of the multimodal treatment. More studies are needed to establish how to combine surgery with medical treatments in the different metastatic diseases of the pancreas.[5]

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Conflicts of interest

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Efficacy, persistence and optimization of ustekinumab in ulcerative colitis: Clinical practice data

Eficacia, persistencia y optimización de ustekinumab en colitis ulcerosa: datos de práctica clínica

Ustekinumab is a monoclonal antibody which was approved by the Food and Drug Administration for the treatment of moderate-to-severe ulcerative colitis in October 2019. As yet, there are therefore relatively few studies in clinical practice.[1–4]

The main aim of this study was to determine the efficacy (clinical and biological remission), the percentage of persistence with the drug, and the need for dose optimisation.

Clinical remission is defined as a partial Mayo score <2 and no sub-index >1; biological remission, as faecal calprotectin (FC) values <150 mg/kg.

The secondary objective was to determine the efficacy of ustekinumab in joint manifestations associated with ulcerative colitis.

This was a retrospective, observational study of a database maintained prospectively in the Inflammatory Bowel Disease Unit at our centre on patients who started ustekinumab from July 2018 to September 2021 ($N = 16$).

A descriptive statistical analysis was performed using the IBM® SPSS® software, version 26, with statistical significance being $p < 0.05$. The qualitative variables are expressed as absolute numbers and percentages. Quantitative variables are expressed as means and standard deviation or medians and interquartile range, as appropriate. The non-parametric Friedman test was used to check for statistically significant differences in the values of the variables analysed during the clinical course.

The baseline characteristics of the patients and the disease are summarised in Table 1.

The mean treatment time with ustekinumab was 17.81 months (standard deviation 12.57) and 81.30% of the subjects started ustekinumab without concomitant corticosteroids. In two patients (12.50%), both previously treated with more than two lines of biological drugs, combination therapy with an immunosuppressant (tacrolimus) was used as induction until clinical remission was achieved (one patient for three months and the other for one month, discontinued due to neurotoxicity).

Steroid-free clinical remission was achieved in 25% at week 4, 50% at week 8, 69.2% at week 16, 54.5% at week 24, 90% at week 52 and 87.5% at 18 months.

Rectal bleeding, present at baseline in 81.30% of the subjects, disappeared in half of them at week 4.

There was a statistically significant decrease in the partial Mayo score during follow-up ($p = 0.000$). The median baseline FC was 1459 mg/kg (interquartile range 1911.5) with figures tending to return to normal ($p = 0.064$); the decrease occurred primarily after week 16. Biological remission was achieved in 56.25% at the end of follow-up.

In 11 patients (68.75%), treatment was optimised every four weeks due to loss of secondary response or partial response. Of these, steroid-free clinical remission was achieved in 86.6% and biological remission in 45.45%. The need for optimisation seemed to be more common in the subgroup of patients with two or more prior biological

Table 1 Baseline characteristics of the patients and the ulcerative colitis ($N = 16$).

Age (years), mean (SD)	49.74 (17.04)
Time since onset of the disease (years), mean (SD)	11.96 (9.87)
Baseline partial Mayo score, mean (SD)	5.75 (2.08)
Gender, *n* (%)	
Male	9 (56.30)
Female	7 (43.80)
Extension of the UC, n (%)	
E1	3 (18.80)
E2	11 (66.80)
E3	2 (12.50)
Extraintestinal signs, *n* (%)	
Yes	6 (37.50)
No	10 (62.50)
Baseline Mayo endoscopic score, *n* (%)	
1	1 (10.00)
2	4 (40.00)
3	5 (50.00)
Previous biological therapy, *n* (%)	
Two or more biologicals	9 (56.25)
Two anti-TNF	2 (12.50)
One anti-TNF + vedolizumab	1 (6.25)
Two or more anti-TNF + vedolizumab	3 (18.75)
Two or more anti-TNF + vedolizumab + tofacitinib	2 (12.50)
One biological	6 (37.50)
Naïve to biologicals	1 (6.25)
Maintenance dose, n (%)	
90 mg sc every 4 weeks	6 (37.50)
130 mg iv every 4 weeks	5 (31.25)
90 mg sc every 8 weeks	3 (18.75)
90 mg sc every 12 weeks	2 (12.50)

drugs (77.77%) compared to patients who were naïve to (bio-naïve)/had only taken one biological drug (57.14%) ($p = 0.596$).

Fourteen of the 16 patients (87.5%) who started ustekinumab were still on the treatment at the end of follow-up. In the two remaining subjects, it was necessary to change the therapeutic target (both to tofacitinib) due to loss of response and the development of *de novo* arthritis.

Data were compared according to the two groups of previous treatments: subjects with failure to $\geq$2 biological drugs ($n = 9$) or failure to one biological drug/bio-naïve ($n = 7$). There were differences in the mean time since onset (17.02 *vs* 6.91 years respectively; $p = 0.021$) and in the percentage of baseline rectal bleeding (100% *vs* 62.50%; $p = 0.05$). In addition, there were differences in the mean baseline partial Mayo score (7.13 *vs* 4.38; $p = 0.006$) at week 16 (4.25 *vs* 0.83; $p = 0.017$) and week 24 (3.43 *vs* 0; $p = 0.039$), and in the FC values at week 4 (1787.4 *vs* 841; $p = 0.028$) and week 24 (853.17 *vs* 16; $p = 0.02$). No differences were found in the mean baseline values of albumin, C-reactive protein and endoscopic Mayo score between the two groups (failure to $\geq$2 biological drugs vs failure to one biological drug/bio-naïve): 4.37 *vs* 4.37 g/dl, $p = 0.881$; 6.43 *vs* 5.04 mg/l, $p = 0.861$ and 2.67 *vs* 2.00, $p = 0.157$ respectively.

These data suggest that the decrease in the inflammatory load of naïve patients or patients with failure to a single biological drug occurs more rapidly than in subjects with failure to more than two biological drugs. Therefore, perhaps initiating ustekinumab earlier in the therapeutic pyramid would achieve better remission outcomes.

Six patients (37.5%) had joint manifestations (5 peripheral arthritis, 1 ankylosing spondylitis) which improved in 83.3% according to the overall assessment by Rheumatology.

In our series, none of the patients had a colectomy or had to go to Accident and Emergency or be hospitalised. There was one adverse effect (*de novo* arthritis) which made it necessary to discontinue the drug.

Conclusions

- Ustekinumab is an effective therapeutic option in achieving and maintaining long-term clinical and biological remission in patients with ulcerative colitis, both in those with failure to two or more therapeutic lines and in early lines (bio-naïve and failure to one biological drug).
- Biological remission was achieved in approximately half of the patients and the decrease in FC was particularly evident after week 16.
- Treatment optimisation due to loss of, or partial, response is effective in achieving clinical remission, but less effective in achieving biological remission.
- Ustekinumab may be effective in the synergistic treatment of mainly peripheral joint manifestations, although further studies are needed.

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Conflicts of interest

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