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Effectiveness and safety of ustekinumab induction therapy for 103 patients with real-world ulcerative colitis: A GETAID multicentre cohort study

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Keywords: ulcerative colitis; ustekinumab; induction therapy; effectiveness; safety.

Abbreviations: UC: Ulcerative colitis; CRP: C-reactive protein ; PRO: patient reported outcome ; UCEIS: Ulcerative Colitis Endoscopic Index of Severity

Conflicts of interest:

Aurelien Amiot received consulting fees from Abbvie, Hospira, Janssen, Tillotts, Pfizer, Takeda, Gilead and Biocodex as well as lecture fees and travel accommodations from Abbvie, Janssen, Biocodex, Hospira, Ferring, Pfizer, Ferring, Tillotts, Takeda and MSD. This author also received advisory board fees from Gilead, Takeda and Abbvie.

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Vered Abitbol received lecture fees from Biogen Amgen Sandoz Mylan Pfizer Takeda Janssen Gilead Tillots

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ABSTRACT

Background: Phase III trials have demonstrated the efficacy and safety of ustekinumab in moderate-to-severe ulcerative colitis (UC), but few real-life data are currently available.

Aim: To assess short-term effectiveness and safety of ustekinumab in patients with UC.

Methods: From January to September 2019, all patients with UC treated with ustekinumab in 20 French GETAID centres were retrospectively included. The primary outcome was steroid-free clinical remission (partial Mayo Clinic score ≤ 2) at weeks 12–16 without a rectal bleeding subscore > 1.

Results: Among the 103 patients included, 70% had been previously exposed to ≥ 2 anti-TNF agents and 85% to vedolizumab. At weeks 12–16, steroid-free clinical remission and clinical remission rates were 35.0% and 39.8%, respectively; the absence of rectal bleeding with normal stool frequency was noted in 19.4% of patients. Two patients discontinued ustekinumab before the week 12–16 visit and underwent surgery. In multivariable analysis, a partial Mayo Clinic score > 6 at inclusion (18.6% vs. 46.7%, p=0.003) and a history of both exposure to anti-TNF and vedolizumab therapies (27.3% vs 80.0%, p=0.001) were negatively associated with steroid-free clinical remission at weeks 12–16. Adverse events occurred in 7.8% of patients and serious adverse events in 3.9% of patients.

Conclusion: In a cohort of highly refractory patients with UC with multiple prior drug failures, ustekinumab provided steroid-free clinical remission in one-third of cases at weeks 12–16. Clinical severity and previous use of anti-TNF and vedolizumab therapies were associated with ustekinumab failure at weeks 12–16.

INTRODUCTION

Ulcerative colitis (UC) is a chronic inflammatory disease of the large intestine [1]. 5-Aminoslicylates, conventional immunosuppressants, tumour necrosis factor (TNF) antagonists and vedolizumab are the main therapeutic agents to obtain clinical and endoscopic remission and prevent disability [2]. These current therapies are limited by increased risks of infection or cancer, as well as by a lack of effectiveness [3,4]. Primary non-response is observed in up to 30% of patients during anti-TNF or vedolizumab therapies and up to 40% of patients who initially respond to the induction regimen will subsequently fail to show a response over time [5–7]. There is a growing demand for novel therapeutic agents targeting alternative disease mechanisms.

Ustekinumab (Janssen Biotech Inc., Horsham, PA, United States), a fully human IgG1 monoclonal antibody targeting the IL-12/IL-23 shared p40 subunit, was recently approved for the treatment of psoriasis, psoriatic arthritis, and Crohn's disease. In a phase III trial for the treatment of moderate-to-severe UC, ustekinumab induced a response at 8 weeks and maintained clinical benefit through 52 weeks of treatment in patients who had an inadequate response or unacceptable side effects from corticosteroids, immunomodulators, anti-TNF agents or vedolizumab[12]. This robust data has driven the approval of ustekinumab by the European Medicines Agency for the treatment of patients with moderate-to-severe UC.

Only one study, including 19 patients, have reported the real-world effectiveness of ustekinumab in UC[8]. Real-world studies allow bridging of some data gaps by describing patient experiences that are lacking in clinical trials that tend to exclude certain groups of patients [9–11]. Real-world experience series bring important data on the effectiveness and safety of new therapeutic options.

The aim of this study was to evaluate the effectiveness and safety of ustekinumab in a multicentre open-label cohort of patients with UC failing conventional treatment.

PATIENTS AND METHODS

Study population

From January 2019 to September 2019, all French centres affiliated with the Groupe d'Etude Thérapeutique des Affections Inflammatoires du tube Digestif (GETAID) were asked to report consecutive patients with UC treated with ustekinumab. Exclusion criteria were age < 18 years, total or partial colectomy, or initiation of ustekinumab for an extra-intestinal manifestation. Ustekinumab was administered intravenously at a dose of 6 mg/kg at week 0 and followed by 90 mg injected subcutaneously every 8–12 weeks according to the investigator's decision and for up to week 16. Subcutaneous induction was also permitted if patients received at least a total dose of 270 mg during the first 8 weeks of treatment. The optimization of ustekinumab therapy at a dose of 90 mg every 4 or 8 weeks was allowed for an insufficient response, according to the investigator's decision. The concomitant use of steroids and/or immunomodulators for UC was recorded at every visit.

The protocol was approved by the Henri Mondor University Hospital Ethics Institutional Review Board (HMN IRB #00011558). All authors had access to the study data and reviewed and approved the final manuscript.

Data collection

Investigators from each participating centre were asked to complete a standardized questionnaire. An on-site visit was then conducted to collect missing data from patient records. The recorded data included patient demographics, a detailed account of the UC diagnosis and history, smoking status, UC phenotype according to the Montreal classification, and medical and surgical treatment history.

All included patients were followed according to routine practice. At the time of introduction of ustekinumab and at the week 12–16 visit, clinical activity was assessed using both the partial and total Mayo Clinic scores [12]. Routine laboratory tests results, including those for leukocyte count, haemoglobin, C-reactive protein (CRP) and albumin, were recorded to assess biological activity. Routine endoscopic assessment at baseline and at weeks 12–16 with the Mayo Clinic endoscopic subscore and Ulcerative Colitis Endoscopic Index of Severity (UCEIS) were also collected without central reading[12,13]. All adverse events occurring during the follow-up period were collected. Severe adverse events were defined as the occurrence of treatment interruption, hospitalization, disability, persistent damage, colectomy or death.

Outcome measures

The primary endpoint was steroid-free clinical remission at weeks 12–16. Clinical remission was defined as a partial Mayo Clinic score ≤ 2, with a combined stool frequency and rectal bleeding subscore ≤ 1. Secondary endpoints included clinical response, as defined by a reduction in the partial Mayo Clinic score of at least 3 points and a decrease of at least 30%, with a decrease of at least 1 point on the rectal bleeding subscale or an absolute rectal bleeding score of 0 or 1 from the baseline score for UC patients, persistence of ustekinumab therapy, dose optimization at weeks 12–16, endoscopic changes between week 0 and weeks 12–16 and occurrence of any adverse event or severe adverse event. The use of either oral and intravenous steroids or budesonide was assessed at the baseline visit and at every subsequent visit. No standardized protocol of steroid tapering and immunomodulatory maintenance was set up.

Statistical analysis

The data were expressed as a number (%) for qualitative data and as the mean ± standard deviation (SD) or median (interquartile range (IQR)) for quantitative data. Pre- and post-treatment

outcomes and clinical, biological and endoscopic scores were compared between week 0 and weeks 12–16 using the chi² test and Wilcoxon matched-pair signed-rank test whenever appropriate. All analyses were performed in an intent-to-treat manner. Patients who discontinued ustekinumab therapy before the week 12–16 visit were considered non-responders in all outcome measures. To identify predictors of steroid-free clinical remission at weeks 12–16, univariate analysis was conducted using the chi² test. Subsequent multivariable analyses using binary logistic regression models were then performed and adjusted for using the above-mentioned variables with an ascending stepwise procedure using the Wald test. The odd ratios (ORs) are provided with 95% confidence intervals (CIs). Quantitative values were converted to qualitative values using the difference from the median value in two distinct groups of equal size. Variables with $p < 0.10$ in the univariate analysis were considered to be potential adjustment variables for the multivariable analysis. All analyses were two-tailed, and p values < 0.05 were considered statistically significant. All statistical evaluations were performed using SPSS statistical software (SPSS Inc., v17, Chicago, IL, USA).

RESULTS

Study population

A total of 103 patients with active UC treated with at least one dose of ustekinumab were included in 20 GETAID centres (**Table 1**). The median age and duration of UC at week 0 was 39.3 [IQR 29.1–52.3] years and 7.6 [3.6–12.9] years, respectively. Most of the patients had left-sided colitis (41.8%) or pancolitis (52.4%). A history of immunomodulator, anti-TNF or vedolizumab therapies was noted in 84.5%, 99.0% and 85.4% of the cases, respectively. The mean partial Mayo score was 5.9 ± 1.9 at week 0. Endoscopic assessment was available in 93 (90.3%) patients at week 0 with a mean value of 2.6 ± 0.6 for the Mayo Clinic endoscopic subscore and 5.1 ± 1.3 for the UCEIS, resulting in a mean total Mayo Clinic score of 8.5 ± 2.1. Concomitant steroid and immunosuppressant use was noted in 48.5% and 23.3% of the cases, respectively.

The ustekinumab induction therapy was delivered with a 6 mg/kg intravenous regimen in 93 (90.3%) patients and with three scheduled subcutaneous injections of 90 mg between week 0 and week 8 in 10 patients. The mean total dose of ustekinumab during the induction phase was 376 ± 110 mg, corresponding to a dose of 5.4 ± 1.3 mg/kg. All patients were scheduled to receive a 90 mg dose at week 8 after the induction phase.

Effectiveness of ustekinumab therapy at weeks 12–16

All 103 patients were assessed at weeks 12–16, including 58 (56.3%) at week 12, 26 (25.2%) at week 14 and 19 (18.4%) at week 16. Two patients discontinued ustekinumab before the week 12–16 visit due to lack of efficacy and were referred for surgery. The primary endpoint, defined by steroid-free clinical remission at weeks 12–16, was achieved in 36 patients (35.0%) (Table 2). Among the 50 patients with concomitant steroids therapy at baseline, 14 (28%) were in steroids

free clinical remission at weeks 12-16. Clinical remission, defined by a partial Mayo Clinic score ≤ 2 with a combined stool frequency and rectal bleeding subscore ≤ 1, was achieved in 41 (39.8%) patients. Clinical response was observed in 55 (53.4%) patients at week 12-16. The global partial Mayo Clinic score decreased between week 0 and weeks 12–16 by a total of 2.3 ± 2.7 points (p = 0.04), whereas the global CRP level decreased by 7.6 ± 33.8 mg/L (p < 0.001). Regarding patient-reported outcomes (PROs) derived from the Mayo Clinic rectal bleeding and stool frequency subscores, rectal bleeding and stool frequency subscores of 0 were noted in 20 (19.4%) patients, whereas a rectal bleeding score of 0 and a stool frequency subscore of 0 or 1 were noted in 41 (39.8%) patients. Due to a lack of efficacy, 16 (15.5%) patients were optimized to four weekly 90 mg subcutaneous injections of ustekinumab before the week 12–16 visit. At the week 12–16 visit, ten (9.7%) patients discontinued ustekinumab due to lack of efficacy.

Endoscopic activity

Among the 93 patients with an assessment of endoscopic activity at week 0, 49 (47.6%) were also re-evaluated at weeks 12–16. The UCEIS significantly decreased from 5.0 ± 1.2 to 3.8 ± 1.9 (p < 0.001) and the Mayo Clinic endoscopic subscore decreased from 2.7 ± 0.5 to 2.2 ± 1.0 (p = 0.001). At weeks 12–16, eight out of 49 (16.3%) patients had a UCEIS score of 0 or 1, and nine (18.4%) had a Mayo Clinic endoscopic subscore of 0 or 1. Among patients with steroid-free clinical remission, the UCEIS and Mayo Clinic endoscopic subscore also decreased from 4.7 ± 1.3 to 1.8 ± 1.4 (p < 0.001) and from 2.5 ± 0.5 to 1.5 ± 1.1 (p = 0.001), respectively. In patients without steroid-free clinical remission, the decrease was much lower with a decrease in the UCEIS from 5.2 ± 1.1 to 4.7 ± 1.2 (p = 0.006) and non-significant in the Mayo Clinic Endoscopic subscore from 2.8 ± 0.4 to 2.5 ± 0.8 (p = 0.06).

Predictors of steroid-free clinical remission at weeks 12–16

Predictors of steroid-free clinical remission at weeks 12–16 were assessed with univariate and multivariable analyses (**Table 3**). In univariate analysis, the presence of steroid-free clinical remission was decreased with a partial Mayo Clinic score > 6 (p = 0.003), total Mayo Clinic score > 8 (p = 0.004), serum albumin level < 37 g/L (p = 0.03), and history of both exposure to anti-TNF and vedolizumab therapies (p = 0.001). In multivariable analysis, steroid-free clinical remission at weeks 12–16 was decreased in patients with a partial Mayo Clinic score > 6 (OR = 0.10, 95% CI [0.01–0.90]; p = 0.04) and history of both exposure to anti-TNF and vedolizumab therapies (OR = 0.03, 95% CI [0.01–0.42; p = 0.01).

Safety

The analysis of adverse events was performed for all patients who received at least one dose of ustekinumab (**Table 4**). Adverse events occurred in eight (7.8%) patients, including three patients with exacerbation of UC leading to hospitalization, one patient with arthralgia, one patient with symptomatic urolithiasis, one with pneumonia, one with a dental abscess and one with a skin rash. Serious adverse events occurred in four (3.9%) cases, including three cases of exacerbation of UC and one case of pneumonia leading to hospitalization. Adverse events led to ustekinumab withdrawal in three (2.9%) patients.

DISCUSSION

In this first large real-world study of ustekinumab in treating UC, we evaluated the effectiveness and safety of short-term induction with ustekinumab in patients with UC that have failed multiple biologics. The rates of steroid-free clinical remission and clinical remission were 35% and 40% at weeks 12–16, respectively. This was associated with evidence of biological and endoscopic response as well as a good safety profile.

Ustekinumab has been evaluated in patients with moderate-to-severe UC in one randomized placebo-controlled trial [14]. In the UNIFI trial, the efficacy and safety of ustekinumab were evaluated in 961 patients at week 8 after induction therapy with intravenous ustekinumab or placebo and at week 44 for maintenance therapy after responders were randomly assigned to subcutaneous injections of ustekinumab or placebo. Clinical remission at week 8 among patients who received intravenous ustekinumab at a dose of 130 mg (16%) or 6 mg per kilogram (16%) was significantly higher than that among patients who received placebo (5%). The percentage of patients who had clinical remission at week 44 was significantly higher among patients assigned to subcutaneous ustekinumab treatment every 12 weeks (38%) or 8 weeks (44%) as compared to those assigned to placebo treatment (24%). It should be noted that 50% and 15% of patients included in the UNIFI trial had experienced previous failure with an anti-TNF agent or vedolizumab, respectively. In UNIFI, ustekinumab was effective for induction and maintenance treatment in patients with previous exposure to biologics as well as in bio-naïve patients. But, as previously observed with other drugs, the rates of the different efficacy outcomes were consistently lower for patients with previous failure while on a biologic in each treatment group. In our cohort, the condition of the study population was more severe and refractory than in the UNIFI trial, with 99% and 85% of patients experiencing failure with an anti-TNF and vedolizumab, respectively.

We still observed a high rate of steroid-free clinical remission in one-third of patients. No data considering clinical remission according to the partial Mayo Clinic score are currently available from the UNIFI trial for comparison. It is conceivable that our study may be counterbalanced by less strictly defined clinical outcome measurements.

As recognized by the STRIDE committee and the US Food and Drug Administration's recognition, PROs, such as resolution of rectal bleeding and normalization of bowel habits, should be a therapeutic target for UC [15]. Complete normalization of rectal bleeding (rectal bleeding subscore of 0) and stool frequency was noted in 19% of patients, whereas normalization of rectal bleeding with a stool frequency subscore of 0 or 1 was noted in 40% of patients. Another therapeutic goal in patients with UC is to induce endoscopic improvement. Inducing endoscopic improvement is another main therapeutic goal, with better subsequent long-term outcomes in patients with UC achieving mucosal healing (16). Our study demonstrated a clinical improvement of both the Mayo Clinic endoscopic subscore and UCEIS. We acknowledge a recruitment bias in the endoscopic assessment. Indeed, only approximatively half of patients had endoscopic assessment of mucosal healing at the end of the induction phase. Furthermore, the rate of patients with either the Mayo Clinic endoscopic subscore or UCEIS of 0 or 1 was close to those reported in the UNIFI trial. Those data emphasize the objective improvement of patients with UC treated with ustekinumab and show that ustekinumab is an efficient therapeutic option in bio-failure patients.

Due to a lack of efficacy, 15% of patients were optimized to four weekly 90 mg subcutaneous doses of ustekinumab over the 12–16-week follow-up period. Even though no similar data over the induction period are available in Crohn’s disease, some retrospective studies reported that up to 50% of patients need dose escalation to optimize their primary response to ustekinumab

induction therapy [16]. The need and effectiveness of ustekinumab optimization to every 4 weeks dosing will require further study.

A decreased partial Mayo Clinic score > 6 and history of both exposure to anti-TNF and vedolizumab therapies were identified as inversely associated with the occurrence of steroid-free remission at weeks 12–16. In both Crohn's disease and UC phase 3 clinical trials, the rates of clinical response and remission at induction were higher in patients who had failed or were intolerant to conventional therapy as compared to patients who had failed anti-TNF therapy[14,17]. In Crohn's disease, there are no data from observational studies comparing the response to ustekinumab between anti-TNF naïve and exposed patients, since all patients included in these studies had failed or were intolerant to anti-TNF therapy [18]. As previously observed in Crohn's disease, concomitant use of an immunomodulator was not associated with the short-term efficacy of ustekinumab in UC.

The safety of ustekinumab in patients with chronic immune-mediated inflammatory diseases (IMIDs) has been extensively evaluated in numerous clinical trials and in post-marketing observational studies included in controlled trials [19–21]. In the UNITI trial, the incidence of serious adverse event with ustekinumab was similar to that with placebo. The most common adverse events were pyrexia, headache and nasopharyngitis; they were mild and did not require withdrawal of ustekinumab [14]. In the present study, short-term use of ustekinumab was found to be safe and well-tolerated, with four serious adverse events. No injection site reactions, deaths or malignancies were reported.

Our study has some limitations. Primarily, this was a retrospective analysis, which introduces the possibility of recall bias. We also acknowledge that during the study period,

ustekinumab could have been maintained because of a lack of other existing drugs to avoid surgery. We attempted to minimize this by using stringent, well-validated and objective definitions of clinical effectiveness as described by internationally endorsed recommendations [15]. Also, this study was conducted only over the induction period cohort without a control group. The biomarkers and pharmacokinetics of ustekinumab could not be assessed. However, this first observational cohort has some strengths, as it is a multicentre national study design, including all consecutive patients with UC treated with ustekinumab.

In conclusion, this first large multicentre real-world study of ustekinumab has shown that it is effective in inducing steroid-free clinical remission in one-third of patients with refractory UC with a good safety profile. Clinical severity and history of both exposure to anti-TNF and vedolizumab therapies are associated with a lower probability of steroid-free clinical remission.

TABLE LEGENDS

Table 1: Demographic, disease characteristics and medication histories of the 103 patients with ulcerative colitis at the time of introduction of ustekinumab therapy

Table 2: Outcome measures at weeks 12–16 for ustekinumab therapy in 103 patients with ulcerative colitis (RBS: rectal bleeding score; SFS: stool frequency score)

Table 3: Predictors of steroid-free remission at week 12-16 in 103 patients with ulcerative colitis treated with ustekinumab

Table 4: Adverse events affecting 103 patients with ulcerative colitis treated with ustekinumab therapy

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Table 1: Demographic, disease characteristics and medication histories of the 103 patients with ulcerative colitis at the time of introduction of ustekinumab therapy

Characteristic	**Patients with ulcerative colitis,** n = 103
Age, years	39.3 [29.1-52.3]
Male gender, n (%)	62 (60.2%)
BMI, kg/m²	24.3 ± 5.9
Smoking habits, n (%)	
Past smoker	30 (29.1%)
Active smoker	7 (6.8%)
Duration of disease, years	7.6 [3.6-12.9]
Age at diagnosis	
A1: ≤16 years	8 (7.8%)
A2: 17 – 40 years	68 (66.0%)
A3: > 40 years	27 (26.2%)
Location	
Proctitis	6 (5.8%)
Left-sided colitis	43 (41.8%)
Extensive colitis	54 (52.4%)
Prior medications exposure	
Immunosuppressant	87 (84.5%)
Purine analogues	85 (82.5%)
Methotrexate	25 (24.3%)
anti-TNF therapy	102 (99.0%)
One anti-TNF agent	30 (29.1%)
≥ 2 anti-TNF agents	72 (69.9%)
Vedolizumab	88 (85.4%)
Tofacitinib	10 (9.7%)
Clinical and endoscopic activity at week 0	
Partial Mayo Clinic score	5.9 ± 1.9
Mayo endoscopic subscore (n = 93)	2.6 ± 0.6

Total Mayo Clinic score (n = 93)	8.5 ± 2.1
Ulcerative colitis Endoscopic Index of Severity (n = 93)	5.1 ± 1.3
Concomitant medications	
Glucocorticoids only	41 (39.8%)
Immunosuppressants only	15 (14.6%)
Glucocorticoids and immunosuppressants	9 (8.7%)
No glucocorticoids or immunosuppressants	38 (36.9%)
Ustekinumab therapy	
Intravenous 6-mg/kg induction	93 (90.3%)
Subcutaneous 270-mg induction	10 (9.7%)
Total induction dose	376 ± 110
Total induction dose per kg	5.4 ± 1.3
Biologic variables	
Hemoglobin level, g/dL	9034 ± 3244
Leukocytes count, 10^9/L	13.1 ± 1.7
CRP level, mg/L	7.1 [3.1-15.0]
serum albumin, g/L	37.2 ±4.9

BMI: body mass index; CRP: high sensitivity C-reactive protein; TNF: tumor necrosis factor-α.

Variables are presented as n (%), mean ± standard deviation or median [interquartile range].

Table 2: Outcome measures from week 6 to week 54 for vedolizumab therapy in 173 patients with Crohn's disease and 121 patients with ulcerative colitis.

	No history of both exposure to anti-TNF and vedolizumab therapies (n = 15)	History of both exposure to vedolizumab and anti-TNF therapies (n = 88)	Overall study population (n = 103)	P
Clinical response	13 (86.7%)	42 (47.7%)	55 (53.4%)	0.005
Steroid-free clinical remission	12 (80.0%)	24 (27.3%)	36 (35.0%)	<0.001
Clinical remission	13 (86.7%)	28 (31.8%)	41 (39.8%)	<0.001
RBS 0 and SFS 0-1	11 (73.3%)	9 (10.2%)	20 (19.4%)	<0.001
RBS 0 and SFS 0	13 (86.7%)	28 (31.8%)	41 (39.8%)	<0.001

Clinical remission was defined as a partial Mayo Clinic score <3 with a combined stool frequency subscore (SFS) and rectal bleeding subscore (RBS) of ≤1. Clinical response was defined as a reduction in the partial Mayo Clinic score of at least 3 points and a decrease of at least 30%, with a decrease of at least 1 point on the rectal bleeding subscale or an absolute rectal bleeding score of 0 or 1 from the week 0 baseline score for patients with ulcerative colitis. The proportions of patients who met the criteria for the latter end points during the present trial of maintenance therapy were analyzed with the reference to the whole population included at week 0.

Table 3: Predictors of steroid-free remission at week 12-16 in 103 patients with ulcerative colitis treated with ustekinumab

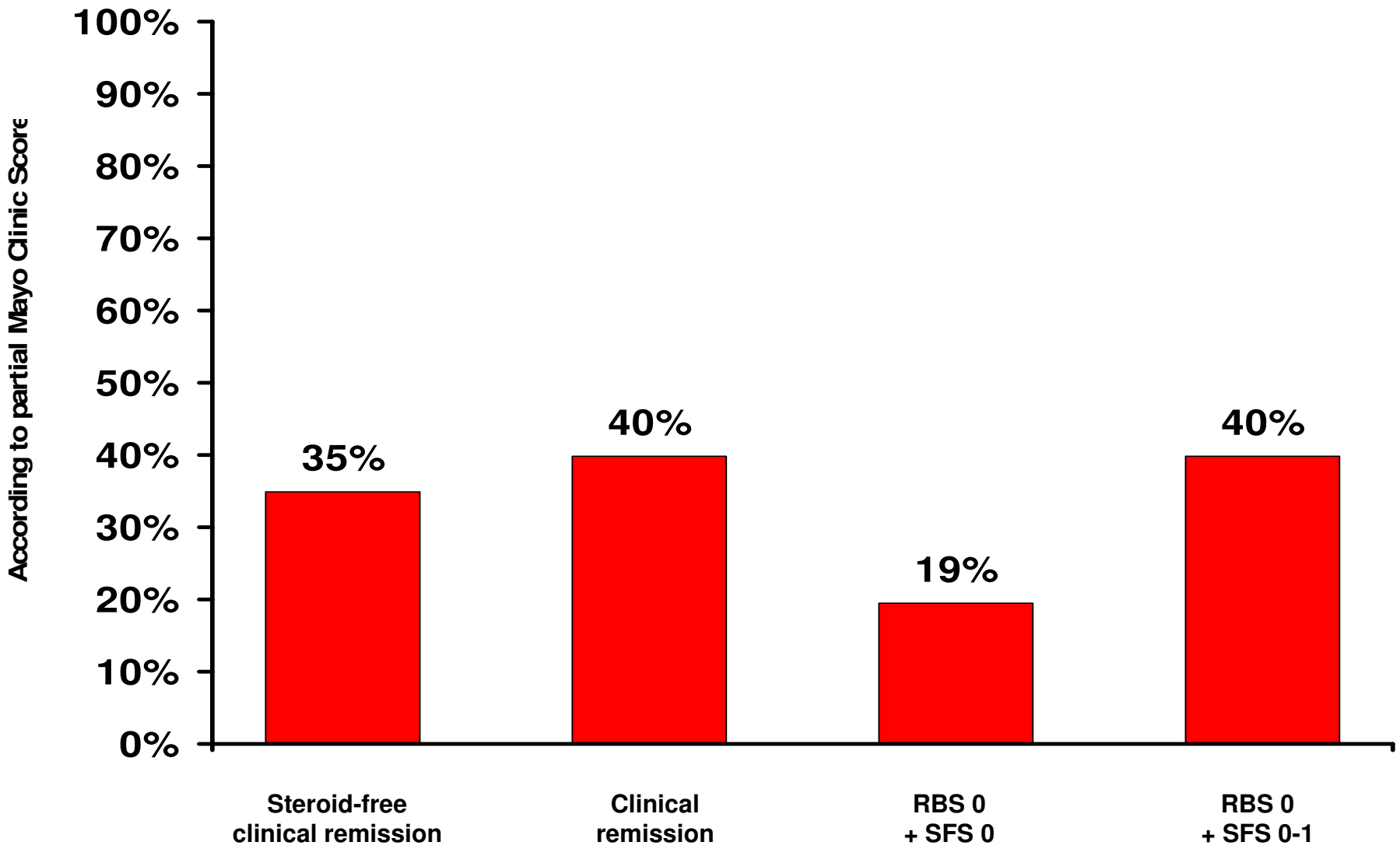
Risk factors	Univariate analysis		Multivariate analysis	
	OR (95%CI)	P value	OR (95%CI)	P value
Partial Mayo Clinic score > 6	0.24 [0.10-0.61]	0.003	0.10 [0.01-0.90]	0.04
Total Mayo Clinic score > 8	0.26 [0.10-0.65]	0.004	-	NS
Serum albumin level < 37 g/L	0.19 [0.05-0.83]	0.03	-	NS
History of anti-TNF and vedolizumab	0.10 [0.03-0.38]	0.001	0.03 [0.01-0.42]	0.01

Odd ratio (OR) with 95% confidence interval (CI) was estimated using Cox models

Table 4: Adverse events affecting 103 patients with ulcerative colitis treated with ustekinumab therapy

Event	Ulcerative colitis (n = 103)
Number of adverse events	8 (7.8%)
Arthralgia	1
IBD exacerbation	3
Pneumonia	1
Dental abscess	1
Skin rash	1
Symptomatic urolithiasis	1
Any serious adverse event*	4 (3.9%)
Any cancer	0

*A serious adverse event was defined as any adverse event when leading to treatment interruption, hospitalization, disability or persistent damage, colectomy and death.


According to partial Mayo Clinic Score
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
35%
40%
19%
40%
Steroid-free clinical remission
Clinical remission
RBS 0 + SFS 0
RBS 0 + SFS 0-1