

Relationship between ustekinumab trough concentrations and both clinical and biological remission in patients with Crohn's disease



Relación entre las concentraciones mínimas de ustekinumab y la remisión clínica y biológica en pacientes con enfermedad de Crohn

The data about TDM of ustekinumab is still limited despite being a potential drug for it.^{1–4} Taking into consideration the potential benefits of TDM, the addition of ustekinumab monitoring to clinical practice could improve clinical decisions in the treatment of Crohn disease (CD) for which it is necessary to provide more data in this regard.

We studied patients with CD undergoing maintenance treatment with ustekinumab who underwent at least one determination of serum ustekinumab level to provide further evidence of the correlation between them and both clinical and biological remission.

All samples were classified according to disease activity at the time of level determination. Clinical remission was established through Harvey-Bradshaw index considering no disease activity when it had a value ≤ 4 . Biological remission was based on analytical values of both CRP (<5 mg/L) and CAL (<250 $\mu\text{g/g}$). Sample extraction was performed just before the next administration of ustekinumab.

Forty one samples from thirty seven patients were collected. Median age was 43 years (IQR: 35–52.5) and 20

patients were women. CD was located in 62.2% ($N=23$) in ileum-colon, 27% ($N=10$) in ileum and 10.8% ($N=4$) in colon. The profile of CD was inflammatory in 43.2%, stenosing in 32.4%, penetrating in 10.8% and stenosing-penetrating in 13.5%. Intestinal resection surgery prior to the onset of ustekinumab was present in 45.9% of the patients. In this group of patients, surgery was performed at least 1 year before its inclusion in the study.

Ustekinumab was used as the third line of biological treatment in 70.3% of patients, 27% in the second and 10.3% in the fourth. The dosing regimen at the time of sample extraction was 90 mg every 8 weeks (68.3%), every 7 weeks (4.9%), every 6 weeks (9.8%) and every 4 weeks (17.1%). The median treatment time was 23 months (IQR: 10–29). Eight patients (10.3%) were reintroduced with an IV dose with a median time between ustekinumab reinduction and sample extraction of 34.6 weeks (IQR: 22.8–38.6). 5.4% of patients were on concomitant immunomodulatory treatment (methotrexate). Albumin serum median level was 4.47 g/dL (IQR: 4.23–4.85).

Trough serum concentration was determined in all patients in the maintenance phase (median of 23 months [IQR: 10–29]). No antibodies (ADA) against ustekinumab were detected in any patient. In general, there was an increasing trend in the percentage of patients in clinical remission as the serum drug level increased (Fig. 1A). In samples from patients with clinical remission, median minimum serum ustekinumab concentrations were 2.78 (IQR: 1.84–4.13) $\mu\text{g/mL}$; in the remaining samples without clinical remission the level was 2.08 (IQR: 1.05–3.5) $\mu\text{g/mL}$.

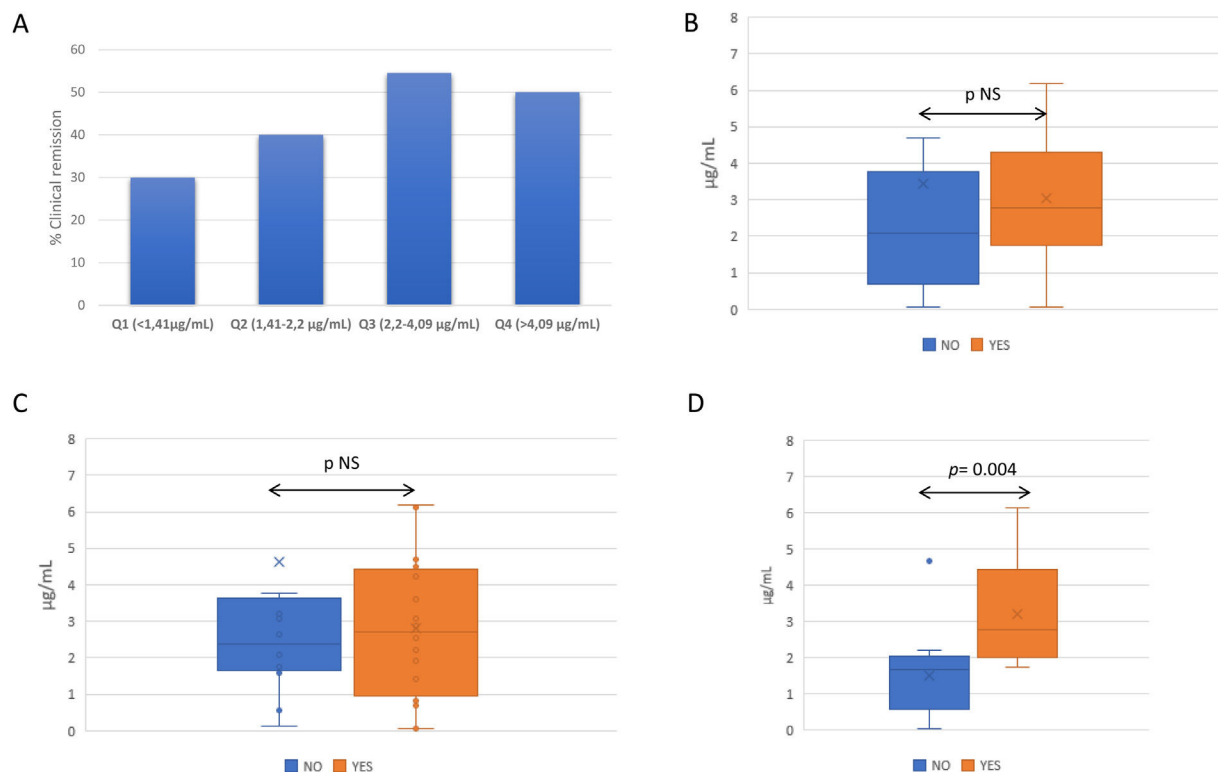


Figure 1 A. Quartile distribution of ustekinumab levels according clinical remission. B. Ustekinumab levels according clinical remission. C. Ustekinumab levels according biological remission. D. Ustekinumab levels according clinical remission in patients without intestinal resection surgery. NS: not significant.

($p=0.337$) (Fig. 1B). The CAL level was available in 68.3% of patients. In patients with biological remission, median CAL and CRP values were 116.7 $\mu\text{g/g}$ (IQR: 71.8–213.9) and 1.9 mg/L (IQR: 1.3–3.1) respectively. In patients without remission the values were 206.4 $\mu\text{g/g}$ (IQR: 64.5–378.1) ($p=0.595$) and 3.9 mg/L (IQR: 1.85–12.3) ($p<0.05$) respectively. Ustekinumab serum level of patients seems to be higher in those with both clinical and biological remission which is consistent with published results on literature, however these differences were statistically non-significant probably due to the low sample size (Fig. 1B and C). On the other hand, range of ustekinumab levels as quartiles has to be interpreted with caution (Fig. 1A), since the possible optimal interval to achieve clinical remission is expected to be very small when ustekinumab is administered subcutaneously and with a long period between doses.

It must be taken into account that in clinical practice conditions, the population is very heterogeneous, with different affected sites, previous lines of treatment, with or without previous surgery. Therefore, the results obtained were also analyzed by dividing them into two groups of patients, with or without intestinal resection surgery prior to ustekinumab. In patients without intestinal resection in clinical remission showed a significant higher in median trough serum drug concentrations compared to patients without clinical remission (2.77 [IQR: 2.01–4.45] vs. 1.67 [IQR: 0.58–2.06] $\mu\text{g/mL}$; $p=0.005$) (Fig. 1D).

In conclusion, our study suggests that in CD patients without intestinal resection surgery ustekinumab serum levels may be related to clinical remission, being higher in those with clinical remission. Regarding all CD patients, ustekinumab serum levels seems to be higher in those with clinical and biological remission, but these differences did not have a statistical significance.

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