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Subcutaneous ustekinumab for the treatment of anti-TNF resistant Crohn's disease—The McGill experience☆

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Abstract

Background: Ustekinumab is a fully human IgG1κ monoclonal antibody that blocks the biologic activity of interleukin-12/23. Ustekinumab is approved for treatment of plaque psoriasis and has been shown to be effective for induction and maintenance of clinical response in anti-TNF resistant Crohn's disease (CD). The aim of the study was to describe the real-life experience with open-label use of ustekinumab in anti-TNF resistant CD patients.
Methods: A retrospective observational open-label study. Clinical response was defined by physician's global assessment combined with decision to continue therapy. The clinical response was evaluated at 3, 6, 12 months and last follow-up.
Results: Thirty-eight patients were included in the study. Initial clinical response was achieved in 28/38 (73.7%) of the patients. Among the initial responders, 80% with follow-up data maintained their response for 6 months. At 12 months of follow-up, 88.9% of patients responding at 6 months maintained their response. At the last follow-up (7.9 ± 5.2 mo) 27/38 (71%) of the patients were responding, and 73.3% were able to discontinue corticosteroids. Dose escalation was required in 47.7% of the patients and was successful in 61.1% of them.
Summary: In this real-life cohort of severe anti-TNF resistant CD, an initial clinical response to subcutaneous ustekinumab was observed in 73.7% of the patients. The initial response was successfully maintained in the majority of patients for up to 12 months. Subcutaneous ustekinumab is an effective therapeutic option in this challenging patient cohort. The optimal dosing and injection schedule remain to be established in future studies.

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1. Introduction

Crohn's disease (CD) is a chronic debilitating inflammatory disease of the digestive tract. For the last decade, the most effective medications used for IBD have been monoclonal anti-TNF antibodies.[1] However, about one-third of the patients do not respond to anti-TNFs initially, and another third lose response to these medications during the course of the treatment and require dose adjustment or switch to another medication.[2] Ustekinumab (Stelara, Janssen, Titusville,NJ, USA) is a fully human IgG1κ monoclonal antibody that blocks the biologic activity of interleukin-12 and interleukin-23 through their common p40 subunit.[3] Currently, ustekinumab is approved for treatment of psoriasis and psoriatic arthritis.[4] Pro-inflammatory cytokines IL23 and IL12 have been recently implicated in the pathogenesis of IBD.[5] Overexpression of the interleukin-12 p35 and interleukin-12/23 p40 subunits was demonstrated in patients with CD.[6] Polymorphisms in genes encoding the interleukin-12/23 p40 subunit and interleukin-23 receptor have been identified on genome-wide association studies and linked to the pathogenesis of IBD.[7–10 11]

Treatment with intravenous ustekinumab (6 mg/kg) resulted in clinical response in patients with anti-TNF refractory Crohn's disease (CERTIFI trial).[3] However, the rate of clinical remission with the single 6-mg/kg dose IV did not differ significantly from the placebo group at 6 weeks. In patients who responded to the intravenous induction therapy, maintenance with subcutaneous ustekinumab (90 mg at weeks 8 and 16) resulted in clinically significant response and remission at week 22.[3]

Currently, ustekinumab is available in Canada for CD patients for off-label use with subcutaneous administration only. The aim of this study was to describe our open-label experience with the use of ustekinumab for treatment of anti-TNF resistant CD in a tertiary academic center.

2. Methods

We included all CD patients that were followed by participating McGill University IBD centers between March 2011 and November 2013 that were treated with ustekinumab for CD after developing loss of response to one or more anti-TNF medications. Clinical, endoscopic and laboratory data were extracted from the patient's files and electronic records. The study was approved by the institutional ethics review board.

2.1. Outcome definitions

Clinical response was defined as improvement in the patient's symptoms coupled with the decision to continue ustekinumab treatment. Clinical response was assessed at the following time-points – initial response (up to 12 weeks or first visit after initiating the treatment if no visit occurred within the first 12 weeks), 6 months, 12 months and last follow-up. Response failure was defined by the absence of significant improvement in symptoms, or if an additional anti-inflammatory medication (ex. immunomodulator, systemic corticosteroids, etc.) was initiated, or if a patient was referred for surgery. A relapse was defined as a therapeutic failure developing after the initial response was achieved. An increase in dose or shortening of the interval between doses was not considered a treatment failure if it resulted in clinical response. Clinical response in patients with perianal disease was defined by the treating physician's assessment. Endoscopic response was defined as a significant reduction in the number of visible ulcerations. Mucosal healing was defined as a lack of any visible ulcerations or friable mucosa.

Clinical and demographic characteristics were compared between the patients who responded to ustekinumab by the end of follow-up and those who did not, in order to identify potential predictive factors for clinical response.

An adverse event was defined as any adverse reaction that occurred after initiating treatment. Its relationship to ustekinumab was according to the treating physician's judgement. Concomitant immunomodulatory treatment at onset was defined as the use of either thiopurines (azathioprine,6-mercaptopurine) or methotrexate during the initiation of ustekinumab treatment. Therapy intensification was defined as either dose increase or shortening the interval between injections.

2.2. Statistical analysis

We used descriptive statistics in percentages with 95% confidence intervals for discrete variables or means with standard deviations (SD). For differences in proportions, the Chi Square test was used; T-test was used for comparison of means of independent samples. Kaplan –Meier analysis was performed for failure-free survival. A p value < 0.05 was considered statistically significant. The analyses were performed with SPSS version 20.0 (SPSS Inc., Chicago, IL, USA) .

3. Results

Forty consecutive patients that were treated with ustekinumab for CD between March 2011 and November 2013 were recruited for the study. Two patients with CD only involving an ileal pouch that was constructed after an initial diagnosis of ulcerative colitis were excluded. The patients were followed for a mean duration of 7.9 ± 5.2 (range: 3 to 21) months. The clinical and demographic characteristics of the included patients are described in Table 1. All the patients had previously failed at least one anti-TNF agent, and 95% failed two or more. Evidence of active disease (laboratory, endoscopic or radiologic) was available in 32/38 (84.2%) patients. C-reactive protein (CRP) was elevated in 68.7% of the patients tested.

3.1. Initial response

An initial response was achieved in 28/38 (73.6%) of the patients. An induction regimen was utilized in 34/38 (89.5%) patients. The other 4 cases received maintenance dosing from the start. The most prevalent induction regimen was 90 mg at weeks 0, 1, 2 for 28/34 (82.4%) of the patients (see Table 2). The mean cumulative first month's dose was 215 ± 93.7 mg (range: 45–270 mg). In patients with perianal disease, an initial response was achieved in 9/13 (69.2%) of the patients.

Table 1 Clinical and demographic characteristics of the CD patients treated with ustekinumab.

Gender (M/F)		18/20
Age at induction (median (IQR)), years		35.5 (22.5)
Duration of disease (median (IQR)), years		13 (8.5)
Montreal classification		
Age at onset	A1 (<17)	14 (36.7)
	A2 (17–40)	20 (52.7)
	A3 (>40)	4 (10.6)
Location	L1 (small bowel)	6 (15.8)
	L2 (colon)	7 (18.4)
	L3 (ileocolonic)	23 (60.5)
	L4 (isolated upper GI disease)	0
Phenotype	B1 (luminal)	18 (47.3)
	B2 (stricturing)	16 (42.1)
	B3 (penetrating)	4 (10.6)
	Perianal disease	13 (35.3)
Extra-intestinal manifestations	Bone and joint	5 (13.2)
	Skin	3 (7.9)
History of surgery		17 (44.7)
Previous medications	Infliximab	38 (100)
	Adalimumab	36 (95)
	Certolizumab	7 (18.4)
	Thiopurines	38 (100)
	MTX	17 (44.7)
	Tacrolimus	1 (2.6)
	Natalizumab	1 (2.6)
Elevated CRP		22/32 (68.7)
Concomitant medications	Systemic corticosteroids	22 (57.8)
	Prednisone dose (median (IQR)), mg	15 (19)
	Azathioprine	2 (5.3)
	MTX	2 (5.3)

IQR – interquartile range, CD – Crohn's disease, CRP – C-reactive protein, MTX – methotrexate.

Clinical response was accompanied by normalization of the biomarkers in 50% of the patients with available testing. Corticosteroids were discontinued in 7/15 of the patients with clinical response, and the dose was decreased (mean decrease of 42 ± 26%) in 5/8 of the patients remaining on corticosteroids (Table 3). Neither the use of concomitant immunomodulator treatment ($p = 0.66$) or the cumulative first month dose ($p = 0.42$) significantly correlated with initial response.

3.2. Maintenance of response

Follow up results were available for 31/38 patients (20/28 of the patients with an initial response) at 6 months. Twenty (64.5%) patients were responding to ustekinumab after 6 months of follow-up, including 16/20 (80%) of the initial responders. Two additional patients who had failed to respond within the first 12 weeks achieved clinical response by 6 months. Two patients who did not have previous visits due to poor compliance also responded at 6 months. Among patients on corticosteroids at entry into the study, 7/12 (58.3%) who responded clinically were able to discontinue prednisone. Twelve month follow-up data were available for 19 patients, including 9/20 patients who achieved a clinical response at 6 months. The overall response rate at 12 months (excluding patients who have not yet reached this time point or failed) was 9/19 (45%), including 8/9 (88.9%) of those who responded to ustekinumab at 6 months. One additional patient had regained response after having a relapse. Only one patient was still on low-dose corticosteroids. At the last follow-up (median – 6 months, range: 3–21 months) 27/38 (71.1%) of the patients were responding; 11/15 (73.3%) were able to discontinue corticosteroids and 4-others decreased the dose by the end of the follow-up period (Fig. 1). For patients with perianal disease, 4/9 patients with an initial response reached 12 months of follow-up; 3/4 sustained their clinical response. CRP decreased in all clinical responders with elevated pre-treatment levels (32.2 ± 45.2 vs. 11.6 ± 19.7 mg/l, $p = 0.026$) and normalized completely in 8/13 (61.5%) patients (Fig. 1). The Kaplan-Meier

Table 2 Loading and maintenance doses of ustekinumab.

Loading dose n, (%)	45 mg week 0/4	2 (5.3)
	90 mg week 0/1/2	28 (73.7)
	90 mg week 0/4	4 (10.6)
Maintenance regimen, n, (%)	45 mg q12 weeks	1 (2.6)
	90 mg q12 weeks	1 (2.6)
	90 mg q8 weeks	28 (73.7)
	90 mg q4 weeks	8 (21)

Table 3 Clinical and steroid-free response to ustekinumab in CD.

Time point		Clinical response		Steroid −free response*	
	Total (N)	N	%	N	%
3 months	38	28/38	73.7	7/15	46.6
6 months	31	20/31	64.5	7/12	58.8
12 months	19	9/19	47.4	4/5	20
End of follow-up	38	27/38	71.1	11/15	73.3

In clinical responders.

survival curve for clinical response to ustekinumab is depicted in Fig. 2.

Five of the 28 (17.9%) initial responders experienced a relapse. The median time to relapse- was 8.0 ± 3.1 months from treatment initiation. Two out of 6 (40%) regained their response to ustekinumab following dose escalation.

Endoscopic evaluation was available for 13/27 responders (9.6 ± 2.9 months from the onset of treatment). All patients had active endoscopic inflammation before treatment. Endoscopic improvement was achieved in 10/13 (76.9%) cases; mucosal healing was demonstrated in 2 of these patients.

Adverse events included a Clostridium difficile infection in 1 patient with an initial clinical response 4 months after the first ustekinumab dose. The patient was receiving concomitant methotrexate at the time. He was successfully treated with antibiotics and regained clinical response. No additional serious adverse effects were reported.

3.3. Predictors of clinical response

None of the potential predictive factors, including the Montreal classification, concomitant medications, induction/maintenance protocol and weight were significantly associated with clinical response to ustekinumab (Table 4).

3.4. Dose escalation

The initial maintenance dose was 90 mg q8 weeks in 73.7% of the patients (see Table 2). The mean ustekinumab dose received in the first month was 215 ± 93.5 mg (range: 45–270 mg) or 3.7 ± 1.53 mg/kg. Dose escalation was required in 18 (47.4 %) patients and was successful in 11/18 (61.1%). The escalation strategy was interval reduction in 17/18 patients. One patient who was initially started on 45 mg/q12w was treated with both dose escalation to 90 mg and interval reduction to 8 weeks, simultaneously. Overall, 51.8% of the patients with clinical response at the last follow-up required therapeutic escalation. The last maintenance regimen in patients with clinical response was q4 weeks in 14/27 patients (51.8%), q8 weeks in 12/27 (44.4%) and q3 weeks in 1/28(3.7%). Out of 27 responders, dose escalation was required in 7/20 (35%) patients initially started on q8; 1/6 (17.4%) patients initially started on q4 (p = 0.63), and 1/1 patients initially started on 45 mg q12.

4. Discussion

The results of our study provide further evidence that subcutaneous ustekinumab treatment is associated with a sustained clinical response in the majority of anti-TNF resistant CD patients. The clinical response was associated with normalization of inflammatory markers, discontinuation of corticosteroids or endoscopic improvement in 75% of the patients.

All the patients in our cohort had failed at least one anti-TNF agent, and 95% failed two or more. Currently, treatment options in anti-TNF resistant CD are very limited, and an agent that can provide a lasting clinical response would be a valuable addition to the therapeutic arsenal.

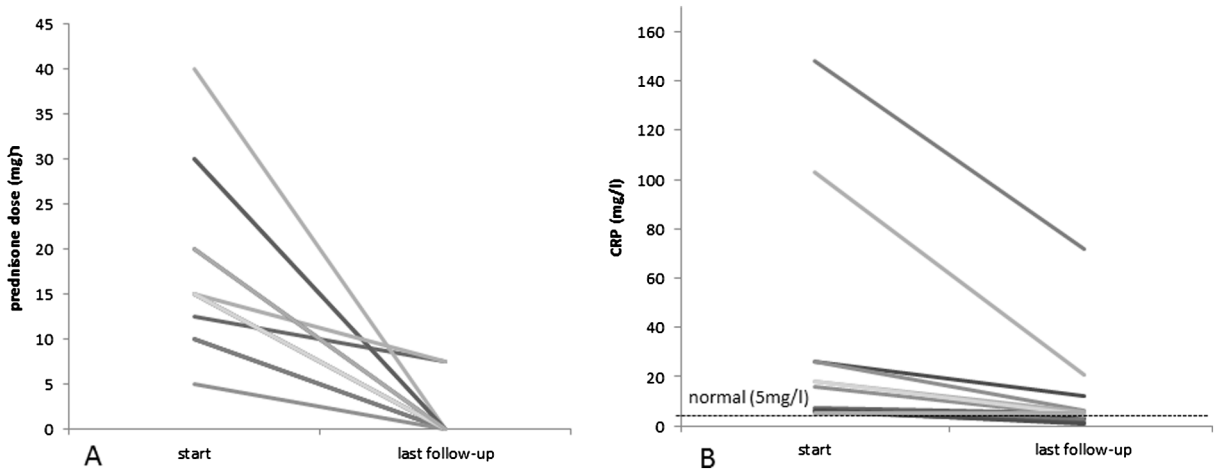

Figure 1 A. Steroid discontinuation and dose reduction in CD patients who responded to ustekinumab. B. CRP levels in CD patients who responded to ustekinumab. CRP – Creactive protein.

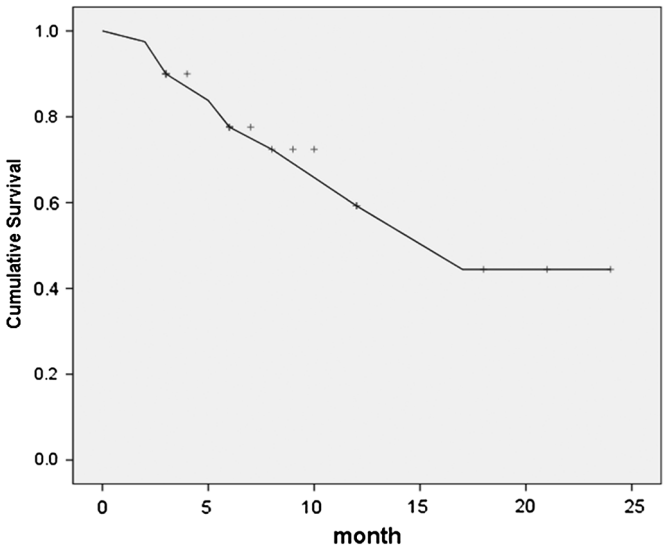

Figure 2 Kaplan-Meier analysis of failure-free response to ustekinumab.

Two randomized controlled studies evaluating the efficacy of ustekinumab in CD have been published. In the phase II study,[12] utilizing both intravenous and subcutaneous ustekinumab (90 mg or 4.5 mg/kg), the clinical response at week 8 was not significantly different from the placebo. However, in the subgroup of patients previously exposed to infliximab, the response rate at week 8 was significantly higher than in the placebo group. In a follow-up phase III

Table 4 Clinical and demographic characteristics of CD patients with and without clinical response to ustekinumab.

		Clinical response at the end of follow-up				
		no (n = 11)		yes (n = 27)		
		n	%	n	%	p
Gender (female) f		5	45.5%	15	55.6%	0.57
Age (mean ± SD)		32.6 ± 13.6		39.2 ± 13.4		0.19
Age of onset (mean ± SD)		21 ± 14.6		23.5 ± 12.3		0.62
Disease duration (mean ± SD)		11.6 ± 4.4		15.5 ± 8.4		0.18
Disease location	ileal	4	36.4%	3	11.1%	0.16
	colonic	1	9.1%	6	22.2%	
	ileocolonic	6	54.5%	18	66.7%	
Disease phenotype	luminal	72.7%	10	37.0%	8	0.12
	penetrating	18.2%	14	51.9%	2	
	stricturing	9.1%	3	11.1%	1	
Concomitant corticosterids		6	54.5%	16	59.3%	0.79
Concomitant immunomodulator	Azathioprine	1	50.0%	1	50.0%	0.9
	Methotrexate	1	50.0%	1	33.3%	
Elevated CRP		8	72.7%	14	51.8%	0.17
Evidence of active disease**		9	81.8%	23	85.2%	0.8
Weight (kg),mean ± SD		63.3 ± 9.7		65.6 ± 16.3		0.75
Loading regimen	45 mg wk 0/4	1	9.1%	3	11.1%	0.92
	90 mg wk 0/1/2	8	72.7%	20	74.1%	
	90 mg wk 0/4	1	9.1%	1	3.7%	
Cumulative first month dose, mg (mean ± SD)		208 ± 107		218 ± 90		0.79
Weight-adjusted cumulative first month dose,mg/kg (mean ± SD)		4.3 ± 6.9		3.6 ± 1.6		0.22
Initial maintenance regimen	45 mg q12wk	0	0.0%	1	4.7%	0.42
	90 mg q12wk	1	9.9%	0	0.0%	
	90 mg q8wk	8	72.3%	20	74.1%	
	90 mg q4wk	2	18.2%	6	22.2%	

F – female, CRP – C-reactive protein.
** Laboratory, endscopic or radographic.

study (CERTIFI) that included only anti-TNF resistant patients,[3] ustekinumab was administered intravenously. Treatment was associated with clinical response in 36.6%, 34.1%, and 39.7% for 1, 3, and 6 mg/kg of ustekinumab per kilogram, respectively, as compared with 23.5% for the placebo group ($p = 0.05$ for the comparison with the 6 mg group). Patients with an initial response to IV induction were re-randomized to receive two subcutaneous doses (90 mg) or placebo at weeks 8 and 16. In these patients, the rate of clinical response and remission at week 22 was significantly higher in patients on active treatment (remission: 41.7% vs. 27.4%, $P = 0.03$, and response: 69.4% vs. 42.5%, $P < 0.001$). As noted in the CERTIFI study, the clinical response in our cohort was highly sustainable in anti-TNF resistant patients who achieved an initial response to ustekinumab.

The optimal dosing of ustekinumab in CD remains to be established. In the phase II trial, both intravenous and subcutaneous induction therapy were utilized,[12] while in CERTIFI the induction was intravenous and the maintenance therapy subcutaneous.[3] In psoriasis, ustekinumab is administered subcutaneously at lower doses.[13] Our patients had access to ustekinumab as a subcutaneous agent on a compassionate use basis. We did not observe a significant correlation between the induction dose and short or long-term response rates. , However, our study was underpowered for this purpose. The ongoing clinical trials evaluating ustekinumab for induction and maintenance treatment in CD (UNITI-I, UNITI-II) are anticipated to provide information the optimal dosing of this agent in CD.

To the best of our knowledge, dose escalation with ustekinumab has not been previously addressed in CD. In our cohort, dose escalation was successful in >60 % of the patients, similar to the psoriasis data.[14]

We did not identify any clinical or demographic factors that predicted clinical response to ustekinumab. However, our study was underpowered to address this issue. Baseline body weight was negatively associated with clinical response in CD;[12] in psoriasis, the response rate for patients with weight above 100 kg was significantly better when treated with 90 mg in comparison to 45 mg.[15] In our cohort, only one patient weighed >100 kg and neither weight nor weight adjusted dose had a significant impact on response.

The safety profile of ustekinumab appears to be very favorable; however the majority of the data comes from psoriasis studies. The incidence of serious infections (including tuberculosis), cancer, cardiovascular morbidity, and laboratory abnormalities was not different between treatment and placebo groups.[16] For CD, serious infections were reported in five patients receiving 6 mg/kg ustekinumab (Clostridium difficile infection, viral gastroenteritis, urinary tract infection, anal abscess, and vaginal abscess) and in one patient receiving 1 mg /kg (staphylococcal infection of a central line) during the induction phase. The only serious adverse effect observed in our cohort was a C. difficile infection in one patient who was also receiving concomitant methotrexate and corticosteroids. Ustekinumab was not administered in our hospital clinics in our study. Consequently minor adverse effects such as local injection-site reactions were probably underreported.

Our study has several limitations. Primarily, it is a retrospective study in a relatively small cohort. Clinical scores were largely unavailable. However, clinical response defined by symptoms and continuation of therapy is a frequently used and clinically relevant surrogate marker of disease activity. Moreover, our data on the discontinuation of corticosteroids, endoscopic improvement and biological biomarkers demonstrates that in ≥75% of our patients, symptomatic response was accompanied by an improvement in at least one of these surrogate markers of inflammatory activity. In addition, as previously discussed, several dosing regimens were utilized as there is currently no consensus on the recommended dose in CD. Despite these limitations, we believe that our study contains a valid representation of the real-life experience with this promising new agent in a very challenging and diverse patient cohort.

In summary, subcutaneous ustekinumab treatment resulted in an initial clinical response in 73.7% of anti-TNF resistant CD patients. The clinical response was maintained in a majority of the initial responders for 6–12 months. Dose escalation was frequently required to achieve or maintain response. Optimal dosing schedule for ustekinumab in CD merits further evaluation in randomized controlled studies.

Conflicts of interest statement

UK, TA, JW, AS – none

WA: Advisory Board Member: Janssen Pharma and Abbvie.

AB: Consultant, Advisory Board: AbbVie, Janssen, Shire, Warner Chilcott, Takeda, Speaker: AbbVie, Janssen, Shire, Warner Chilcott, Aptalis

TB: lecture fees from Aptalis and Takeda, and consultancy for Abbott, Janssen, Shire

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UK – study design, data collection and analysis, manuscript drafting

WA, AC, AB,TB, ES – study design, review of the manuscript for intellectual content

GW,TB,JW,TA. AS – data collection , review of the manuscript for intellectual content

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