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Real-life efficacy and safety of Ustekinumab as second- or third-line therapy in Crohn's disease: results from a large Italian cohort study

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Abstract. – OBJECTIVE: Ustekinumab (UST) is an anti-IL12/23 antibody for the treatment of Crohn's Disease (CD). The aim of this study was to compare the efficacy and safety of UST in a large population-based cohort of CD patients who failed previous treatment with other biologics.

PATIENTS AND METHODS: 194 CD patients (108 males and 86 females, mean age 48 years

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(range 38-58 years) were retrospectively reviewed. 147 patients were already treated with anti-TNFα (75.8%), and 47 (24.2%) patients were already treated with anti-TNFα and vedolizumab. Concomitant treatment with steroids was present in 177 (91.2%) patients.

RESULTS: At week 12, clinical remission was achieved in 146 (75.2%) patients. After a mean follow-up of 6 months, clinical remission was maintained in 135 (69.6%) patients; at that time, mucosal healing was assessed in 62 (31.9%) patients, and it was achieved in 33 (53.2) patients. Three (1.5%) patients were submitted to surgery. Steroid-free remission was achieved in 115 (59.3%) patients. Both serum C-Reactive Protein and Fecal Calprotectin (FC) levels were significantly reduced with respect to baseline levels during follow-up.

A logistic regression, UST therapy as third-line therapy (after both anti-TNFα and vedolizumab), FC >200 μg/g, and HBI ≥8 were significantly associated with lack of remission.

Adverse events occurred in 5 (2.6%) patients, and four of them required suspension of treatment.

CONCLUSIONS: UST seemed to be really effective and safe in CD patients unresponsive to other biologic treatments, especially when used as second-line treatment.

Key Words:
Adverse events, Anti-TNFα, Clinical remission, Crohn's disease, Mucosal healing, Ustekinumab.

Introduction

One of the two main forms of Inflammatory Bowel diseases (IBDs) is the Crohn's disease (CD), that may occur due to a complex relationship between genes and environmental factors[1]. The clinical course of the disease is characterized by a relapsing and remitting course, and an aggressive therapeutic approach is often required in order to prevent complications occurrence[1]. Following the discovery of the key pathogenetic role in IBDs of tumor necrosis factor α (TNFα)[1], monoclonal anti-TNFα antibodies have been developed and successfully used. However, a significant number of primary responders relapse in spite of treatment continuation or dose escalation, leading to a substantial rate of early discontinuation of these therapies[2-5]. Thus, novel therapeutic agents targeting alternative disease mechanisms have been required and, therefore, developed.

Ustekinumab (UST) is a monoclonal antibody blocking the p40 subunit of the anti-interleukin (IL) 12/23[6]. It showed significant efficacy and safety to treat any form of chronic arthritis[7]. Since IBD and chronic arthritis share several pathogenetic mechanisms, researchers tried to use UST in managing IBD, in particular in managing CD. Two controlled studies (CERTIFI e UNITI-IM) showed significant efficacy and safety of UST in managing CD patients[8-10], and recent real-life studies have confirmed its efficacy also in daily practice[11-18].

On September 2018 UST has been approved by the Italian Regulatory Agency (AIFA, Agenzia Italiana per il Farmaco) for the treatment of CD refractory to other treatments, including anti-TNFα antibodies[19]. We aimed to assess the efficacy and safety of UST in CD patients as second- or third-line treatment for CD in real-life daily clinical practice. We set out also to identify clinical parameters that may influence the response to UST.

Patients and Methods

This study consisted of a retrospective, observational, multicenter study on CD outpatients who failed biological therapies (including anti-TNFα antibodies and vedolizumab) and were treated with UST (Stelara™) in 25 Italian IBD centres (recognized by The Italian National and Regional Health Systems). All patients completing at least the induction treatment until 31st December 2019 were included.

Men and women, at least 18 years of age, and having an established diagnosis of CD according to standard endoscopic and/or radiology and/or histological criteria (1) were considered eligible.

We built a common shared database to collect demographic and clinical data. In particular, at baseline, we collected the following data: gender, age at diagnosis, disease duration, presence of comorbidities, appendectomy, disease extension, smoking status, Harvey-Bradshaw Index (HBI), Simple Endoscopic Score for CD (SES-CD), C-Reactive Protein (CRP), fecal calprotectin (FC) levels, concomitant medications at baseline, and prior immunosuppressive therapies (including biologics). Patients were clinically assessed at entry, after 2, 3, 6, and then every 6 months. Patients without clinical and biochemical baseline and at 8-12-week data were excluded.

The study was conducted according to the clinical practice guidelines. All patients gave written informed consent. The present study follows the principles of the Declaration of Helsinki. Ethic Committee approval was obtained by "Brotzu" Hospital (Cagliari, Italy; PROT. PG/2020/9414, April 29, 2020).

Study treatment

All patients were treated uniformly during induction with a baseline intravenous infusion according to the weight ranges: <55 kg: 260 mg, 55-85 kg: 390 mg, >85 kg: 520 mg. After induction, subcutaneous UST 90 mg was administrated every 8 weeks in order to maintain remission.

The need of treatment discontinuation, as well as the need for dose escalation, was left to the investigators' judgment. Also, concomitant medications, such as oral and topical aminosalicylates, steroids and/or immunosuppressants, were left to the investigators' judgment.

Clinical assessment

The Montreal classification was used to assess the disease extension (20), and the Harvey-Bradshaw Index (HBI) (21) score was used to assess the severity of the disease. All the patients included in the study had active disease, defined as HBI score >5 points (21), despite concomitant treatment.

Clinical assessment of the patients was performed at entry, after 2, 3, 6, and then every 6 months.

Endoscopy

The participating centers adopted the same protocol for the endoscopic assessment of the patients under treatment with biologics. Ileo-colonoscopy was therefore performed in all the enrolled patients at entry, after 6, 12 and every 12 months thereafter during treatment. Patients having upper gastrointestinal location of the CD underwent both esophagogastroduodenoscopy and ileo-colonoscopy: if upper gastrointestinal location was the only location of the disease, the patients underwent just esophagogastroduodenoscopy during follow-up.

Finally, Simple Endoscopic Score for CD (SES-CD) (22,23) was used to assess the endoscopic severity of the disease.

End-points

We assessed the following primary end-points:

- reaching of clinical remission, defined as HBI ≤5 at 3-month follow-up (24);
- safety of UST, defined as the absence of adverse events (AE) during treatment.

We subdivided the AEs as early (occurring during infusion), and late (occurring at least one week after the infusion) events and graded them as mild (not requiring to stop treatment) and severe (requiring to stop treatment). If opportunistic infections occurred, they were also considered as an AE. They were defined as any infection caused by microorganisms that, in normal conditions, have limited pathogenic capacity but can have the chance to cause disease due to the predisposing effect of another disease or its treatment[25].

Secondary endpoints were:

- reduction of CRP and FC during the study and at 6-month follow-up;
- reaching of mucosal healing (MH), defined as SES-CD score ≤2, during the study and at 6-month follow-up;
- steroid-free remission during the study and at 6-month follow-up;
- occurrence of any surgical procedure related to the disease;
- need of dose escalation (namely increases of doses infused/injected or shortening of the time between two injections).

Statistical analysis

MedCalc® Release 14.8.1 (Ostend, Belgium) was used to analyze data. The median interquartile range (IQR) for continuous non-parametric variables was used to analyze the characteristics of the study group and as number (percentage) for categorical variables. The categorical variables were compared by using Fisher's exact test. We considered the clinical remission at 2-month follow-up as the primary end-point. Associations of clinical remission with dichotomic variables were assessed in binary logistic regression models. Multivariate analysis was performed after univariate analyses, for significant associations. Multivariate models were obtained by simultaneous entering of all the input variables and using a p-value > 0.1 for removal from the model. The Odds ratios (OR) are presented with 95% confidence intervals (CI) and p-values. An OR higher than unity implies a higher probability of event compared to the reference group. The Friedman test was used to investigate any change of CRP and FC levels during follow-up. P-values < 0.05 were considered statistically significant.

Results

Baseline Characteristics

Baseline characteristics of the study group are reported in Table I. The indication to UST was the failure of previous therapy with biologics: 147 patients were submitted to previous therapy with anti-TNFα (75.8%), while 47 (24.2%) subjects assumed both anti-TNFα and vedolizumab. Con-

Table I. Demographic and clinical characteristics of the study group at enrolment.

Characteristics	Ustekinumab (n=194)
Sex, female	86 (44.3)
Age, years	48 (38-58)
CD duration, years	13 (7-22)
CD duration > 10 years	105 (54.1)
Previous appendectomy	48 (24.7)
Current smoking	43 (22.2)
Co-morbidities	74 (38.1)
Previous therapy	
Mesalazine	127 (65.5)
Steroids	148 (76.3)
Azathioprine	97 (50.0)
Methotrexate	24 (12.4)
Biologics	
Anti-TNF-α	147 (75.8)
Anti-TNF-α + vedolizumab	47 (24.2)
Age > 40 years	132 (68.0)
Location	
Ileal	50 (25.8)
Colonic	37 (19.1)
Ileocolon	105 (54.1)
Isolated upper disease	2 (1.0)
Behaviour	
Non-stricturing, non-penetrating	87 (44.8)
Stricturing	87 (44.8)
Penetrating	20 (10.3)
Perianal disease	27 (13.9)
Extraintestinal diseases*	24 (12.4)
C-reactive protein, mg/L	12 (5-22)
Fecal calprotectin, µg/g	234 (150-482)
HBI	8 (7-11)
SES-CD	11 (9-13)
Indication for ustekinumab	
Primary failure of biologics therapy	52 (26.8)
Secondary failure of biologics therapy	98 (50.5)
Allergy to biologics	15 (7.7)
Loss of response to biologics	10 (5.2)
Adverse event	3 (1.5)
Sepsis	7 (3.7)
Paradox reaction	9 (4.6)

CD: Crohn disease; HBI: Harvey-Bradshaw Index; SES-CD: Simple Endoscopic Score-Crohn's Disease. *17 articular disease, 4 erythema nodosum, 1 uveitis, 1 sclerosing cholangitis; 1 hidradenitis suppurativa.

comitant treatment with steroids was present in 177 (91.2%) patients.

Clinical Outcome

At the end of induction, clinical remission was achieved in 146 (75.2%) patients, by 116/147 (78.9%) patients treated with UST as second-line therapy, and by 30/47 (63.8%) patients treated as third-line therapy (p=0.037).

The patients were followed up for an average mean period of 6 (6-12) months, and clinical remission was maintained in 135 (69.6%) patients up to 6 months.

At that time, MH was assessed in 62 (31.9%) of patients, and it was achieved in 33 (53.2%) of patients; moreover, steroid-free remission was achieved in 115 (59.3%) patients. Dose adjusting (reduction of injection to every 4 weeks) was necessary in one patient.

Twenty-seven (13.9%) patients had active perianal disease at UST initiation, and twenty-one patients (77.8%) had setons placement. Nineteen (70.9%) have been already treated with anti-TNFα, and eight (29.6%) have been already treated with anti-TNFα plus vedolizumab. The mean follow-up of those patients was 12 months. At the end of follow-up, clinical remission was obtained in 14 (51.9%) of patients with seton withdrawal.

Three (1.5%) patients were submitted to surgery. All of them suffered from ileo-colonic disease (one patient already treated with anti-TNFα, and two already treated with anti-TNFα plus vedolizumab) and underwent surgery due to failure to respond to UST.

Both serum CRP and FC levels were significantly reduced with respect to baseline levels during follow-up (Figure 1 and Figure 2).

Predictors Of clinical remission

The factors associated with remission at 2-month follow-up are reported in Table II.

At univariate analysis, previous therapy with both anti-TNFα and vedolizumab, presence of perianal disease, FC >200 µg/g and HBI ≥8 was significantly associated with lack of remission.

At logistic regression therapy with both anti-TNFα and vedolizumab, FC >200 µg/g, and HBI ≥8 was significantly associated with lack of remission.

Evolution of Extraintestinal Diseases With Ustekinumab Treatment

As reported in Table I, extraintestinal diseases occurred in 24 patients (12.3% of the overall population): 17 (79.8%) articular disease (9 ankylosis spondylarthritis, 3 rheumatoid arthritis, 5 seronegative arthritis), 4 (16.7%) erythema nodosum, 1 (4.2%) uveitis, 1 (4.2%) sclerosing cholangitis; 1 (4.2%) hidradenitis suppurativa. Twenty (83.3%) have been already treated with anti-TNFα, and four (16.7%) have been already treated with an-

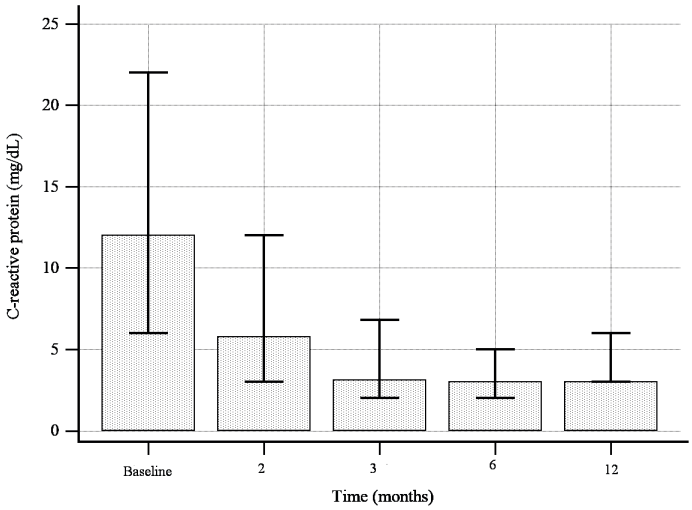

Figure 1. C-reactive protein over time in the study group. A significant decrease with respect to baseline was observed (p<0.000, Friedman test).

ti-TNFα plus vedolizumab. The mean follow-up of those patients was six months.

Three patients with ankylosis spondylarthritis and all patients with seronegative arthritis patients reported arthralgia at UST initiation, and it disappeared in all patients at the six-month of treatment. Surprisingly, one patient with ankylosis spondylarthritis in remission at UST initiation developed de novo significant arthralgia at month 3.

The patient suffering from sclerosing cholangitis had the disease under remission at UST initiation, and no occurrence of cholangitis was reported during the follow-up. Patients with the other extraintestinal diseases (erythema nodosum, uveitis, and hidradenitis suppurativa) had active disease at UST initiation, and remission of the diseases was obtained in all of them.

Adverse Events

Adverse events occurred in 5 (2.6%) patients. One patient suffered from blood hypertension without the need to stop UST therapy. Four patients had a severe adverse event during therapy: allergy, sacro-ileitis, Herpes zoster infection, and psoriatic arthritis.

Discussion

We present data from the first large Italian multicenter cohort study reporting the real-life

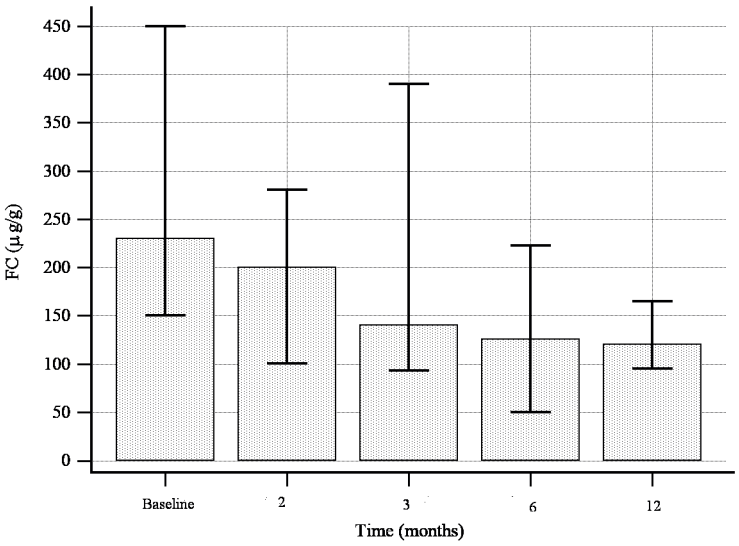

Figure 2. Fecal calprotectin over time in the study group. A significant decrease with respect to baseline was observed (p<0.050, Friedman test).

Table II. Predictors of clinical remission in CD patients at 2-month follow-up.

	Remission	No remission	Univariate OR (95%CI)	*p*	Multivariate OR (95%CI)	*p*
Number	146 (75.2)	48 (24.8)				
Sex, female	63 (43.2)	23 (47.9)	1.21 (0.63-2.33)	0.565	1,66 (0.76-3.64)	0.200
Disease duration ≥ 10 years	79 (54.1)	26 (54.2)	0.99 (0.52-1.92)	0.994	0.67 (0.29-1.52)	0.338
Previous appendectomy	34 (23.3)	14 (29.2)	0.74 (0.35-1.53)	0.637	0.85 (0.36-1.99)	0.707
Smoking	31 (21.2)	12 (25.0)	0.81 (0.38-1.74)	0.587	1.24 (0.47-3.30)	0.658
Co-morbidities	52 (35.9)	18 (40.0)	0.84 (0.42-1.66)	0.616	0.56 (0.21-1.51)	0.257
Previous exposure to anti-TNFα						
Anti-TNFα	116 (79.5)	31 (64.6)	Reference	Reference		
Anti-TNFα +vedolizumab	30 (20.5)	17 (35.4)	0.47 (0.23-0.96)	**0.037**	0.40 (0.17-0.93)	0.033
Age > 40 years	102 (69.9)	30 (62.5)	1.39 (0.70-2.75)	0.344	1.68 (0.71-3.95)	0.235
Location						
Ileal	38 (26.0)	12 (25.0)	Reference	Reference		
Colonic/Ileocolonic	108 (74.0)	36 (75.0)	0.95 (0.45-2.01)	0.888	1.66 (0.64-4.35)	0.298
Behaviour						
Non-stricturing, non-penetrating	63 (43.2)	24 (50.0)	Reference	Reference		
Stricturing/penetrating	83 (56.8)	24 (50.0)	1.32 (0.68-2.53)	0.409	1.84 (0.77-4.37)	0.167
Perianal disease	16 (11.0)	11 (22.9)	0.41 (0.18-0.97)	**0.038**	0.46 (0.16-1.34)	0.155
Extraintestinal disease	16 (11.0)	8 (16.7)	0.61 (0.24-1.54)	0.299	0.75 (0.20-2.83)	0.678
C-reactive protein > 10 mg/dL	86 (58.9)	24 (50.0)	1.43 (0.74-2.76)	0.281	1.94 (0.86-4.38)	0.109
Fecal calprotectin >200 µg/g	78 (53.4)	34 (70.8)	0.47 (0.23-0.95)	**0.035**	0.41 (0.17-0.96)	0.039
HBI ≥8	80 (54.8)	38 (79.2)	0.32 (0.15-0.69)	**0.003**	0.25 (0.10-0.63)	0.003
SES-CD >11	64 (43.8)	23 (47.9)	0.85 (0.44-1.63)	0.623	0.69 (0.32-1.52)	0.364

OR, odd ratio; CI, confidence interval; HBI, Harvey-Bradshaw Index; SES-CD, Simple Endoscopic Score-Crohn's Disease.

clinical practice management of CD patients with UST after failure of other therapies with biologics. Patients had a long-standing disease, and most of them had failed at least one biological agent before initiation of UST. A major strength of this study is the nationwide inclusion of centers in Italy administrating UST after approval from Italian Authorities, enrolling a large real-life population.

Our cohort differs from the patients included in the pivotal studies demonstrating the efficacy and safety of UST in CD. In fact, the UNITI-1 trial included patients nonresponders or with unacceptable side-effects to anti-TNFα, while patients in the UNITI-2 trial were either naïve to biologics or anti-TNFα experienced without failing and in the IM-UNITI less than half (44%) of the patients had prior treatment with anti-TNFα[8-10].

In this study we assessed two main endpoints, namely the reaching of remission and the safety of UST in CD patients already exposed to biological treatments. We obtained a significantly high remission rate, higher than 75%, and it was maintained in almost 70% of patients at 6-month follow-up. Also, the safety was excellent in our cohort, because AEs occurred in only 5 (2.6%) patients. These results are in line with that reported by a preliminary Italian experience in using UST in CD. Pugliese et al[18] found that the cumulative probability of remission at 6 months was 84.7%, a remission rate not too far from our findings. These Italian experiences are significantly better than the ones reported by two recent meta-analyses. The first study found eight relevant real-life studies, enrolling 578 patients (97.7% already treated with anti-TNFα). Pooled remission rate was 39% at 24 weeks and pooled endoscopic response rate was 63% after about one year of treatment; 134 (21%) AEs were collected, they were severe in 19 patients (5%)[26]. The second study analyzed thirteen observational studies enrolling 1450 patients (the range of patients previously treated with anti-TNFα ranged from 68.5 to 100%). At induction, UST was administered subcutaneously in 7 studies and intravenously in 6 studies; at induction, the pooled estimate rate of remission was 34%; at maintenance, the pooled estimated rates of remission was 40%; the pooled estimated rate of total AEs was 19.1%[27]. The remission rate in the Italian studies seem to be quite different also from two recent real-life studies from Belgium and United States, in which a lower rate of clinical remission and a higher rate of adverse events were re-

corded[12,17]. It is not easy to explain these results. Both Pugliese et al[18] and our findings reported the higher remission rate in CD patients treated with UST, we can speculate that this is due to specific characteristics of the Italian population. This hypothesis is reinforced by the multivariate analysis. For example, we did not find any significant influence of the disease location in responding to UST, while severity of the disease in terms of HBI score, FC levels and use of multiple biologics are independent factors for therapy failure. It is also possible that high remission rate achieved could be due to most patients were under corticosteroid treatment. However, the steroid-free remission rate during the follow-up was also high, suggesting that UST was effective independently to steroids, not only in a short-term course to reach remission.

Significantly, duration of the disease and other factors such as smoking are not significant factors for therapy failure, confirming a finding already reported in our previous research in treating CD patients with vedolizumab[29]. Overall, these findings lead to two important conclusions. The first one is that UST seems to be very effective in reaching remission even in patients already treated with more than one monoclonal antibody. This is confirmed also by the very low number of patients requiring dose escalation to reach remission (just one patient). The second one is that UST may work better whether it is administered in CD patients after a first treatment with an anti-TNFα and not after multiple failure with monoclonal antibodies. In other words, UST seems to work better when used in CD patients with active disease and as second line treatment.

Our results seem to differ also about the safety. AEs occurred in only 5 patients (2.6%), a rate significantly lower than the one reported in other experiences[12,17,26,27]. Again, it is not easy to explain these findings, and difference in the characteristics of the Italian population may explain this. About the AEs requiring stopping treatment, two patients had occurrence of arthritis during therapy (one had sacro-ileitis, and one had psoriatic arthritis). This is an AE already reported in the literature[12,29,30], and likely linked to a paradoxically activation of immune system.

With respect to the secondary end-points, UST obtained a significant MH, achieved in 33/62 (53.2%) of patients (again, a rate similar to that reported by Pugliese et al[18]) and significant steroid-free remission, achieved in 115/177 (59.3%) patients. Just one patient required dose adjusting, and only three (1.5%) patients were submitted to surgery. Finally, both CRP and CF significantly dropped under treatment with UST. Overall, these results were better than the ones reported in other studies[12,17,26,27], even if the low number of patients undergoing to colonoscopy may have influenced our results. Thus, UST seems to be able to reach significant improvement of several parameters that confirm its significant efficacy also in CD patients who have already failed the treatment with other biologics.

This study has some limitations. The first limitation is its retrospective nature, that could induce an overestimation of the positive response and an underestimation of adverse events. This last point may be particularly true especially for mild adverse events, that may be not reported by investigators. However, we had few missing data, and the large population enrolled seem to overcome this limit. The second limit is that UST was probably maintained also in some patients without adequate clinical response due to the absence of other therapeutic options, since all patients were previously treated with other biologics. Hence, the rate of primary nonresponders could be overestimated. The third limit is that endoscopic data assessing mucosal healing were available only in one third of patients. However, it has been already reported that the early (3-6 months) endoscopic monitoring of treatment in patients who achieve clinical remission in the real-life does not reflect that of randomized studies and recommendation of international guidelines[5]. Again, also the rate of MH may have been overestimated. Finally, also FC analyses could be difficult due to different cut-offs and variability in methods of measurement among the centers involved in this study.

Conclusions

This large, real-life study confirms the efficacy and safety of UST in CD patients with prior exposure to anti-TNFα ± vedolizumab, especially in patients with mild-to moderate disease and when used as second-line biologic therapy. Finally, few adverse events were observed, showing therefore good tolerability.

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Drafted the article or revised it critically for important intellectual content

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Final approval of the version to be submitted

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Conflict of Interest

The Authors declare that they have no conflict of interests.

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