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Ustekinumab in Crohn's disease: real-world outcomes and predictors of response.

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ABSTRACT

Background

Ustekinumab is a monoclonal antibody that inhibits interleukins (IL)- 12 and -23 and it is approved for the treatment of Crohn's disease (CD) and more recently also ulcerative colitis (UC). Our aim was to evaluate the effectiveness and safety of Ustekinumab, as well as to identify possible predictive factors of response in a real-life setting.

Methods

Observational, retrospective, and multicenter study carried out in 4 hospitals in Andalusia. Adult patients with a confirmed diagnosis of CD treated with Ustekinumab

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from 2017 to 2019 were included. Clinical response was analyzed at 3, 6, and 12 months of treatment. Clinical disease activity was assessed with the Harvey Bradshaw index (HBI) and the Crohn's Disease Activity Index (CDAI); and the biochemical response was assessed with analytical parameters such as CRP and ESR. One-year ustekinumab drug-survival was analyzed.

Results

98 patients were analyzed (mean age 43 and 52% men). 56% had failed to ≥2 previous biologicals therapies. At 3 months, 69% of the patients were in response and 40.8% in remission. At 6 months, 56% were in clinical remission. At 12 months, 73.7% in clinical response and 60.5% in remission. Corticosteroid-free remission was 32.4%, 44%, 47.4% at 3, 6, and 12 months, respectively.

The cumulative survival at one year of treatment with ustekinumab was 85.3%. Biochemical parameters, such as CRP and ESR showed a statistically significant decrease between baseline and control levels at 3, 6, and 12 months. A lower HBI at baseline and female sex were predictors of corticosteroid-free clinical remission in a univariate analysis. In the multivariate analysis, no variables were found as predictors of corticosteroid-free clinical remission

Conclusion

Ustekinumab therapy is safe and useful inducing a clinical response in more than 50% of patients including patients who have failed other biological therapies.

Keywords

Inflammatory bowel disease, Crohn's disease, ustekinumab.

Abbreviations

Crohn's disease (CD), Ustekinumab (UST), Harvey Bradshaw index (HBI), Crohn's disease activity index (CDAI), C-reactive protein (CRP), Erythrocyte sedimentation rate (ESR).

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BACKGROUND

The therapeutic arsenal for Crohn's disease (CD) has evolved widely in recent years, especially with the introduction of anti-TNF drugs. However, despite its great efficacy, up to a third of patients present a primary non-response to anti-TNF (1) and a variable percentage, a secondary loss of response (2). This represents an important challenge in daily clinical practice, objectifying the need for new therapies.

Ustekinumab (UST) is a fully human monoclonal antibody, targeting the p40 subunit of interleukin-12 and interleukin-23. It was approved by the European Medicines Agency (EMA) in 2016 (3) for the treatment of moderate to severe Crohn's disease in patients who have had an insufficient response or loss of response to anti-TNFα agents or who are intolerant or contraindication for its use.

Ustekinumab efficacy inducing and maintaining clinical remission in moderate to severe CD was evaluated in the UNITI and IM-UNITI registration trials (4). However, clinical trials do not fully reflect routine care and therefore real-world studies are needed. Data on ustekinumab effictiveness and safety in the real-life setting is still scarce (5). In our country, the Spanish short and long-term experience has been published with good results in terms of efficacy and safety (6)(7). The aim of this study was to evaluate the long-term efficacy and safety of ustekinumab in daily clinical practice in our community, Andalusia. Secondly, evaluate possible predictors of clinical response.

METHODS

Study design

Observational, retrospective and multicenter study carried out in Andalusia in 4 hospitals. All adult CD patients receiving Ustekinumab therapy from July 2017 to December 2019 were included. The induction regimen was a single intravenous dose of approximately 6mg/kg (260 mg <55 kg, 390 mg between 55-85 kg, and 520 mg if more than 80 kgs), followed by a subcutaneous administration of ustekinumab 90mg at week 8 and every 8 (q8w) or 12 weeks (q12w) thereafter. The patients were

followed for one year at their regular check-up visits. The medical records were exhaustively reviewed to gather information from the patients.

Variables

Demographic and clinical data were collected from the clinical records, previous and concomitant treatments, previous surgeries, luminal and perianal activity in order to analyze possible predictors of remission. The Harvey Bradshaw index (HBI) and the Crohn's Disease Activity Index (CDAI) and objective analytical markers such as fecal calprotectin, C-reactive protein (CRP) and baseline glomerular sedimentation rate (ESR) were used to assess the clinical response at 3 months, 6 months and 12 months of treatment.

Definitions

Clinical response was defined as a decrease of ≥3 points in the HBI index from the baseline score. Clinical remission was defined as an HBI score ≤4 points. For the effectiveness analysis, patients who were already in remission at the beginning of treatment (n = 11) or without HBI data (7) were excluded. Corticosteroid-free clinical remission was defined as clinical remission plus complete tapering of systemic corticosteroids. Intensification was defined as any dose interval shorter than q8w.

Statistical analysis

For the descriptive analysis, the absolute frequency (N) and the relative frequency (%) were calculated for the categorical variables. For continuous variables results were presented as mean and standard deviation or median and interquartile range (IQR). For the quantitative variables, normal distribution was evaluated with the Shapiro-Wilk test. Change from baseline in quantitative variables was assessed with a paired T-test or the Wilcoxon-rank test for normally or not normally distributed variables. To analyze the probability of maintaining treatment or drug-survival, the Kaplan-Meier method was used.

Variables associated with corticosteroid-free clinical remission at 3, 6 or 12 months were investigated using univariate binary logistic regression. The odds ratio (OR) of the

statistically significant variables in the model was calculated. Independent variables with a *p*-value < 0.2 in the univariate analysis were included in the multivariate analysis. This multivariate analysis used the backward elimination (conditional) method. A 95% confidence level has been taken into account, so the experimental *p*-value has been compared with a significance level of 5%. The statistical analysis was carried out using the statistical package IBM SPSS Statistics 22®.

Ethical considerations

The study was reviewed and approved by the ethics committee of the participating centers.

RESULTS

98 patients were included, baseline characteristics and concomitant medications are detailed in Table 1. The mean age at ustekinumab initiation was 43 years with a median disease duration of 10 years [IQR 4-18], 52% were men, the most frequent phenotype was inflammatory (50.4%) and the most frequent location was ileocolic (52.6%). Only 1 patient (1.1%) was naïve to biological therapy, 42.8% had previously failed one biologic and 56% two or more. The main reason for starting ustekinumab was clinical disease activity (72.5%), with a median HBI of 8 [IQR 6-10] and a median CDAI of 200 [IQR 170-235]. Previous intestinal resection was reported in 41 patients (41.8%). The flow chart of patients reaching each follow-up visit is depicted in Figure 1. Cumulative ustekinumab survival is detailed in Figure 2. The mean follow-up was 7.02 months and the maximum follow-up was 12 months. Of the 98 included patients, 12 (12.2%) discontinued ustekinumab after a mean duration of 36 weeks. The probability of continuing with ustekinumab after one year of treatment was 85.3% (Fig. 2A). In addition, the durability of the treatment was also analyzed according to the number of previous biological therapies, 0 or 1 vs 2 or more, the comparison showed a non-significant difference in ustekinumab persistence between the two groups (Fig. 2B). Similarly, there was also a non-significant difference when comparing different treatment maintenance regimens, q8w or q12w (according to the summary product characteristics) vs an interval shorter than q8w. (Fig. 2C).

Ustekinumab clinical effectiveness was assessed in patients with documented HBI variable and with at least 3-month follow-up. Patients in clinical remission (HBI≤4) at baseline (n=11) were not included in the analysis. The proportion of patients with a clinical response to ustekinumab was 69% at 3 months, 82% at 6 months and 73.7% at 12 months. The proportion of patients in clinical remission at 3, 6 and 12 months were 40.8%, 56% and 60.5% respectively. Whereas the percentage of patients achieving corticosteroid-free clinical remission, at 3, 6 and 12 months were was 32.4%, 44%, and 47.4% respectively (Figure 3).

Patients clinical evolution according to the CDAI and HBI indices throughout the follow-up visits are shown in Figure 4 A and B respectively. There was a progressive decrease in the median of both clinical indices, at 3, 6, and 12 months, a statistically significant decrease vs baseline was observed for both CDAI and HBI.

Biochemical parameters were also recorded to objectively assess the degree of systemic inflammation. A statistically significant decrease vs baseline in the mean C-reactive protein (CRP) concentration was observed at 3, 6, and 12 months (Fig. 5A). Similarly, the mean erythrocyte sedimentation rate (ESR) decreased significantly from 6 months compared to baseline levels (Fig. 5B).

To identify predictive factors of corticosteroid-free clinical remission at 3, 6 and 12 months, a univariate and multivariate analysis was performed (Table 2). Patients in clinical remission (HBI≤4) at baseline were excluded from this analysis. Multivariate analysis was performed only in variables with $p<0.2$ in the univariate analysis. In the univariate analysis, a lower HBI at baseline was associated with higher rates of corticosteroid-free remission at 3 (OR 0.73 95% CI 0.6-0.9) and 12 months (OR 0.83 95% CI 0.7-0.9). Female sex was also identified as a predictor of corticosteroid-free remission at 6 months (OR 3.89 95% CI 1.19-12.68). However, these factors did not reach statistical significance when assessed as multivariable predictors.

The safety profile of ustekinumab in our 98 patients was consistent with previous reports. During follow-up, 4 adverse events were recorded, most of them mild. One patient had an herpes zoster infection after 11 months with ustekinumab. A mouth sore after 6 months of treatment. One infusion reaction after the intravenous dose that did not require treatment discontinuation, And lastly, and thrombosis of the

superior mesenteric and portal vein after abdominal surgery (colectomy) in a patient who had already suspended ustekinumab treatment, therefore, although we report it in this study, we consider that it is probably not related to ustekinumab therapy.

DISCUSSION

To date, the treatment of CD remains a challenge despite new available therapeutic options. We often observe adverse events, primary and secondary non-response, and contraindications to some therapies. With a limited therapeutic arsenal it is paramount to assess the real-world effectiveness of novel therapies. (8)(9)

Our cohort includes complex patients,98.9% were biological-experienced patients, with long-standing Crohn's disease with a median duration from diagnosis of 10 years. Also, there was a significant prevalence of perianal disease (35.8%) and up to 40% of patients had required abdominal surgery. Despite the refractory and complex to treat nature of our cohort, 85.3% of patients maintained ustekinumab therapy after one year, moreover, corticosteroids-free clinical remission was achieved in 32.4% of patients as early as 3 months, 44% at 6 months and 47.4% at 12 months. Clinical remission was observed in 40.8%, 56% and 60.5% of patients at 3, 6 and 12 months respectively. Whereas clinical response was achieved by 69%, 82% and 73.7% of patients at 3, 6 and 12 months.

In comparison, the UNITI-1 induction registration trial evaluated the efficacy of ustekinumab in patients with previous failure to biological therapy, similar to patients in our cohort. The proportion of patients in clinical response at week 8 in the 6 mg/Kg arm was 37.8%, while 20.9% were in clinical remission. (4) Other real-world observational studies, such as the Spanish ENEIDA registry, have reported higher remission rates than the pivotal trials. Eight weeks after induction, 47.4% of patients achieved clinical remission. The authors argue that this higher remission rate could be accounted by the absence of washout periods between drugs in clinical practice and the associated treatments that were not permitted in the clinical trial (7) or Miyazaki et al. (10)

In the long-term, the IM-UNITI maintenance registration trial, reported clinical remission rates at week 44 of 53.1% in the q8w arm and 48.8% in the q12w arm.

Corticosteroid-free clinical remission was achieved by 46.9% of patients in the q8w arm and 42.6% of patients in the q12w arm. These results are in line with remission rates reported in our study. Real-world studies that assess long-term efficacy, such as the meta-analysis by Macaluso et al (11), the German cohort by Kubesch et al (12) and Hoffmann et al. (13) Iborra et (6) al and Biemans et al (5) similar or even higher response rates were observed, compared to the pivotal trials. This could be explained because in real-life studies associated treatments are allowed that could improve the response. (5)

We also assessed biochemical markers of disease activity. We found a significant decrease in inflammation markers (CRP and ESR) during follow-up, which has also been observed in the pivotal trials (4) and other observational studies. (7)

We attempted to identify predictor factors of response to ustekinumab. Predictors of response to biological treatment have been extensively studied. (14) (15) Knowing which patient will respond to a therapy and which will need the use of other therapeutic routes would allow us to avoid delay in starting an effective drug. Also, it has been shown in multiple studies that patients with failure to previous biologicals therapies have a lower response rate than naïve patients. Previous studies have reported the use of concomitant immunomodulatory drugs, disease pattern, disease location, and clinical severity as predictors of response to ustekinumab. (16) (17). In our cohort, we found that a low HBI at baseline and female sex were associated with corticosteroid-free clinical remission in a univariate analysis.

Hoffman et al, also found a similar association between sex and responsiveness to ustekinumab, in their study male sex was a predictor of non-response to ustekinumab therapy (17). However, more studies and larger cohorts are needed to evaluate this relationship.

Our study shows that ustekinumab is a safe therapeutic option for CD patients. In our cohort, the rate of adverse events was low 0.04 (4/98), the majority being mild herpetic infections or skin reactions. These findings are similar to previous reports (5) (18) (19).

Our study has several limitations. First, the retrospective nature of the study, with the limitations that this entails in the existence of biases and quality of evidence. However,

it is a multicentric study with an adequate number of patients. Our primary endpoint of response to therapy is measured by clinical activity indexes. Another limitation is the lack of endoscopic results to assess mucosal healing, in clinical practice, endoscopic examinations are not performed as frequently, as they are invasive tests. Clinical activity was measured with the HBI and CDAI indices, however, CDAI values were available in less than half of the patients since it is a more laborious index to perform and less practical for daily use. Fecal calprotectin was recorded at baseline, however it was not available for most follow-up visits and therefore no further analysis could be performed. In contrast to pivotal studies, in our cohort, only one patient received ustekinumab as first-line treatment, therefore comparison of our data to the pivotal studies should be done with caution.

CONCLUSION

Our data suggests that ustekinumab is safe and efficacious at inducing a durable clinical response in more than 50% of patients including patients who have failed other biological therapies.

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Table 1. Baseline patient characteristics. IQR, interquartile range; CRP, C-reactive protein; ND, no data

Patients characteristics	**N**
Number of patients	98
Age; *median, IQR*	41 (35-50)
Gender (M/F); *n, %*	51(52%) /47(48%)
BMI (Kg/m²); *median, IQR*	24.6 (21.5-27.3)
Smoking status; *n, %*	
Former smoker	12 (14,6%)
Current smoker	23 (28%)
No smoker	47 (57,3%)
Median disease duration (years); *median, IQR*	10 (4-18)
Age at diagnostic; n, %	

< 17 years (A1)	10 (10.3%)
17-40 years (A2)	73 (75.3%)
> 40 years (A3)	14 (14.4%)
CD location; n, %	
Ileal (L1)	31 (32%)
Colonic (L2)	9 (9.3%)
Ileocolonic (L3)	51 (52.6%)
Upper gastrointestinal (L4)	6 (6.2%)
Phenotype; n, %	
Inflammatory (B1)	49 (50.4%)
Stenosing (B2)	24 (24.7%)
Penetrating (B3)	24 (24.7%)
Perianal (p)	34 (35.8%)
Extraintestinal manifestations; n, %	***51 (53%)***
Joint manifestations	39 (40.6%)
Previous intestinal resections; n, %	41 (41.8%)
Harvey-Bradshaw index; median, IQR	***8 (6-10)***
CDAI; median, IQR	***200 (170-235)***
CRP (mg/L); median, IQR	1 (0.4-3)
Faecal calprotectin (mg/Kg); median, IQR	550 (332.1488)

Therapies	
Number of patients	98
Previous therapy; n, %	
Mesalazine	61 (62%)
Steroids	89 (91%)
Thiopurines (AZA/6MP)	81 (82.6%)
Methotrexate	48 (49%)
Failure previous biological therapies; n, %	
Naïve	1 (1.1%)
1 failure	42 (42.8%)
2 failure	36 (36.7%)
3 o more failures	19 (19.4%)
Reason of initiation ustekinumab; n, %	
Steroids refractory	3 (3%)
Steroid dependency	43 (50%)
Clinical activity	69 (72.5%)
Extraintestinal manifestations	30 (31.6%)
Perianal disease	12 (12.6%)
Concomitant therapies; n, %	
Mesalazine	21 (21.8%)
Steroids	27 (27.5%)
Thiopurines	13 (13.9%)
Methotrexate	2 (2.0%)

Harvey-Bradshaw index at baseline; n, %	
Remission (HBI≤4)	11 (11,2%)
Mild disease (HBI 5-7)	28(28,6%)
Moderate disease (HBI 8-16)	48 (48,9%)
Severe disease (HBI>16)	4 (4,1%)
ND	7 (7,1%)

Table 2. Univariate and multivariate analysis. OR: Odds ratio. CI: confidence interval.

*** statistically significant.**

Corticosteroid-free clinical remission at 3 months	Univariate analysis			Multivariate analysis		
	OR	**95% CI**	***p-value***	**OR**	**95% CI**	***p-value***
Age	1.039	0.991-	0.117	1.026	0.979-	0.284
Sex						
Male	Ref			Ref		
Female	Mujer	0.688	0.241-	0.484	-	-
Smoking status						
Smoker	1.118	0.302-	0.868	-	-	-
No smoker and former	Ref.			Ref.		
Harvey Bradshaw index	0.731	0.596-	0.003*	0.876	0.714-	0.202
Faecal Calprotectin (mg/Kg)	1.000	0.998-	0.521	-	-	-
Perianal disease	0.302	0.069-	0.111	0.761	0.214-	0.673
Corticosteroid-free clinical remission at 6 months	**Univariate analysis**			**Multivariate analysis**		
	OR	**95% CI**	***p-value***	**OR**	**95% CI**	***p-value***
Age	1.000	0.960-	0.842	-	-	-
Sex						
Male	Ref			Ref		
Female	3.89	1.19-	0.025*	3.600	0.870-	0.077
Smoking status						
Smoker	1.538	0.359-6.599	0.562	-	-	-
No smoker and former smoker	Ref.			Ref.		
Harvey Bradshaw index	0.90	0.79-	0.121	0.906	0.751-	0.301
Faecal Calprotectin (mg/Kg)	1.00	1.00-	0.401	-	-	-
Perianal disease	1.23	0.34-4.44	0.750	-	-	-
Corticosteroid-free clinical remission at 12 months	**Univariate analysis**			**Multivariate analysis**		

	OR	95% CI	*p-value*	OR	95% CI	*p-value*
Age	1.010	0.935-	0.806	-	-	-
Sex						
Male	Ref			Ref		
Female	1.286	0.292-	0.740	-	-	-
Smoking status						
Smoker	5.091	0.518-	0.163	-	-	-
No smoker and former	Ref.			Ref.		
Harvey Bradshaw index	0.829	0.691-	0.043*	-	-	-
Faecal Calprotectin (mg/Kg)	0.999	0.997-	0.149	-	-	-
Perianal disease	3.316	0.353-31.158	0.294	-	-	-

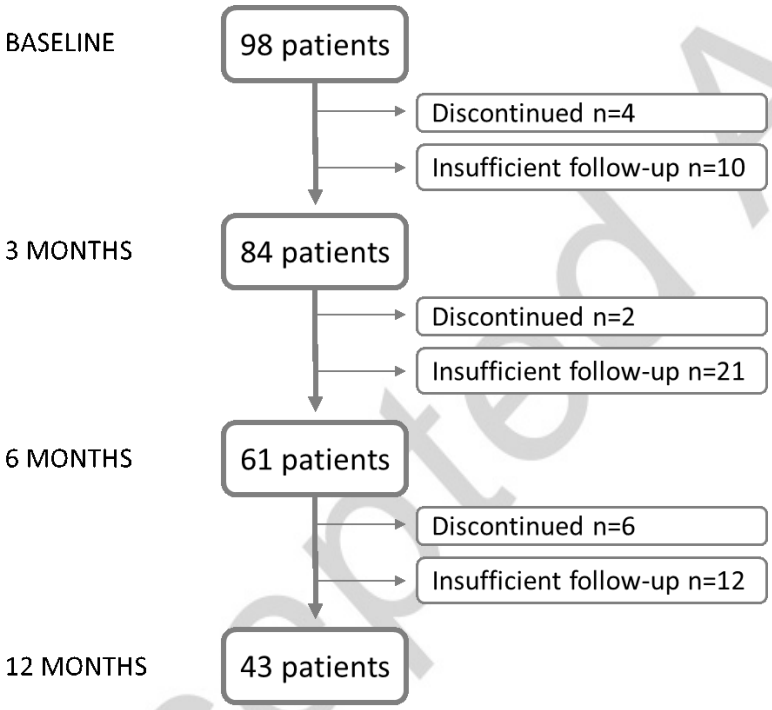

Figure 1. Flow chart of the patients included in the study.

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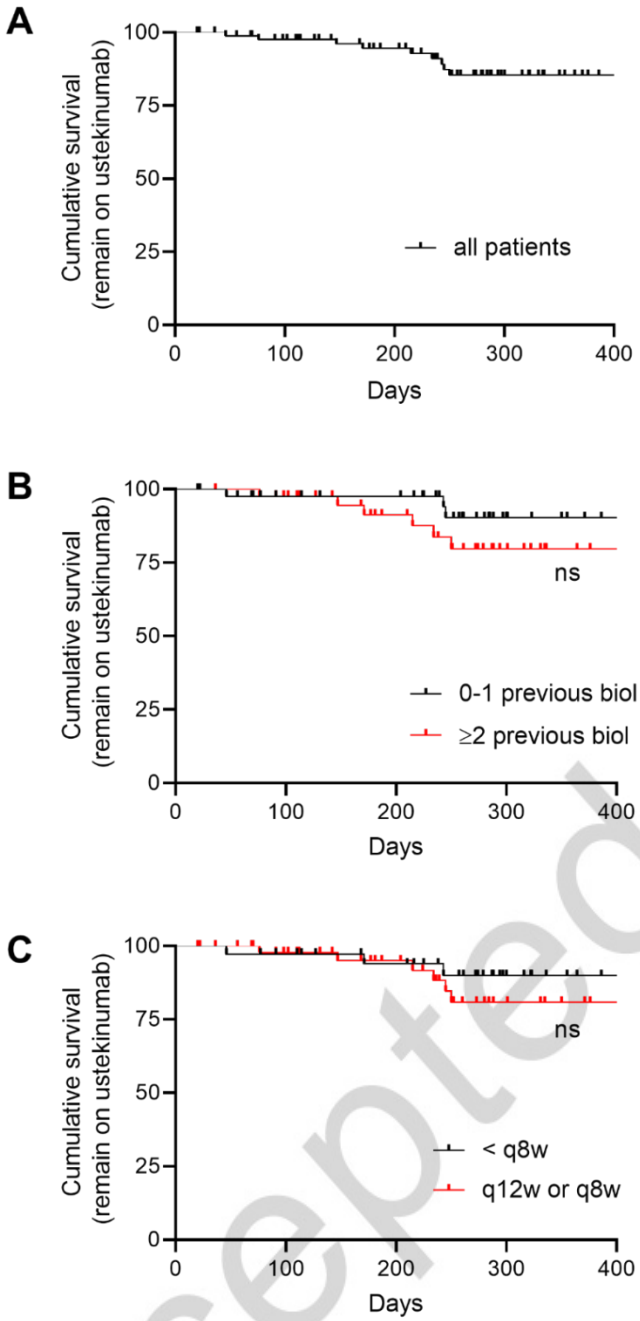

Figure 2. Kaplan-Meier survival curve for the probability of maintaining Ustekinumab treatment at 12 months. Biol: biological treatment.

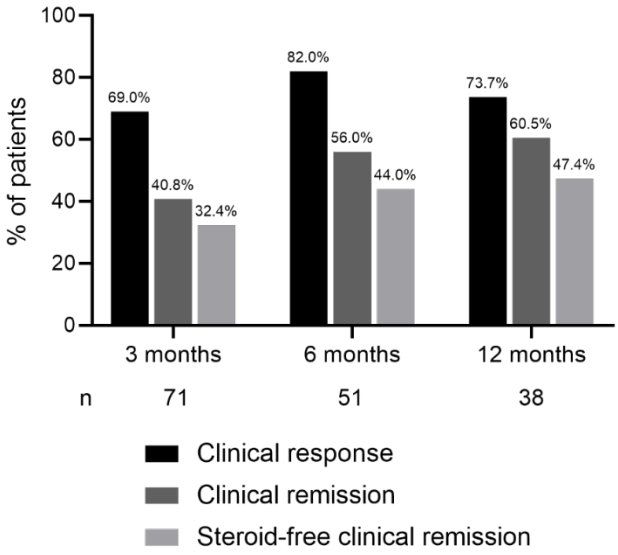

Figure 3. Proportion of patients in clinical response (reduction of at least 3 points in HBI from baseline), clinical remission (HBI≤4), and steroid-free clinical remission. Patients in clinical remission at baseline were excluded from the analysis.

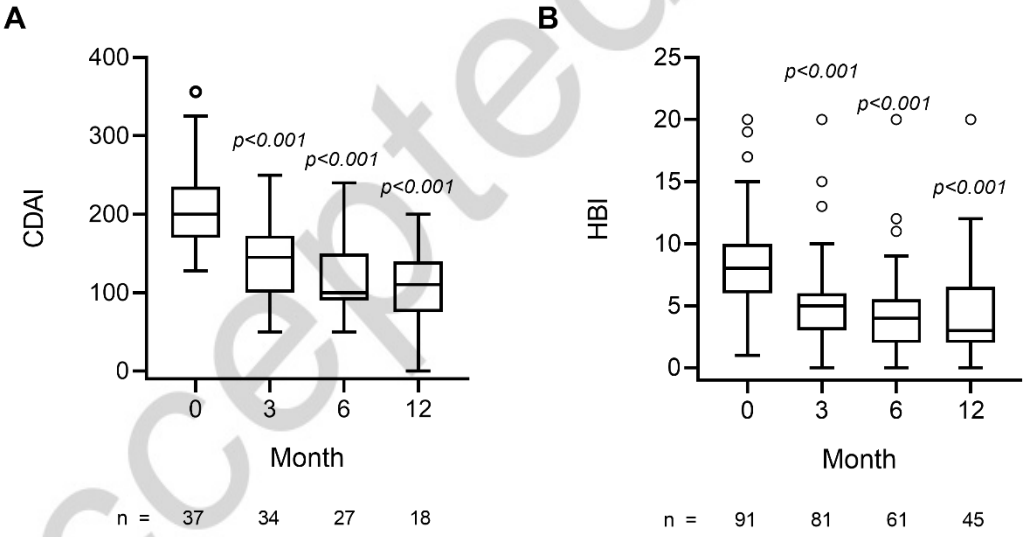

Figure 4. A: median CDAI. B: median HBI. Box represents median with interquartile 25th–75th range; whiskers show 10th–90th percentile range; dots show values beyond defined percentiles. For the statistical analysis, follow-up visits were compared to baseline.

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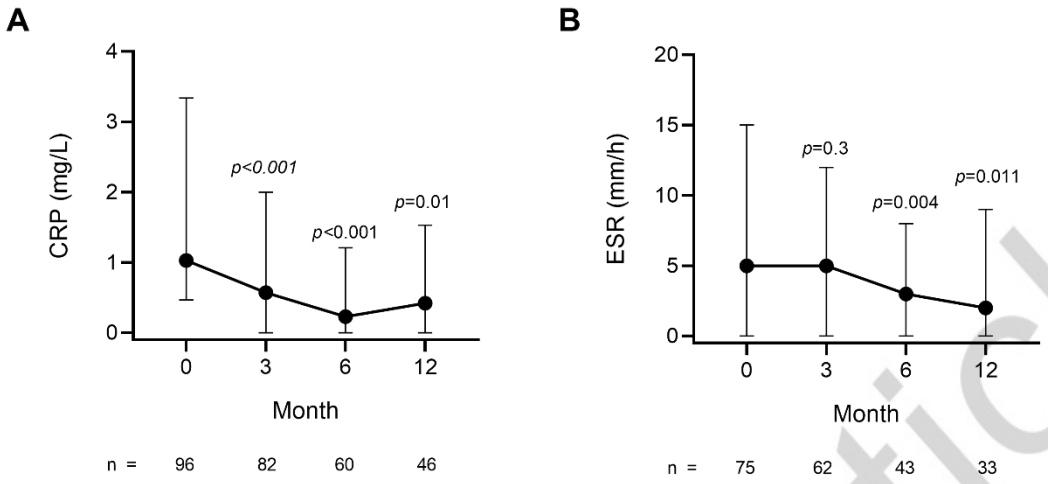

Figure 5. Mean concentration of C-reactive protein (CRP) and mean erythrocyte sedimentation rate (ESR). Error bars represent the standard deviation. For the statistical analysis, follow-up visits were compared to baseline.