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The impact of ustekinumab on extraintestinal manifestations of Crohn's disease: A *post hoc* analysis of the UNITI studies

Neeraj Narula[1] | Achuthan Aruljothy[1] | Emily C. L. Wong[1] | Ravi Homenauth[1] | Abdul-Aziz Alshahrani[1,2] | John K. Marshall[1] | Walter Reinisch[3]

[1]Department of Medicine (Division of Gastroenterology) and Farncombe Family Digestive Health Research Institute, McMaster University, Hamilton, Ontario, Canada

[2]Department of Gastroenterology, Najran University, Najran, Saudi Arabia

[3]Department of Internal Medicine III, Division of Gastroenterology and Hepatology, Medical University of Vienna, Vienna, Austria

Correspondence
Neeraj Narula, McMaster University Medical Centre, 1280 Main St West, Unit 3V67, Hamilton, ON L8S 4K1, Canada.
Email: Neeraj.narula@medportal.ca

Abstract

Summary: This post hoc analysis of the UNITI studies found ustekinumab (UST) did not significantly improve overall extraintestinal manifestations (EIMs) of Crohn's disease compared to placebo-treated patients at weeks 6 and 52.

Background and Aims: The UNITI trials demonstrated that UST was effective in inducing and maintaining clinical remission in Crohn's disease (CD). However, limited data exists regarding its effectiveness for treatment of EIMs. This *post hoc* analysis evaluated the efficacy of UST in treatment of EIMs.

Methods: Data from UNITI-1/2 and IM-UNITI (NCT01369329, NCT01369342, NCT01369355) were obtained from the Yale Open Data Access Project (2019-4104). Nine hundred and fourty-one patients eligible for UST induction and 263 patients eligible for maintenance UST were included. The primary outcome of interest was EIM resolution at Week 6 in UST and placebo-treated patients using the chi-square test. EIM resolution at Week 52 was also assessed. McNemar's test was used to compare the proportion of patients who reported active EIMs at weeks 6 and 52 versus baseline.

Results: From 941 UST-treated patients in UNITI-1/2, 504 had 527 EIMs at baseline. Overall, there was no significant difference in EIM resolution observed in UST-treated patients (186/504, 36.9%) compared to placebo (90/230, 39.1%; $p = 0.564$) at Week 6. Patients treated with continuous UST (91/119, 76.4%) had no significant difference in overall EIMs resolved at Week 52 compared to placebo (72/90, 80.0%; $p = 0.542$). Although many EIMs demonstrated reduction in prevalence compared to baseline at initiation of UST, only erythema nodosum was more likely to improve at Week 52 on treatment versus placebo.

Conclusion: Overall, UST did not lead to significant resolution of EIMs for CD compared to placebo at weeks 6 and 52.

KEYWORDS
Crohn's disease, extraintestinal manifestations, resolution, ustekinumab

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Key Summary

Summarise the established knowledge on this subject

- Summarise the established knowledge on this subject
- In a systematic review, ustekinumab was found to be effective in treating
- dermatologic manifestations such as psoriasis, pyoderma gangrenosum and erythema nodosum, and rheumatologic manifestations such as arthralgias and psoriatic arthritis in IBD
- However, existing evidence is limited due to retrospective evaluations, small sample sizes and lack of comparator groups
- Overall, there is a paucity of data regarding the effectiveness of ustekinumab for treatment of extraintestinal manifestations in Crohn's disease

What are the significant and/or new findings of this study?

- Patients with Crohn's disease treated with ustekinumab had overall no significant resolution of EIMs as compared to those treated with placebo at week 6 and week 52
- Among individual EIMs, only erythema nodosum was significantly reduced in patients treated with ustekinumab at week 52 compared to placebo-treated patients

INTRODUCTION

Crohn's disease (CD) usually presents with luminal symptoms such as elevated stool frequency and abdominal pain. Extraintestinal manifestations (EIMs) are frequently reported by patients and reflect the systemic nature of inflammatory bowel disease (IBD).[1,2] They are common in CD patients, with a prevalence from 6% to 47%, and have a substantial impact on morbidity and quality of life.[2,3] Patients with CD tend to have EIMs more frequently than patients with ulcerative colitis (UC), and data from the Swiss IBD cohort have shown that up to 25% of patients with IBD have multiple EIMs.[3,4]

EIMs can be broadly divided into musculoskeletal (axial or peripheral arthritis/arthralgias), dermatological [erythema nodosum (EN), pyoderma gangrenosum (PG), and Sweet's syndrome), ocular (scleritis, episcleritis, uveitis), hepatobiliary (primary sclerosing cholangitis [PSC]), hematological (anemia, thromboembolism) and less commonly renal and pulmonary manifestations.[1–3] Anemia in particular is very common, with a prevalence of 44%–74% at diagnosis and 25%–58% at one year follow-up, but is commonly under recognized and undertreated.[5] These EIMs are inflammatory conditions that follow either an independent trajectory or a parallel course to the luminal disease activity in IBD. Approximately 25.8% of patients present with EIMs prior to their diagnosis of IBD and the presence of one or more EIMs is associated with the development of additional EIMs.[6]

There have been several immunological mechanisms described regarding the pathogenesis of EIMs; however, it remains poorly understood. It has been proposed that antigen-specific immune responses from active luminal intestinal disease may also target nonintestinal sites.[7–9] Alternatively, EIMs may be independent inflammatory events that arise due to the same genetic or environmental factors that predispose patients to IBD.[10,11] Data from various studies and the European Crohn's and Colitis Organisation (ECCO) guidelines on EIMs have established the use of antitumor necrosis factor (anti-TNF), nonsteroidal anti-inflammatory drugs, and methotrexate as treatments for some of the manifestations listed above.[2,4,12]

Ustekinumab (UST) is a human IgG1κ monoclonal antibody that inhibits the biologic activity of cytokines interleukin-12 and interleukin-23 through their common p40 subunit, which are involved in the pathogenesis of CD. UNITI-1/2 and IM-UNITI demonstrated that UST was effective in inducing and maintaining clinical remission in moderate to severe CD patients.[13] UST has also demonstrated clinical efficacy in chronic plaque psoriasis or active psoriatic arthritis treatment.[14,15] A systematic review on UST for treatment of EIMs in IBD suggested that UST was effective, in particular for treatment of dermatologic manifestations such as psoriasis, PG and EN, and rheumatologic manifestations such as arthralgias and psoriatic arthritis.[16] However, the existing literature is limited due to mainly retrospective evaluations (eight of nine studies), small sample sizes (total of 254 patients included in the review) and lack of comparator groups. This *post hoc* analysis of UNITI-1/2 and IM-UNITI aimed to evaluate the efficacy of UST in treatment of EIMs in moderate-severe CD patients.

METHODS

Study design

Data from clinical trials of patients with moderate-severe active CD, UNITI-1 (ClinicalTrial.gov number: NCT01369329), UNITI-2 (NCT01369342), and IM-UNITI (NCT01369355) were obtained from the YODA (Yale Open Data Access #2019-4104) Project and by permission from Janssen Inc.[13] Data can be made available through the YODA Project. All authors had access to the study data and reviewed and approved the final manuscript.

Ethical considerations

The Hamilton Integrated Research Ethics Board determined that a local ethics review was not necessary because previously collected and de-identified data were being used.

Participants

The UNITI study designs and eligibility criteria have been previously published.[13] In summary, adult patients with moderate-severely active CD, defined as Crohn's Disease Activity Index (CDAI) score 220–450, were eligible if they had anti-TNF failure (UNITI-1), or loss of response/failure to conventional therapy (i.e., corticosteroids, 6-mercaptopurine, azathioprine, and methotrexate; UNITI-2).

Intervention

Participants were randomized in a 1:1:1 ratio to receive a single intravenous (IV) dose of either placebo, UST 130 mg IV, or UST approximately 6 mg/kg IV (weight-based dosing). The primary endpoint for the induction trials (UNITI-1/2) was clinical response (reduction in the CDAI of 100 points) at Week 6, at which point eligibility of participating in the maintenance study was determined.

At 8 weeks, patients who responded to IV UST in UNITI-1/2 were eligible to participate in IM-UNITI and be randomized in a 1:1:1 ratio to one of three subcutaneous (SC) maintenance treatment groups: placebo, UST 90 mg every 8 weeks, or UST 90 mg every 12 weeks. Subjects who responded to placebo IV infusion received placebo SC throughout the maintenance study. The primary endpoint for the maintenance trial was clinical remission (CDAI < 150) at Week 44 (or Week 52 from start of UNITI-1/2). The total study duration was 52 weeks (8 weeks for the induction studies and at 44 weeks for the maintenance study).

Variables and outcomes

Assessment of EIMs

The CDAI is a tool used to measure activity of CD and was used in the UNITI studies to assess symptomatic clinical response and remission.[17] The CDAI captures the presence or absence of EIMs, including: (1) anal fissure, fistula, or abscess; (2) aphthous stomatitis (AS); (3) arthritis or arthralgia; (4) EN; (5) fever (temperature >100°) during the previous 7 days; (6) iritis or uveitis; (7) PSC; and (8) PG. The CDAI was assessed at baseline prior to study initiation, at Week 6 after induction, and at week 52 after maintenance therapy. For this study, the presence of EIMs was assessed based on these individual components of the CDAI being reported as present or absent. However, anal disease such as fistula and abscesses are penetrating complications of CD as opposed to EIMs, so these were omitted from this analysis. Fever and AS are also not conventionally considered to be EIMs, so they were excluded for this analysis. Lastly, although PSC is considered an EIM of IBD, it is not known to be responsive to any treatments used for IBD.[18] Furthermore, magnetic resonance cholangiopancreatography or liver biopsy would need to be performed in order to assess for any improvement, which was not performed as part of this study, so PSC was also omitted from this analysis.

Definitions

"Prevalence" was defined as the presence of an EIM of interest at the respective visit. "Resolution" was defined as the absence of an EIM which had previously been reported as present. "*De novo*" was defined as the development of new or return of EIMs at weeks 6 or 52 of UST therapy that were not present at baseline.

Statistical analysis

Descriptive statistics were used to summarize baseline demographics and disease characteristics of CD patients. Patient characteristics were described using proportions for categorical variables. Continuous data were presented as means with standard deviations for parametric distributions and medians with interquartile ranges for nonparametric distributions.

Primary analysis

Our primary outcome of interest was overall EIM resolution between UST and placebo-treated patients at Week 6.

Secondary analysis

For secondary analyses, we evaluated overall EIM resolution in UST and placebo-treated patients at Week 52 using the chi-square test. This test was also used to compare resolution of individual EIMs, and de novo EIM development, at weeks 6 and 52. For Week 52 comparisons, patients treated with UST for induction and maintenance (UST/UST) were compared to patients who received placebo induction and maintenance (placebo/placebo), and those patients who were re-randomized (i.e., UST for induction and placebo for maintenance) were excluded.

We also used McNemar's test to find a change in the proportion of active EIMs (i.e., prevalence) at weeks 6 and 52 compared to baseline in UST-treated patients. Prevalence values were compared given that a portion of patients without EIMs at baseline can subsequently develop EIMs and vice versa. For Week 52 comparisons, prevalence of EIMs in UST/UST-treated patients at Week 52 was compared to baseline.

TABLE 1 Baseline characteristics of included patients

Patients included in UNITI studies	Ustekinumab (*n* = 941)	Placebo (*n* = 457)
Number of patients with EIMs	504 (53.6)	230 (50.3)
Age, mean (SD)	38.2 (12.8)	39.0 (12.6)
Male, *n* (%)	294 (41.6)	151 (40.8)
Disease duration in years, median (IQR)	5.4 (2.0–9.2)	6.1 (2.2–10.4)
Disease location, *n* (%)		
Ileal	136 (19.2)	67 (18.1)
Colonic	135 (19.1)	59 (15.9)
Ileocolonic	433 (61.2)	241 (65.1)
Proximal gastrointestinal tract	121 (17.1)	52 (14.1)
CD-related concomitant medications, *n* (%)		
Prednisone	131 (18.5)	98 (26.5)
Azathioprine	93 (13.2)	100 (27.0)
Budenoside	26 (3.7)	11 (3.0)
Mercaptopurine	26 (3.7)	16 (4.3)
Mesalazine	129 (18.2)	96 (25.9)
Methotrexate	37 (5.2)	33 (8.9)
Iron therapy, *n* (%)	60 (6.4)	20 (4.4)
Presence of perianal disease, *n* (%)	182 (25.7)	115 (31.1)
Prior use of TNF antagonists, *n* (%)		
Adalimumab	102 (14.4)	67 (18.1)
Certolizumab pegol	41 (5.8)	21 (5.7)
Infliximab	161 (22.8)	90 (24.3)
CDAI score at baseline, mean (SD)	312.9 (58.0)	308.4 (57.4)
EIMs, *n* (%)		
Arthritis/arthralgia	471 (50.1)	232 (50.8)
Erythema nodosum	28 (3.0)	10 (2.7)
Iritis/uveitis	23 (2.4)	16 (4.3)
Pyoderma gangrenosum	5 (0.5)	0

Abbreviations: CD, Crohn's disease; CDAI, Crohn's Disease Activity Index; EIM, extraintestinal manifestation; IQR, interquartile range; SD, standard deviation; TNF, tumor necrosis factor.

Subgroup analyses

Subgroup analyses using McNemar's test were performed to evaluate the impact of UST dosing regimens on EIM resolution at either weeks 6 or 52 of therapy. The following groups were compared:

1. Induction-dosing regimen (UST 130 mg IV or weight-based dosing of 6 mg/kg IV) at Week 6 compared to baseline
2. UST induction and maintenance dosing of 90 mg SC every 8 weeks or every 12 weeks at Week 52 compared to baseline.

Results are presented as *p*-values and statistical significance was chosen to be at a two-sided *p*-value <0.05. Data were analyzed using IBM SPSS Statistics version 23.0.

RESULTS

Demographics

A total of 941 patients were treated with UST in UNITI-1/2, of whom 504 (53.6%) had EIMs at baseline. Baseline characteristics from patients who had active EIMs at entry into UNITI-1/2 are presented in Table 1. There was a total of 527 EIMs among the 504 CD patients treated with UST who reported EIMs. Specifically, 339 (36.0%) patients had one EIM, 62 (6.6%) had two EIMs, 20 (2.1%) had three EIMs, and 1 (0.1%) had four EIMs. Baseline EIMs in UST-treated patients included: 471 (50.1%) patients with arthritis or arthralgia; 28 (3.0%) patients had EN; 23 (2.4%) patients had iritis or uveitis; and 5 (0.5%) had PG.

TABLE 2 Week 6 comparisons of EIM outcomes in ustekinumab and placebo-treated patients

EIM	UST, n/N (%)	Placebo, n/N (%)	*p*-value
Overall EIM resolution	186/504 (36.9)	90/230 (39.1)	0.564
Overall de novo EIMs among the treatment group	41/941 (4.4)	20/457 (4.4)	1.000
Individual EIM resolution			
Arthritis/arthralgia	151/471 (32.1)	75/232 (32.3)	0.504
Erythema nodosum	19/28 (67.9)	6/10 (60.0)	0.653
Iritis/uveitis	15/23 (65.2)	9/16 (56.3)	0.571
Pyoderma gangrenosum	1/5 (20.0)	0	N/A

Note: *n* = number of patients who report EIM resolution; *N* = number of patients with EIM at baseline.
Abbreviations: EIM, extraintestinal manifestation; UST, ustekinumab.

TABLE 3 Week 52 comparisons of EIM outcomes in patients treated with continuous ustekinumab compared to continuous placebo

EIM	UST/UST, n/N (%)	Placebo/Placebo, n/N (%)	*p*-value
Overall EIM resolution	91/119 (76.4)	72/90 (80.0)	0.542
Overall de novo EIMs among the treatment group	3/263 (1.1)	0/133 (0)	N/A
Individual EIM resolution			
Arthritis/arthralgia	89/129 (69.0)	44/72 (61.1)	0.258
Erythema nodosum	10/10 (100.0)	0/3	<0.0001
Iritis/uveitis	7/8 (87.5)	7/8 (87.5)	1.000
Pyoderma gangrenosum	0	0	N/A

Note: *n* = number of patients who report EIM resolution; *N* = number of patients with EIM at baseline.
Abbreviations: EIM, extraintestinal manifestation.

UST compared to placebo for EIM resolution at Week 6

There was no significant improvement in EIMs observed among patients treated with UST (186/504, 36.9%) compared to placebo (90/230, 39.1%) ($p = 0.564$) at Week 6. Patients treated with UST (41/941, 4.4%) developed similar de novo EIMs at Week 6 compared to placebo (20/457, 4.4%; $p = 1.0$). With regards to individual EIM resolution at Week 6, no significant improvements were observed for any of arthritis/arthralgias ($p = 0.504$), EN ($p = 0.653$), or iritis/uveitis ($p = 0.571$). No placebo-treated patients had PG so a comparison with placebo could not be performed. The results are outlined in Table 2.

UST compared to placebo for EIM resolution at Week 52

Patients treated with UST/UST (91/119, 76.4%) had no significant difference in overall EIMs resolved at Week 52 compared to the placebo/placebo group (72/90, 80.0%; $p = 0.542$). Development of de novo EIMs in the UST/UST group (3/263, 1.1%) was similar to that of the placebo/placebo group at Week 52 (0/133, 0%). With regards to individual EIM resolution at Week 52, EN ($p < 0.0001$) showed significant reductions in the UST/UST group compared to the placebo/placebo group, but no differences were observed in resolution of arthritis/arthralgias or iritis/uveitis. The results are outlined in Table 3.

Impact of UST on EIMs at Week 6 and 52 compared to baseline

Overall impact on EIMs

Among the 941 CD patients included in the UNITI-1/2 analysis who received UST at induction, there were 527 EIMs at baseline of which 186 resolved at Week 6 ($p < 0.0001$). In the IM-UNITI analysis, 263 CD patients received UST/UST. These patients reported 147 EIMs at baseline, of which 106 resolved at Week 52 ($p < 0.0001$). These results are outlined in Tables 4 and 5, and Figures 1 and 2.

Arthritis/Arthralgia

Among 941 patients who received UST at induction there were 471 (50.1%) with baseline arthritis/arthralgia of which 151 (16.0%) resolved at Week 6 ($p < 0.0001$). In the IM-UNITI analysis, 263 patients received UST/UST. Of 129 (49.0%) with arthritis/arthralgia at baseline, 89 (33.8%) resolved at Week 52 ($p < 0.0001$). Furthermore, 35 (3.7%) out of 941 patients who developed arthritis or arthralgia by Week 6. Only 3 (1.1%) out of 263 patients with no baseline arthritis/arthralgia reported this EIM at Week 52.

TABLE 4 Week 6 EIM outcomes after induction ustekinumab dose[a]

	Baseline	Week 6			
EIM	n/N (%)	Resolution n/N (%)	De novo EIM n/N (%)	Prevalence n/N (%)	*p*-value[b]
Arthritis/arthralgia	471/941 (50.1)	151/941 (16.0)	35/941 (3.7)	355/941 (37.7)	<0.0001
Erythema nodosum	28/941 (3.0)	19/941 (2.0)	1/941 (0.1)	10/941 (1.1)	0.002
Iritis/uveitis	23/941 (2.4)	15/941 (1.6)	4/941 (0.4)	12/941 (1.3)	0.019
Pyoderma gangrenosum	5/941 (0.5)	1/941 (0.1)	1/941 (0.1)	5/941 (0.5)	1.000
Total	527	186	41	382	<0.0001

Note: n = number of EIMs of interest; *N* = number of patients per protocol who received UST at induction.

Abbreviations: CD, Crohn's disease; EIM, extraintestinal manifestation; UST, ustekinumab.

[a]Among 941 CD patients who received UST at induction.

[b]*p*-value comparing prevalence of EIMs at week six to baseline.

TABLE 5 Week 52 EIM outcomes after induction and maintenance ustekinumab[a]

	Baseline	Week 6	Week 52			
EIM	n/N (%)	De novo EIM n/N (%)	Resolution n/N (%)	De novo EIM n/N (%)	Prevalence n/N (%)	*p*-value[b]
Arthritis/arthralgia	129/263 (49.0)	6/263 (2.3)	89/263 (33.8)	3/263 (1.1)	43/263 (16.3)	<0.0001
Erythema nodosum	10/263 (3.8)	0	10/263 (3.8)	0	0	0.002
Iritis/uveitis	8/263 (3.0)	1/263 (0.4)	7/263 (2.7)	0	1/263 (0.4)	0.070
Pyoderma gangrenosum	0	0	0	0	0	N/A
Total	147	7	106	3	44	<0.0001

Note: n = number of EIMs of interest; *N* = number of patients per protocol who received UST at induction and had clinical response at week 6 and subsequently received UST during maintenance.

Abbreviations: CD, Crohn's disease; EIM, extraintestinal manifestation; UST, ustekinumab.

[a]Among 263 CD patients who received UST at induction and maintenance.

[b]*p*-value comparing prevalence of EIMs at Week 52 to baseline.

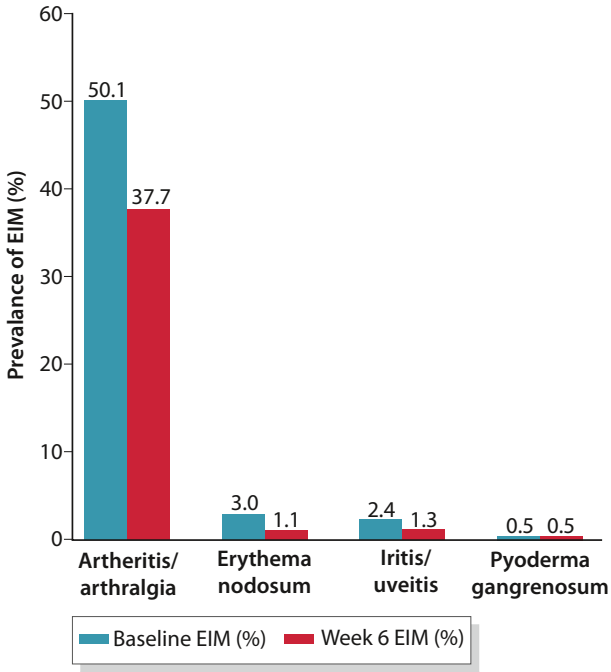

FIGURE 1 Prevalence of extraintestinal manifestation at Week 6 in ustekinumab-treated patients

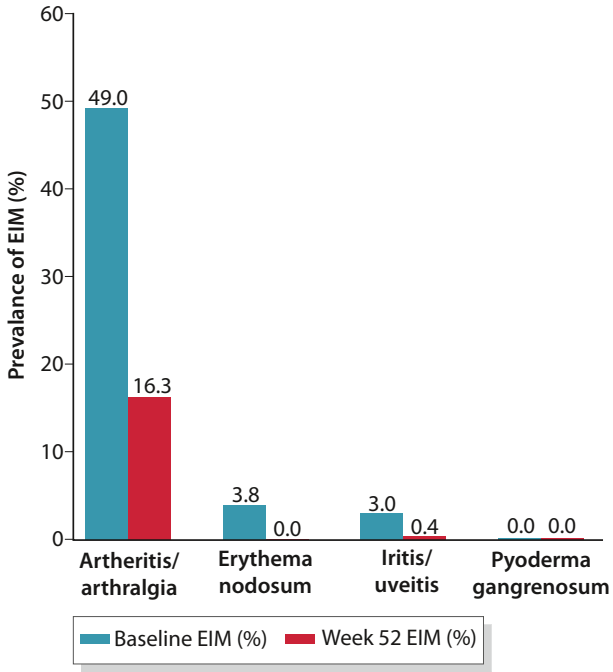

FIGURE 2 Prevalence of extraintestinal manifestation at Week 52 in ustekinumab-treated patients

Erythema nodosum

Among 941 patients who received UST at induction there were 28 (3.0%) with baseline EN of which 19 (2.0%) resolved at Week 6 ($p = 0.002$). In the IM-UNITI analysis, 263 patients received UST/UST. Of 10 (3.8%) with EN at baseline, 10 (3.8%) resolved at Week 52 ($p = 0.002$). Furthermore, 1 (0.1%) out of 941 patients with no baseline EN developed the EIM at Week 6. No patients developed the EIM at Week 52.

Iritis/Uveitis

Among 941 patients who received UST at induction there were 23 (2.4%) with baseline iritis/uveitis of which 15 (1.6%) resolved at Week 6 ($p = 0.019$). Out of the 263 patients who received UST/UST in the IM-UNITI analysis, there were eight (3.0%) with baseline iritis/uveitis, and seven (2.7%) resolved at Week 52 ($p = 0.070$). Furthermore, 4 (0.4%) out of 941 patients with no baseline EIM developed iritis/uveitis at Week 6. Of 263 patients who received UST/UST, 1 (0.4%) developed iritis/uveitis at Week 6 and no patients developed the EIM at Week 52.

Pyoderma gangrenosum

Among 941 patients who received UST at induction there were a total of 5 (0.5%) with baseline PG and one (0.1%) resolved at Week 6 ($p = 1.000$). No patients had baseline PG in the IM-UNITI analysis. Furthermore, one (0.1%) patient with no baseline EIM developed PSC at week 6 on UST induction therapy.

Impact of UST dosing regimen on EIM resolution

Subgroup analyses were performed evaluating the 309 patients who received UST 130 mg IV for induction only or the 316 patients who received UST weight-based dosing of 6 mg/kg (Tables S1 and S2). EIM resolution at Week 6 of UST treatment was similar in patients who received either induction-dosing regimen. Furthermore, similar EIM resolution at Week 52 of UST treatment was seen in both maintenance regimens, UST 90 mg SC every 8 or every 12 weeks (Tables S3 and S4).

DISCUSSION

In this *post hoc* analysis of UNITI-1/2 and IM-UNITI, UST-treated patients had no significant overall EIM resolution compared to placebo-treated patients at weeks 6 and 52. Overall, approximately half of the subjects had reported at least one EIM before induction, which is similar to what has been previously described.[19,20]

There is limited data for using UST to treat EIMs of IBD. There is high-quality evidence for the effectiveness of TNF antagonists and UST in psoriatic arthritis, specifically for enthesitis and dactylitis.[21,22] Real-life observational data support the use of UST for cutaneous EIMs (PG and EN) in IBD patients who have failed TNF antagonists.[23] Low-quality evidence has suggested some effectiveness of UST in patients with refractory uveitis who have failed to respond to TNF-inhibitors.[24,25] Conversely, there are no robust data for UST or other biologic therapies in treatment of PSC.[26]

For patients with CD and EIMs, TNF antagonists tend to be preferred by gastroenterologists, and the ECCO guidelines recommend the use of TNF antagonists for patients with CD patients with various EIMs.[2] A pooled analysis of 11 induction, maintenance, and open-label extension studies of ADA demonstrated that more than 50% of patients receiving ADA achieved resolution of any EIM and arthritis/arthralgia at 6 months and 1 year in a significantly greater proportion of ADA versus placebo.[19] The results from these studies were similar to the findings from our analysis when comparing prevalence of EIMs at weeks 6 and 52 compared to baseline in UST-treated patients.

However, overall EIMs were not significantly improved at weeks 6 and 52 compared to placebo. EN resolution at Week 52 was significant improved for UST-treated patients as compared to placebo, although EN tends to be transient and improvements could reflect luminal disease control, concomitant medication use (i.e., steroids), or chance alone. For some of the EIMs where no significant difference was seen (e.g., iritis/uveitis at Week 6), this could be due to low power to detect a difference although numerically higher resolution rates were seen in those treated with UST. For others (i.e., arthritis/arthralgia at Week 6), this might be due to differential use of concomitant therapies, as use of systemic steroids and immunomodulators was somewhat higher in those treated with placebo.

This study had several strengths. First, the UNITI studies were double-blinded, placebo-controlled trials, so patients reporting the absence or presence of EIMs were blinded to their treatment allocation. Second, the UNITI trials had a large sample size of patients with EIMs. Third, we were able to analyze and include a wide variety of EIMs within this analysis.

Our *post hoc* analysis of the UNITI trials had several limitations. First, the use of CDAI has not been validated as a measurement tool for EIMs specifically, nor does it measure severity of EIMs. It is possible EIMs could have improved but not resolved, which would not be captured within the CDAI. Furthermore, gastroenterologists performed these assessments, thus it is unclear if reported EIM findings would be reproducible if assessed by rheumatologists or dermatologists. Second, the UNITI trials included patients with a baseline CDAI of 220–450. Patients with milder symptoms, or very severe symptoms, were thus not enrolled, and this could also introduce selection bias into our analyses and affect generalizability of our findings. Studies using prospective data collected by physicians trained in assessment of these EIMs should be considered, using instruments dedicated to measurement of EIMs, in order to validate these findings. Third,

given the small proportion of CD patients with ocular or cutaneous EIMs at baseline, it is difficult to assess the effectiveness of UST on resolution of this EIMs. Finally, despite IM-UNITI assessing clinical endpoints until Week 52, the relative short-term nature of the study does not provide information on long-term UST effectiveness on EIM resolution.

CONCLUSION

The results of this *post hoc* analysis of moderate to severe CD patients suggest UST does not lead to improvement in overall EIM resolution as compared to placebo. Further controlled data using validated techniques with assessments performed by trained physicians should be considered to further explore whether UST could be an efficacious therapy for IBD patients with EIMs.

CONFLICTS OF INTEREST

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AUTHOR CONTRIBUTIONS

Neeraj Narula: Study concept and design, acquisition and compilation of data, statistical analysis, data interpretation, and drafting of the manuscript. Achuthan Aruljothy: Acquisition and compilation of data, statistical analysis, and drafting of the manuscript. Emily Wong: Acquisition and compilation of data, and statistical analysis. Ravi Homenauth: Drafting of the manuscript. Abdul-Aziz Alshahrani: Drafting of the manuscript. John K. Marshall: Study concept and design, and drafting of the manuscript; Walter Reinisch: Study concept and design, and drafting of the manuscript.

DATA AVAILABILITY STATEMENT

Data can be made available through the YODA Project.

ORCID

Neeraj Narula https://orcid.org/0000-0002-1536-8436
Emily C. L. Wong https://orcid.org/0000-0001-9472-201X

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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