A Single Center Experience With Long-Term Ustekinumab Use and Reinduction in Patients With Refractory Crohn Disease

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Background: Ustekinumab was approved for moderate and severe Crohn's disease (CD) in 2016, but little is known about long-term outcomes.

Methods: A retrospective study evaluated all patients with CD treated with ustekinumab, including patients with reinduction. C-reactive protein (CRP), Harvey-Bradshaw Index (HBI), Short Inflammatory Bowel Disease (SIBDQ), and endoscopy outcomes were collected prospectively.

Results: Ninety-six patients received ustekinumab, resulting in improvement in CRP, HBI, and SIBDQ scores with 68% endoscopic improvement/remission. Thirty-four patients underwent reinduction, resulting in improved HBI and CRP.

Conclusions: Ustekinumab in refractory CD results in significant clinical and endoscopic improvement and reinduction may be a viable option to recapture response.

Lay Summary: This study shows that ustekinumab can be used to improve symptoms and disease markers in patients with severe Crohn disease who have failed prior medications. The study also demonstrates that reinduction can help regain response if needed.

Key Words: Crohn disease, ustekinumab, reinduction, response

INTRODUCTION

Crohn disease (CD) is an autoimmune condition that leads to widespread inflammation in the gastrointestinal tract, manifesting symptoms of abdominal pain, diarrhea, and weight loss.[1] Treatment options for CD vary and often initially include steroids, immunomodulators, and biologic modulators such as anti-tumor necrosis factor (TNF) agents, anti-integrin agents, and now anti-IL-12/IL-23 agents.[2] Maintaining remission with CD can be difficult, as some patients are primary or secondary nonresponders, or become dependent on corticosteroids.[3,4] It is estimated that up to 40% of patients are primary nonresponders to anti-TNF agents, and of those who respond, another half lose their response to the medication or develop severe side effects.[3,4] In these patients with refractory CD, additional biologic agents that target alternative inflammatory pathways are needed.

Ustekinumab was Food and Drug Administration (FDA) approved in September 2016 for patients with moderate and severe CD. It is given initially as a weight-based intravenous (IV) infusion, followed by subcutaneous injections every 8 weeks. The drug is a human IgG monoclonal antibody that binds the p40 subunit of interleukins (IL) 12 and 23, decreasing the activation of inflammatory cytokines.[5,6] The reduction in proinflammatory cytokines leads to decreased production of Th1 and Th17 cells.[7] A Study to Evaluate the Safety and Efficacy of Ustekinumab Induction Therapy in Patients With Moderately to Severely Active Crohn's Disease (UNITI-2), a phase 3 clinical trial, compared ustekinumab to placebo and found a significant difference in the ability of ustekinumab to obtain remission, improve quality of life, and decrease inflammatory markers compared to placebo.[8] Unlike anti-TNF agents that have high rates of antibody development, the Study to Evaluate the Safety and Efficacy of Ustekinumab Maintenance Therapy in Patients With Moderately to Severely

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Active Crohn's Disease (IM-UNITI) phase 3 study showed only 2.6% of patients developed antibodies over the course of 52 weeks, leading to a much lower immunogenicity profile as compared to anti-TNF drugs.[9] In addition to having lower immunogenicity, ustekinumab is also well tolerated; in a study of safety in the Psoriasis Longitudinal Assessment and Registry trial with ustekinumab in psoriasis, there was no increased rate of adverse events or infections over placebo. Notably, there was no increased risk of malignancy or serious infections.[10]

The recent findings of ustekinumab in clinical and open label trials are encouraging regarding its ability to treat refractory CD. In a recent study by Iborra et al, which monitored short term effectiveness (14 weeks) of ustekinumab in refractory CD patients, they found that after 14 weeks, 47% of patients were able to achieve clinical remission.[11] Despite studies that show short term effectiveness of ustekinumab, the long-term "real-world" effects of ustekinumab, specifically in those who have failed multiple anti-TNF therapies and/or vedolizumab are not well studied. Additionally, there remains a lack of guidance for dose adjustment, escalation, or reinduction for those who have either primary or secondary loss of response to ustekinumab. Therefore, the goal of this study was to evaluate a subset of patients from a tertiary care inflammatory bowel disease clinic with moderate to severe CD. We evaluated patients who had previously failed anti-TNF agents, and subset of patients who had failed both anti-TNF and vedolizumab. Within this cohort of ustekinumab patients, we also studied those who underwent reinduction for loss of response or restart after interruption in dosing. These patients were monitored on ustekinumab to determine the effectiveness of obtaining and maintaining remission.

MATERIALS AND METHODS

A retrospective study including all patients with CD started on ustekinumab from September 2009 through November 2017 at Vanderbilt University Medical Center Inflammatory Bowel Disease Clinic. There were 96 patients in this study, all of whom had active disease refractory to other therapies. All 96 patients had failed prior anti-TNF therapy and 31 had also failed prior vedolizumab therapy. There were no exclusion criteria for this study. The outcomes measured included C-reactive protein (CRP), Harvey-Bradshaw Index (HBI), Short Inflammatory Bowel Disease Questionnaire (SIBDQ) scores, and presence of extraintestinal manifestations. These outcomes were measured at baseline and at follow-up, every 3–6 months after initiation of treatment. Endoscopic evaluation was determined in a subset of patients prior to ustekinumab start, based on provider discretion. Endoscopic improvement and remission was determined by changes in the prior area of most severe inflammation. The same endoscopist performed pre- and post-treatment endoscopy for each patient, allowing continuity of disease evaluation. Endoscopist documented improvement or remission as part of routine clinical care at each segment for each endoscopy. Histologic response was determined by improvement in active chronic inflammation, categorized as severe, moderate, or mild in the area of prior most severe inflammation. Histologic remission was determined by either chronic inflammation that was inactive or normal appearing tissue. The rates of adverse events and the need for hospitalization or surgical intervention were also documented. All information was gathered from patients' electronic medical record, including clinical care notes and endoscopic and serologic data. Statistical analysis was performed using χ^2 and Wilcoxon rank sum test.

Ninety-one of the 96 patients started ustekinumab prior to FDA approval and received induction of ustekinumab subcutaneously using novel dosing with ustekinumab 90 mg given subcutaneous at weeks 0, 4, and 12. Some patients also received a 270 mg dose at week 8 if no clinical response was noted, based on provider discretion. Standard maintenance therapy was 90 mg subcutaneous every 8 weeks. Within the 96 patients studied, 34 people underwent reinduction with ustekinumab. If patients had reinduction with ustekinumab prior to FDA approval of ustekinumab for CD, they received a modified reinduction with 270 mg given subcutaneously. For those patients who underwent reinduction after FDA approval, they received appropriate weight-based intravenous doses for reinduction.

Ethical Considerations

Institutional review board approval at Vanderbilt University Medical Center was obtained for this retrospective chart review.

RESULTS

A total of 96 patients were included in this study, with their demographics and characteristics summarized in Table 1. The median age of the patients was 37 years, with 50% female. Seventy-six percent of the patients had ileocolonic disease and greater than 50% of patients had either fistulizing, perianal, or stricturing disease. All of the patients had previously been treated with an anti-TNF agent and 60% of patients had been treated with multiple anti-TNF agents. In addition to anti-TNF therapy, 31 of the patients (32%) received prior treatment with vedolizumab. Thirty-three patients were on oral prednisone at the time of ustekinumab start. Additionally, of the 96 patients on ustekinumab, 43 patients were concurrently taking immunomodulator therapy.

Ustekinumab treatment resulted in improvement in CRP, HBI, and SIBDQ scores after a median of 62 days (range 30–340). CRP decreased significantly after starting ustekinumab ($P < 0.05$). HBI decreased, although this was not statistically significant, and SIBDQ decreased significantly ($P < 0.05$). A majority of patients had endoscopy before and after ustekinumab start (n = 51), with follow-up endoscopy occurring a median of 144 days after start (range 56–557). Thirty-five patients (68%) had endoscopic improvement and 13 (25%) had endoscopic remission. Twenty-nine patients (57%) had histologic response, defined by improvement from severe, moderate, or mild

inflammation on pathology, and 13 (25%) had histologic remission. In the subset of patients with prior vedolizumab and anti-TNF treatment, 56% of patients had endoscopic response, 17% had endoscopic remission, 50% had histologic response, and 22% had histologic remission (Tables 2 and 3).

Ustekinumab also improved extraintestinal manifestations. Of the 96 patients who received ustekinumab, 56 patients reported extraintestinal symptoms before starting the medication. Prior to ustekinumab use, 3 patients reported uveitis, 3 had oral lesions, 33 had joint symptoms, and 17 had skin lesions. After these 56 patients started ustekinumab, 16 (29%) reported improvement with joint symptoms and skin lesions. In a subset of the 31 patients who had previously failed anti-TNF and vedolizumab therapy, there were 17 that reported extraintestinal manifestations prior to ustekinumab use; 2 patients with oral lesions, 12 patients with joint symptoms, and 3 patients with skin lesions. Of this 17 patient cohort, 10 patients (59%) reported improvement in their joint symptoms and skin lesions. Despite improvement in other extraintestinal manifestations, no patient reported improvement in uveitis or oral lesions.

Thirty-four patients underwent reinduction with ustekinumab. Within this cohort 21 underwent modified reinduction with subcutaneous ustekinumab prior to FDA approval, and 13 received intravenous reinduction after FDA approval. These patients were followed for a median of 440 days (range 64–2196) after reinduction. For those who had intravenous reinduction the median follow-up was 282 days (range 64–605). Three patients (9%) underwent reinduction due to lapse in insurance approval of ustekinumab, 26 patients (76%) for active disease with loss of response, and 5 patients (15%) after surgery. Of the 26 patients who underwent reinduction for active disease with loss of response, 6 were for partial response and 20 were for secondary loss of response. Those with partial response underwent reinduction at a median of 132 days after ustekinumab start, with a range of 108–161 days. The 20 patients with secondary loss of response underwent reinduction at a median of 535 days after ustekinumab start, with a range of 216–1196 days. Of the patients who underwent ustekinumab reinduction, 6 (18%) were on oral prednisone at the time of reinduction and 13 (38%) were concurrently taking immunomodulators at the time of

TABLE 1. Patient Demographics and Characteristics for All 96 Patients Who Received Ustekinumab and for the 34 Patients Who Underwent Ustekinumab Reinduction

Characteristics	All Ustekinumab Patients (n = 96)	All Reinductions (n = 34)	Intravenous Reinduction Only (n = 13)
Median age (range)	37 (20, 72)	38 (21, 64)	43 (21, 52)
Female sex	48 (50%)	15 (44%)	5 (38%)
Disease type			
Ileal	4 (4%)	2 (6%)	1 (8%)
Colonic	9 (9%)	2 (6%)	1 (8%)
Ileocolonic	73 (76%)	29 (85%)	10 (77%)
Small bowel only	8 (8%)	1 (3%)	1 (8%)
Perianal only	2 (2%)	0 (0%)	0 (0%)
Perianal disease history	52 (54%)	18 (53%)	6 (46%)
Fistulizing disease history	52 (54%)	19 (56%)	6 (46%)
Stricturing disease history	57 (59%)	21 (62%)	7 (54%)
Surgical history			
None	23 (24%)	6 (18%)	4 (31%)
IC resection	24 (25%)	8 (24%)	2 (15%)
Partial colectomy	5 (5%)	1 (3%)	1 (8%)
Multiple	35 (36%)	18 (53%)	5 (38%)
Other	4 (4%)	1 (3%)	1 (8%)
Current smokers	14 (15%)	6 (18%)	5 (38%)
Prior anti-TNF use	96 (100%)	34 (100%)	13 (100%)
Multiple prior anti-TNFs	58 (60%)	30 (88%)	10 (77%)
Prior vedolizumab use	31 (32%)	10 (29%)	6 (46%)

TABLE 2. Improved Disease Activity Markers After Ustekinumab Use in All Patients (n = 96), Median of 62 Days (Range 30–340); and a Subset of Refractory Patients With Prior Vedolizumab Use (n = 31), Median of 85 Days (Range 45–260)

		All Ustekinumab Patients (n = 96)	Subset of Refractory Patients (n = 31)
CRP, median (range)	Before ustekinumab	7.8 (0, 187.56)	10 (2, 187.6)
	After ustekinumab	5.4 (0, 127.5)**	5.5 (0.1, 3.5)
HBI, median (range)	Before ustekinumab	6 (0, 27)	6 (0, 19)
	After ustekinumab	5 (0, 22)	4.5 (0, 22)
SIBDQ, median (range)	Before ustekinumab	46 (12, 70)	45 (12, 68)
	After ustekinumab	47 (10, 69)**	45 (10, 67)

Values are expressed as median along with ranges.
**P value < 0.05.

reinduction. Only 4 patients discontinued ustekinumab after subcutaneous reinduction at a median of 152 days (range 118–210) after reinduction: 2 stopped for surgery, 1 switched to infliximab, and 1 stopped given no response. All 13 patients who received intravenous reinduction with ustekinumab remained on ustekinumab by the end of the study period. Of the 34 patients who underwent reinduction, 13 patients also transitioned to every 4–6 week dosing after reinduction. Harvey-Bradshaw Index and CRP results decreased for all patients who underwent reinduction. In patients who underwent intravenous reinduction with ustekinumab, HBI decreased significantly ($P < 0.05$) as summarized in Table 4. Prior to IV reinduction, ustekinumab levels were collected in 5 patients with a median value of 1.6 µg/mL (range 0.4–4.9). Of these 5 patients, 2 patients had levels drawn after reinduction, 0.7 and 3.6 µg/mL, respectively. Of all 34 patients who underwent ustekinumab reinduction, 4 patients had ustekinumab levels after reinduction with a median value of 2.1 µg/mL (range 0.7–3.6). Fourteen patients had endoscopic evaluation after reinduction: 5 patients who had endoscopic inflammation on prior endoscopy were found to be in endoscopic remission, 2 patients had endoscopic improvement, and 7 patients had no change endoscopically.

In total of the 96 patients evaluated, 63 remained on ustekinumab at the end of the study period. Ustekinumab was stopped in 33 patients for reasons of: no response (n = 16), loss of response (n = 7), side effects (n = 5), or surgery (n = 5), after a median 172 days (range 4–955).

TABLE 3. Improved Endoscopic and Histologic Response and Remission After Ustekinumab Use in All Patients With Available Data (n = 51), Median 144 Days (Range 56–557), Including a Subset of Refractory Patients With Prior Anti-TNF and Vedolizumab Use (n = 18), Median 120 Days (Range 70, 480)

	All Ustekinumab Patients (n = 51)	Subset of Refractory Patients (n = 18)
Endoscopic response	35 (68%)	10 (56%)
Endoscopic remission	13 (25%)	3 (17%)
Histologic response	29 (57%)	9 (50%)
Histologic remission	13 (25%)	4 (22%)

DISCUSSION

This study found that ustekinumab is effective in a subset of patients with refractory CD with failure to multiple biologic medications. We also found that in a group of these patients who lose response, reinduction with ustekinumab can recapture response and allow for continuation of ustekinumab. Most patients were able to continue ustekinumab therapy throughout the follow-up period.

This is a difficult patient population to gain response and remission to subsequent therapy. Therefore, understanding novel dosing strategies for patients receiving ustekinumab will be extremely important. In one study of 38 anti-TNF nonresponder patients, they found nearly half of patients required changes in dose frequency from every 8 weeks to every 4 weeks, and that this change in dose frequency was successful in obtaining clinical response in 61% of patients.[12] In addition to novel dosing strategies, the incorporation of therapeutic drug monitoring can also be used as an adjunct mechanism to help optimize therapy, though not proven. In the IM-UNITI study, which included every 8 week dosing, an ustekinumab serum concentration of greater than 1.1 mg/mL was associated with clinical response and normal CRP levels at 24 weeks, with a P value of <0.0001.[13] Indeed there is some data suggesting in the "real-world" setting, higher dosing of ustekinumab may be needed. In a

TABLE 4. Improved Disease Activity Markers After Ustekinumab Reinduction in All Patients (Subcutaneous and Intravenous, n = 34), Median 86 Days, Range 16–177, and a Subset of Patients Who Underwent Intravenous Reinduction (n = 13), Median 89 Days, Range 23–157

		All Reinduction Patients (n = 34)	Subset of Patients With IV Reinduction (n = 13)
CRP, median (range)	Before ustekinumab reinduction	3 (0.2, 197)	5.3 (0.2, 56.8)
	After ustekinumab reinduction	2.6 (0.1, 134)	2.4 (0.1, 134)
HBI, median (range)	Before ustekinumab reinduction	5 (0, 28)	7 (1, 15)
	After ustekinumab reinduction	7 (0, 21)	7 (0, 13)**
SIBDQ, median (range)	Before ustekinumab reinduction	53 (23, 70)	54 (23, 63)
	After ustekinumab reinduction	57 (20, 69)	48 (20, 64)

Values are expressed as median along with ranges.
**P value < 0.05.

study at McGill University of 62 patients receiving subcutaneous ustekinumab, the authors found that a trough serum ustekinumab concentration of 4.5 µg/mL at 26 weeks was associated with CRP reduction and endoscopic response, with a sensitivity of 67% and specificity of 70%. Notably, the majority of patients in that study received subcutaneous ustekinumab dosing every 4 weeks.[6]

Our study had several strengths. We were able to evaluate patient reported outcomes and provide long-term follow-up in a cohort of refractory patients with CD who had failed multiple prior biologic therapies in a real-world setting. Limitations include a retrospective study design and starting ustekinumab before FDA approval, so dosing strategies for induction and reinduction were different for some patients than current available dosing strategies. However, we found that even in those patients utilizing dosing strategies that are different than current FDA approved guidelines, significant improvement in disease and patient reported outcomes occurred.

In patients who have failed multiple biologic therapies, limited options remain if patients start to flare while on medications such as ustekinumab. Other biologic therapies such as anti-TNF agents have shown improvement with short dose increases, also known as microreinduction. For instance, in the Pegylated Antibody Fragment Evaluation in Crohn's Disease: Safety and Efficacy 4 trial, Sandborn et al found that the microreinduction of certolizumab in relapsed CD patients was able to maintain response in 55%–59% of CD patients after 52 weeks.[14,15] We have found in prior studies that novel small or "micro" reinduction for other biologics, such as adalimumab, allowed for the majority of patients to maintain on their medication with good response.[16] A study by Heron et al published in 2018 assessed the ustekinumab reinduction in 11 patients with loss of response to ustekinumab treatment and found that 55% of patients achieved endoscopic response or remission and 66% obtained clinical remission. Notably in this study 5 patients had ustekinumab levels drawn prior to reinduction, all with levels greater than >1 µg/mL, with a median level of 5.5 µg/mL, well above the cutoff found in previous studies to be sufficient.[17] Although small number of patients in both groups (11 in the Heron et al's study and 34 in our study), there is a striking similarity to clinical and endoscopic improvement in the majority of patients undergoing reinduction in both studies. Interestingly, the median preinduction ustekinumab levels in the Heron et al's study appear to be higher than our patients. Even with preinduction drug levels >1 µg/mL in both groups, a significant number of patients had clinical and endoscopic improvement after ustekinumab reinduction. Therefore, with ustekinumab it may be difficult to base the need for reinduction on drug levels alone. Clinical symptomatology and endoscopic activity may be the important driver for need for ustekinumab reinduction.

CONCLUSIONS

This study demonstrates that ustekinumab has good response for patients with refractory CD who have failed prior medications including anti-TNF agents and vedolizumab. In a subset of patients who lose response, reinduction of ustekinumab can be beneficial and even allow for continuation of regular maintenance dosing of every 8 weeks. The ability to undergo reinduction to obtain and maintain remission could result in long-term health care savings and optimization. Understanding strategies to regain or maintain remission in patients who have failed other biologic therapy to facilitate long-term control of CD will continue to be an important issue in the treatment of inflammatory bowel disease.

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