Disease activity was assessed by Ankylosing Spondylitis Disease Activity Score (ASDAS) at baseline, W24 and W52, and every 6 months thereafter until treatment discontinuation, regardless of the reason. Non-clinically important improvement was defined by ASDAS<1.1. The association between serum levels during the early stages and clinical outcomes (non-clinically important improvement at W52, drug survival and drop-out due to secondary inefficacy) was investigated through logistic regression models and Kaplan Meier curves. Receiver operating characteristic (ROC) curves were employed to determine the best cut-off for serum ITL.

Results: Out of the 81 patients, 45 (56%) did not achieve clinical improvement at W52. These patients had lower serum ITL at W12 compared to those who improved: ITL [median (IQR)]; 4.1 (0.9-8.3) µg/mL vs 7.1 (4.3–11.3) µg/mL, respectively; p = 0.007). ITL<6.7 µg/mL at W12 was significantly associated with: i) not achieving clinical improvement at W52 (OR: 2.3; 95%CI: 1.3–3.9); ii) shorter drug survival (5.0 years 95% CI 3.8–6.2) vs 7.0 years (95% CI 4.8–6.9; p = 0.04), and iii) higher drop-out rates due to secondary inefficacy (OR: 3.5; 95% CI: 1.2–10.2).

Conclusion: Low serum ITL at W12 were associated with long-term clinical failure in patients with axSpA, due to secondary inefficacy.

In axial spondyloarthritis (axSpA), tumour necrosis factor inhibitors (TNFi) have been shown to be effective for improving signs and symptoms in cases of persistently high disease activity (1). Accordingly, TNFi are recommended as the first biological therapy for patients with axSpA. In such cases, infliximab, a chimeric TNFi, is widely used in clinical practice. However, data from clinical registries have shown that after 2 years of treatment, up to 30–45% of patients experience therapy interruption, with clinical inefficacy being the main reason for discontinuation (2, 3). Of these patients, 19–23% experience lack of efficacy from the very beginning of treatment, while the rest initially respond to infliximab but then lose this response over time.

Serum infliximab levels are closely associated with clinical response in patients with axSpA (4, 5). Several variables may affect the pharmacokinetics–pharmacodynamics of infliximab and the clinical response of patients to this drug. These include the degree of disease activity (inflammatory burden), the development of anti-drug antibodies (ADAs), the concomitant use of conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs), and patient-related characteristics such as body mass index (BMI) (6).

As high disease activity is associated with higher concentrations of tumour necrosis factor-α (TNF-α) in both swollen tissue and serum, such patients require greater amounts of drug to neutralize TNF-α (6). This situation is known as an ‘inflammatory sink’ (7, 8) and results in lower available drug levels. Accordingly, an inverse correlation has been found between serum TNFi concentration and disease activity in all inflammatory diseases (6).

Monitoring serum drug concentrations, known as therapeutic drug monitoring, during the early stages of treatment, could be a feasible approach for predicting non-response to biologicals. In this regard, determining the serum drug concentration that best correlates with clinical results has been the principal aim of several studies carried out in other inflammatory diseases (9–13). However, there are scant data about the value of infliximab levels for this purpose in axSpA patients (14).

The aim of the present work was to study whether serum infliximab trough levels (ITLs) during the early stages of treatment (within the first 12 weeks) could help to predict long-term clinical failure of the TNFi infliximab in patients with axSpA.
Method

Study design and patients

This longitudinal, observational study included patients with axSpA recruited from the SpA-Paz cohort (15). This is an ongoing cohort, started in 2006 (15), which prospectively includes all patients with axSpA initiating biological therapy at the Rheumatology Department of La Paz University Hospital (Madrid, Spain). In addition, since 2010, serum samples have been collected to measure serum drug levels and the presence of ADAs. For this study, the data set was locked in September 2017.

All included patients were diagnosed with axSpA by their treating physician and began infliximab therapy in accordance with national guidelines (16), presenting predominant axial disease and active disease at the start of TNFi treatment. Patients received intravenous infusions of infliximab (5 mg/kg) at weeks (W) 0, 2, and 6, and every 8 weeks thereafter. Serum samples were collected at baseline and immediately before each infusion.

The study was approved by the Medical Ethics Committee of La Paz University Hospital (PI-1155) and all patients provided signed informed consent.

Clinical disease activity and treatment response

Disease activity was assessed by the Ankylosing Spondylitis Disease Activity Score using C-reactive protein (CRP-ASDAS) at baseline, W24, and W52. Non-clinically important improvement was defined by a ΔASDAS value < 1.1 and clinically important improvement by an ΔASDAS ≥ 1.1 (17, 18). In addition, long-term clinical failure was assessed by drug survival and the development of secondary inefficacy (patients who lost clinical improvement after 6 months of therapy).

Measurement of serum ITLs

Serum ITLs were measured by a capture enzyme-linked immunosorbent assay (ELISA), as has been previously described. Serum ITLs > 10 ng/mL were considered positive (19). In total, 304 serum samples were analysed. Serum samples were available from all patients at baseline, at W2 in 72, at W6 in 74, and at W12 in 77 patients.

Statistical analysis

Descriptive statistics are reported as median and interquartile range (IQR), mean and standard deviation (mean ± sd), or absolute numbers and relative frequencies, depending on normal distributions. First, the associations between serum infliximab levels at the different time-points (W2, W6, and W12) and ΔASDAS at W24 and W52 were assessed using the Mann–Whitney U-test. For this purpose, patients were classified into two groups according to the degree to which they achieved clinically important improvement (ΔASDAS ≥ 1.1) (R) or not (ΔASDAS < 1.1) (non-R). In case of dropout or missing data before W52, last observation carried forward analysis was performed. Secondly, serum-dependent receiver operating characteristics (ROC) curves were used to determine the serum ITL cut-off point that best predicted treatment failure (ΔASDAS < 1.1). The sensitivity and specificity of the serum ITL cut-off points were compared to select the best cut-off for predicting clinical failure. Thirdly, univariable and multivariable logistic regression models were used to investigate this association. To this end, the identified cut-off serum ITL at W12, age, gender, human leucocyte antigen-B27, methotrexate (MTX), sulphasalazine, BMI, smoking status, prednisone, and ASDAS at baseline were included as independent variables in the univariable analyses. The variables with significant associations (p < 0.1) in the univariable analysis were included as independent variables in the multivariable analyses. Finally, survival throughout infliximab therapy (median of 3 years), according to the predictive ITL cut-off, was studied using Kaplan–Meier curves and a multivariate Cox regression model.

All analyses were performed with GraphPad Prism 6 (San Diego, CA, USA) and SPSS 21.0 (IBM Corp., Armonk, NY, USA) software, taking a p-value < 0.05 as significant.

Results

Baseline demographics and clinical data

Eighty-one consecutive patients with axSpA starting infliximab therapy were included. All patients had predominant axial involvement and 64 (79%) also presented some peripheral (enthesitis, arthritis, dactylitis) or extra-musculoskeletal involvement (uveitis, psoriasis, inflammatory bowel disease). Baseline demographic and clinical characteristics are shown in Table 1. The median (IQR) age was 45 (37.5–53) years, 55% were men, and 22% were currently smokers.

At W52, 45 patients (56%) were classified in the group of non-R and 36 (44%) were classified as R. Globally, 41 patients (51%) dropped out of infliximab therapy during follow-up [median (IQR) 3 (1.3–5.9) years].

Baseline ASDAS were significantly lower in patients who did not achieve clinically important improvement [mean ± sd 3.9 ± 1 in the R group vs 3.1 ± 0.9 in the non-R group, p < 0.001], as were CRP levels [median (IQR) 16.3 (5.5–31.5) in the R group vs 4.2 (2.2–10.3) in the non-R group, p = 0.001]. Twenty-seven patients (33%) received concomitant MTX because of extra-axial manifestations, 18 (47%) in the R group and nine (21%) in the
Table 1. Baseline characteristics of patients with axial spondyloarthritis (axSpA) (total population, non-responders, and responders).

| Characteristic                      | Total population (n=81) | ΔASDAS < 1.1 (n=45) | ΔASDAS ≥ 1.1 (n=36) | p     |
|------------------------------------|------------------------|---------------------|---------------------|-------|
| Age (years)                        | 45 (37.5–53)           | 43 (37–53)          | 46.5 (38–54)        | 0.5   |
| Body mass index (kg/m²)            | 26.6 (24.4–29.7)       | 27.8 (24.5–29.5)    | 25.6 (23.1–30.5)    | 0.5   |
| Male                               | 48 (55)                | 21 (47)             | 24 (67)             | 0.2   |
| Disease duration (years)           | 8.3 (4–17.1)           | 7.3 (3.3–12.5)      | 8.4 (5.5–19.8)      | 0.07  |
| HLA-B27 positive                   | 43/70 (61)             | 19/36 (53)          | 24/34 (71)          | 0.1   |
| Smoking status                     |                        |                     |                     |       |
| Current smoker                     | 18 (22)                | 12 (28)             | 6 (50)              | 0.2   |
| Non-smoker                         | 47 (58)                | 24 (56)             | 23 (61)             |       |
| Ex-smoker                          | 14 (17)                | 5 (12)              | 9 (24)              |       |
| Subtype of SpA                     |                        |                     |                     |       |
| Ankylosing spondylitis             | 42 (52)                | 18 (42)             | 24 (63)             |       |
| Undifferentiated SpA               | 30 (37)                | 20 (47)             | 10 (26)             |       |
| Psoriatic SpA                      | 3 (4)                  | 2 (5)               | 1 (3)               |       |
| Spondyloarthropathy with inflammatory bowel disease | 6 (7) | 3 (7) | 3 (8) |       |
| ASDAS                              | 3.5 ± 1                | 3.1 ± 0.9           | 3.8 ± 1             | < 0.001 |
| BASDAI                             | 6 ± 2                  | 5.7 ± 2             | 6.2 ± 2             | 0.27  |
| CRP level (mg/L)                   | 7.6 (3–25.7)           | 4.2 (2.1–10.3)      | 16.3 (5.5–31.5)     | 0.001 |
| Monotherapy                        | 35 (43)                | 20 (44)             | 15 (42)             | 0.17  |
| Concomitant treatment              |                        |                     |                     |       |
| Methotrexate                       | 27 (33)                | 12 (27)             | 15 (47)             | 0.01  |
| Other csDMARDs                     | 32 (39)                | 17 (38)             | 15 (42)             | 0.3   |
| Prednisone                         | 15 (19)                | 7 (16)              | 8 (22)              | 0.08  |

Data are shown as median (interquartile range), n (%), or mean ± sd.
ASDAS, Ankylosing Spondylitis Disease Activity Score; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; CRP, C-reactive protein; csDMARD, conventional synthetic disease-modifying anti-rheumatic drug; HLA, human leucocyte antigen; SpA, spondyloarthritis.

Association between early serum ITL and baseline variables with non-clinical improvement at week 52

Figure 1 shows serum ITL values at W2, W6, and W12 in the non-R and R groups. During the early stages, serum ITL values were similar, although slightly lower in the non-R group compared to the R group at W2 and W6 [37.6 (22–50.8) µg/mL vs 38.9 (27–52) µg/mL, p = 0.7; and 18.7 (12.6–26.6) µg/mL vs 24.2 (13.6–34.6) µg/mL, p = 0.2; respectively]. However, they were significantly and statistically different at W12 [4.1 (0.9–8.3) µg/mL vs 7.1 (4.3–11.3) µg/mL, p = 0.007].

An ROC curve for not achieving clinically important improvement at W52, as defined by ΔASDAS < 1.1, was calculated in relation to the serum ITL at W12 (Figure 2). The area under the curve (AUC) was 0.678 [95% confidence interval (CI) 0.558–0.797, p = 0.007]. The cut-off value chosen to discriminate between non-R

![Figure 1](https://example.com/figure1.png)

Figure 1. Differences in serum infliximab (Ifx) trough levels at (A) week 2 (W2), (B) W6, and (C) W12 according to clinical response [change in Ankylosing Spondylitis Disease Activity Score (ΔASDAS) < 1.1 and ΔASDAS ≥ 1.1] at W52. Non-R, non-responders; R, responders. ***p < 0.001; ns, not significant.
and R (with a sensitivity of 55%, specificity of 70%, positive predictive value of 63%, and negative predictive value of 64%) was at infliximab serum trough concentrations of 6.7 µg/mL. Of the 77 patients with available serum samples at W12, 45 (58%) had a serum ITL below the threshold and 32 (42%) above it. Most patients in the non-R group had serum ITLs < 6.7 µg/mL [29/41 (71%)] below vs 12/41 (29%) above, p = 0.02 (Figure 3).

In the univariable analysis, two variables were significantly associated with not achieving clinically important improvement at W52: serum ITL below 6.7 µg/mL at W12 (odds ratio (OR): 3.0, 95% CI 1.2–7.7) and lower baseline ASDAS (OR: 2.4, 95% CI 1.4–4.0). In the multivariable analysis, both variables, serum infliximab levels < 6.7 µg/mL at W12 (OR: 3.8, 95% CI 1.3–11.2) and lower baseline ASDAS (OR: 2.3, 95% CI 1.3–3.9), remained significantly associated with the non-clinically important improvement at W52.

Value of early serum ITL (week 12) monitoring to predict drug survival and secondary inefficacy over long-term follow-up

The survival curve depicted in Figure 4 shows that from the early stages (the first 3 months) of treatment, having low serum ITLs was associated more with an early dropout from therapy compared to having levels above this cut-off: 5.0 years (95% CI 3.8–6.2) in patients with ITL < 6.7 µg/mL versus 7.6 years (95% CI 4.8–6.9) in patients with ITL ≥ 6.7 µg/mL (p = 0.04) (Figure 4).

In the multivariable Cox regression analysis, only serum ITL ≥ 6.7 µg/mL at W12 independently predicted longer drug retention in patients with axSpA (hazard ratio 2.17, 95% CI 1.04–4.53, p < 0.05).

To evaluate the association between ITL at W12 and the predictive accuracy of secondary inefficacy, we performed an analysis in which those patients who dropped out (n = 6) before 52 weeks of treatment were excluded. There were no differences between this cohort (n = 75) and the original cohort with 81 patients in terms of either clinical or demographic baseline characteristics (data not shown). Of 75 axSpA patients, 28 (37%) developed secondary inefficacy and seven (17%) dropped out for other reasons (adverse effects, loss of follow-up, etc.). The median (IQR) time under infliximab therapy of 28 patients with secondary inefficacy was 2.1 (1.4–4.8) years and the median for patients who dropped out for other reasons (n = 8) was 2.4 (0.7–4) years. The logistic regression analysis showed that infliximab concentrations below the cut-off at W12 (OR: 3.5, 95% CI 1.2–10.2), but not the baseline ASDAS (OR: 0.9, 95% CI 0.5–1.5), were statistically significantly associated with dropping out of treatment due to secondary inefficacy. In addition, most of the patients who dropped out due to secondary inefficacy had infliximab concentrations < 6.7 µg/mL at W12: 19/26 (73%) with ITL, while only 7/26 (27%) had at an ITL above the cut-off at W12 (p = 0.01) (Figure 5).
Discussion

In this study, we have shown an association between serum ITLs during the early stages of the treatment (at week 12) and long-term clinical failure of infliximab, based on non-clinically important improvement at W52, drug survival, and dropout due to secondary inefficacy in patients with axSpA. In addition, we defined an ITL cut-off at W12 as predictive of long-term clinical failure in patients with axSpA treated with infliximab.

It is known that TNFi must be available in sufficient quantities to achieve their effects, and a concentration-dependent effect has been described (20). Most of the good clinical responders presented significantly higher serum concentrations than non- and moderate responders during the first year of treatment (10, 11), although a wide variation in pharmacokinetics has been described (15, 21, 22). Among the factors influencing TNFi pharmacokinetics, it should be noted that the development of immunogenicity increases drug clearance and is associated not only with low serum drug levels, but also with a consequent lack of response (23). The concomitant use of csDMARDs such as MTX is also associated with the presence of serum drug, in part due to the prevention of ADA formation (24–26). The Assessment of SpondyloArthritis international Society and European League Against Rheumatism (ASAS-EULAR) advise against using csDMARDs to control axial disease in patients with axSpA (1); however, in clinical practice, csDMARDs are used for treating peripheral joint and extra-musculoskeletal manifestations (24).

Some publications highlight the unmet need to identify predictive factors of clinical response to TNFi, pointing to the role played by serum TNFi levels in this context (9, 12, 27, 28). Most published studies have involved patients with rheumatoid arthritis (RA) treated with infliximab or another monoclonal antibody to TNF, such as adalimumab (9, 27, 28). These studies report that serum drug levels during the first 3 months of therapy can help to predict patient response to treatment. One study conducted in patients with ulcerative colitis observed that infliximab levels at W2 are useful for predicting short- and long-term outcomes (12). Only one previous study correlated serum ITLs during the early stages with the onset of immunogenicity, albeit without clinical outcomes, in patients with spondyloarthritis (SpA) (14). The present study is the first to demonstrate that low serum ITLs 3 months after starting therapy are associated with worse clinical outcomes in long-term follow-up in patients with axSpA.

Recent efforts have focused on identifying a cut-off point for serum drug levels during the early stages to predict clinical outcomes. The majority of studies...
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involved patients with RA (9, 14, 29) or with inflammatory bowel disease (12). Ducourau et al (14) found that ITLs > 6.5 mg/L in patients with SpA at W12 were associated with longer infliximab survival; however, no clinical outcomes were investigated with this cut-off value. In our axSpA cohort, serum ITLs < 6.7 µg/mL at W12 were associated with three clinical outcomes: diminished clinical improvement during the first year of therapy, a higher frequency of dropping out due to secondary inefficacy, and shorter survival time using this treatment.

We observed that lower baseline ASDAS and CRP levels were associated with a lower probability of achieving clinically important improvement as measured by ASDAS. These findings are consistent with data previously published in patients with SpA, where higher baseline ASDAS and CRP values correlated with elevated TNF-α serum levels. One possible explanation could be that high ASDAS and CRP values at baseline reflect the high proinflammatory burden produced by inflammatory cytokines such as TNF-α (30–33). This would mean that the higher the levels of TNF in serum, the higher the resulting efficacy of the response to TNFi.

Many predictors have been associated with TNFi survival in axSpA. Female gender, steroid use, and persistently high inflammatory levels are found to be negative predictors of treatment response (34). One of the other hand, the concomitant use of csDMARDs and TNFi has been linked to better drug survival in patients with SpA (35–37). In our study, the median maintenance time was 3 (1.3–5.9) years, which is similar to that of the study involving the Danish nationwide clinical register for patients with rheumatoid arthritis (DANBIO), which reported a median (IQR) of 2.4 (IQR 1.0–4.8) years (38). In both studies, the median drug survival was longer than the time under therapy (no more than 1 year) described in the study by Ducourau et al (14). Another study, involving patients with ankylosing spondylitis (AS) over a 5 year treatment period showed that half (35/70) of them discontinued therapy due to insufficient response or adverse events resulting from the use of infliximab (34). These results are similar to the 51% of patients in our cohort dropping out of infliximab therapy over the studied period. However, there are few data correlating serum ITL as a predictor of drug survival. Only one previous study, involving 22 patients with AS, showed that infliximab concentration > 6.4 µg/mL seems to predict sustained efficacy to the same infliximab regimen observed throughout treatment (39).

It is important to point out that ITLs during the early stages are associated with shorter drug survival. In the present study, patients with ITLs < 6.7 µg/mL at W12 had shorter drug survival and a 3.5-fold greater probability of dropping out due to secondary inefficacy than those with higher ITLs.

The main limitations of our study are the relatively low number of patients (n = 81) and the unavailability of all serum samples throughout the studied time-points. We are aware that the low number of patients may be the reason that, despite recording lower ITLs at W2 and W6 in non-R compared with R at W52, we did not observe statistically significant differences until W12. Moreover, administering doses of 5 mg/kg of infliximab in these patients may be another reason why significant differences during the very early time-points were difficult to detect. The studied cohort included SpA patients comprising all entities of SpA with axial involvement, in which clinical disease activity and clinical improvement were assessed by ASDAS and ΔASDAS, respectively, as is recommended in axSpA patients (40). We decided to use clinical response as a measure of clinical outcome (which is feasible in clinical practice), rather than using an outcome of disease activity, which may not necessarily be associated with clinical improvement. The treatment of this cohort represents standard clinical practice in our hospital.

Conclusion

Low serum infliximab levels during the early stages (W12) of treatment are associated with long-term clinical failure (W52) in patients with axSpA treated with infliximab. Moreover, low infliximab concentrations at W12 are associated with shorter drug survival time and a higher proportion of patients who dropped out due to secondary inefficacy. However, further long-term studies, including more inclusive cohorts, are required to validate the present results.

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