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Crohn's disease outpatients treated with adalimumab have an earlier secondary loss of response and requirement for dose escalation compared to infliximab: A real life cohort study☆

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Abstract

Background: The efficacy of anti-tumor necrosis factor alpha agents in maintaining remission in Crohn's disease may wane over time, leading to secondary loss of response that can often be overcome with dose escalation. Comparison of secondary loss of response of adalimumab and infliximab during long-term treatment of CD in a real-life IBD clinic has not been previously evaluated.

Methods: A retrospective cohort study was conducted evaluating outpatients with CD on a maintenance regimen with adalimumab or infliximab from 200 to 2013 and who experienced a secondary loss of response. All infliximab-treated patients were anti-TNF naïve. Adalimumab-treated patients were stratified by prior anti-TNF exposure. Kaplan–Meier analysis was conducted to compare time to loss of response.

Results: 218 CD patients met inclusion criteria (117 infliximab, 101 adalimumab). Median follow-up duration was 170.0 weeks for infliximab and 122.0 weeks for adalimumab (p = 0.61). The proportion of patients with secondary loss of response was similar for infliximab-treated — 51.3% (60/117) compared to adalimumab patients naïve to anti-TNF therapy — 60.5% (23/38) (p = 0.32), and adalimumab patients with prior anti-TNF exposure — 65.1% (41/63) (p = 0.08). Median time to secondary loss of response was longer for infliximab patients (99.3 wk, IQR 55.7–168.5) compared

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to both adalimumab patients naïve to anti-TNF therapy (58.9 wk, IQR 29.0–85.7) ($p = 0.03$), and adalimumab patients with prior anti-TNF exposure (52.7 wk, IQR 20.1–85.0) ($p < 0.001$).
Conclusions: Over 50% of CD patients treated with infliximab and adalimumab develop secondary loss of response. Time to loss of response was shorter in patients treated with adalimumab compared to those treated with infliximab. Prior anti-TNF exposure further accelerated time to loss of response.

1. Introduction

Biologic agents targeting tumor necrosis factor alpha (TNF-α), including infliximab and adalimumab have offered significant advances in the management of inflammatory bowel disease. Randomized controlled trials have demonstrated efficacy of both agents for the induction and maintenance of remission of Crohn's disease.[1–4] Nevertheless, following a successful induction, a significant subset of patients will lose therapeutic benefit leading to a secondary loss of response.[5] Indeed, in the ACCENT I and II trials for infliximab in the treatment of CD, secondary loss of remission among initial responders occurred in 62% and 42% of patients at 54 weeks, respectively.[2,3] Similar rates have also been demonstrated for adalimumab in the treatment of patients with CD (57% at 56 weeks in the CHARM trial[1]). In the open label cohort literature, rates of secondary loss of response to anti-TNF therapy vary widely, ranging from 11 to 54% with significant heterogeneity in median time to loss of response.[6–9]

While the etiology of secondary loss of response to anti-TNF therapy is not fully understood, the development of anti-drug antibodies and/or low serum drug concentrations plays a major role.[10] The management of secondary loss of response involves confirmation of active disease and, in most cases, subsequent dose escalation. Dose escalation in patients on infliximab can be achieved by increasing the dose from 5 mg/kg to 10 mg/kg every eight weeks or decreasing the infusion interval from every eight weeks to every four or six weeks.[11] For adalimumab, dose escalation generally involves reducing the injection frequency from 40 mg every other week to 40 mg weekly or increasing the dose to 80 mg subcutaneously per injection. A failure to respond to dose escalation subsequently requires switching within the anti-TNF class or switching outside of class.[12]

Recent efforts have been made to reduce secondary loss of response through strict adherence to scheduled dosing,[13] measurement of serum trough drug levels,[14] combination therapy with immunosuppressives,[15–17] and concomitant corticosteroid administration at the time of infliximab infusion.[18] Nevertheless, reported time to secondary loss of response and dose escalation, and regional practices for prevention of secondary loss of response vary widely. Additionally, comparison of secondary loss of response and therapeutic escalation between infliximab and adalimumab has not been well evaluated.

In this study we assessed, in a real-life clinical setting, the long-term response to adalimumab and infliximab in the management of CD outpatients. During maintenance therapy, we evaluated the proportion of patients developing secondary loss of response requiring dose escalation and the time to secondary loss of response. Secondarily, we examined risk factors predicting secondary loss of response.

2. Materials and methods

2.1. Study design, setting, and data source

This retrospective cohort study was performed using data collected from CD outpatients receiving infliximab or adalimumab from January 2003 to November 2013, at the University of Alberta, Edmonton, Canada. Patients were identified from the Division of Gastroenterology Inflammatory Bowel Disease Electronic Database. Electronic records were available up to November 1, 2013.

2.2. Patient population

Patients were eligible for inclusion if they met the following criteria: (1) endoscopically and histologically confirmed CD; (2) achieved primary response to induction therapy with infliximab 5 mg/kg at weeks 0, 2, and 6 or adalimumab 160 mg at week 0 and 80 mg at week 2; and (3) advanced onto a scheduled maintenance outpatient anti-TNF regimen of infliximab 5 mg/kg every 8 weeks or adalimumab 40 mg every other week. All patients treated with infliximab were previously anti-TNF naïve. Patients treated with adalimumab were stratified by previous anti-TNF exposure. Minimum follow-up duration was 16 weeks. All patients were primary responders to adalimumab and infliximab induction therapy, defined by decrease in post-induction Harvey Bradshaw Index of more than 3 points.[19]

Initial choice of anti-TNF agent (i.e. infliximab versus adalimumab) was at the discretion of the patient and their attending gastroenterologist. All patients followed a regional structured protocol for 'step-up' to initiation of anti-TNF therapy. Prior to induction, patients must have developed steroid refractory or steroid dependent disease or failed immunosuppressive therapy (azathioprine or methotrexate) due to lack of response or intolerance for these agents. Steroid refractory disease was defined by absence of clinical response to 40 mg/day oral prednisone or equivalent dose within 30 days of initiation. Steroid dependent disease was defined as the inability to wean oral prednisone to <10 mg/day (or equivalent steroid dose) within 3 months of therapy without relapse of disease.[20] Azathioprine failure was defined as non-response or inability to tolerate azathioprine 2 mg/kg/day. Methotrexate failure was defined as non-response or inability to tolerate methotrexate 15 mg/week.

2.3. Outcomes and definitions

The primary objective of this study was to determine the proportion of CD patients who experienced a secondary loss of response to maintenance therapy of adalimumab or infliximab, necessitating therapeutic dose escalation, as well as to assess the time to secondary loss of response. The secondary objective was to determine risk factors associated with secondary loss of response.

Secondary loss of response was defined by the attending gastroenterologist based on the following structured approach: (1) confirmation of disease activity using clinical disease activity index (Harvey Bradshaw Index [HBI][19] score greater than 5); and (2) elevated inflammatory marker (C-reactive protein > 8.0 mg/L and/or fecal calprotectin > 50 μg/g) or (3) endoscopic or CT enterography evidence of disease activity. Additionally, enteric infection with *Clostridium difficile* or other intestinal pathogens was excluded. In order to identify secondary loss of response accurately, a nurse completed a structured feedback form capturing a modified HBI score (comprising patient general well-being, abdominal pain, and number of liquid stools) and adverse events at each infliximab infusion. For patients on adalimumab, a structured bi-monthly verbal report capturing efficacy and adverse events was obtained by an IBD nurse specialist. No specific changes to our institution's clinical monitoring protocol were made during the study period.

Dose escalation was defined as an increase in administered anti-TNF dose or a shortened interval of administration. For infliximab, dose escalation consisted of increasing the dose to 10 mg/kg per infusion or increasing the frequency of infusions to less than every eight weeks. A dose increase due to increased patient weight was not considered therapeutic escalation. For adalimumab, escalation consisted of increasing the dose to 80 mg or increasing the frequency to weekly injections.

Total follow-up time was determined from the start of therapy to the last date of anti-TNF administration or anti-TNF discontinuation. Patients who maintained their clinical response from induction to the end of the study period were considered censored cases.

2.4. Data collection

Data were extracted by authors CM and DF from two sources using a standardized case report form: (1) physician office-based electronic files (including all clinic follow-up notes, nursing and direct patient correspondence, outpatient prescriptions, and consultation letters) and (2) region-wide electronic health care database (including all inpatient and outpatient laboratory investigations, diagnostic imaging, histology and pathology reports, hospital admission and discharge summaries, and operative procedures including endoscopy reports). Data were reviewed by authors VH, KIK, LAD, BPH and RNF.

Baseline patient data collected included gender, age, date of diagnosis (as confirmed by endoscopy or histology where available, or by history), disease location and behavior (as per Montreal Classification for CD[21]), and previous treatments for CD (including mesalamine, azathioprine or 6-mercaptopurine, and methotrexate). For anti-TNF induction, we identified date of first administered dose, duration of disease prior to anti-TNF therapy, initial maintenance regimen, pre-medications for infliximab infusions, concurrent medications at induction, and albumin, C-reactive protein, and Harvey Bradshaw index score at time of induction. We also collected time to loss of response requiring dose escalation.

2.5. Statistical methods

The Kaplan–Meier method was used to assess maintenance of infliximab and adalimumab therapy by comparing the proportion of patients that dose escalated to time before escalation. A log-rank test for equality of survivor functions was performed, and clinical outcomes in the infliximab and adalimumab groups were compared using the student *t*-test and Chi-squared test. For continuous variables, mean, median, standard deviation, and interquartile range were calculated. Independent 2-group Mann–Whitney U testing was used to compare non-normally distributed continuous variables. Both univariate unadjusted and multivariate adjusted logistic regression analysis was performed to assess risk factors for loss of response, expressed as odds ratios with 95% confidence intervals (CI). Additionally, hazard ratios with 95% CI for loss of response were calculated using a Cox proportional hazards model. Patients with incomplete baseline data were excluded from the multivariate logistic regression and Cox survival models, but baseline characteristics of this group of patients were similar to that of the total cohort (Supplemental Table 1).

Due to the long inclusion period (2003–2013), subgroup analysis was performed to assess for potential differences in outcomes with time: we divided the inclusion period into roughly equal time frames and patients were stratified according to date of induction therapy (2003–2008 vs. 2009–2013).

Statistical analysis was performed with SPSS 21.0 statistical software (Armonk, NY: IBM Corporation).

3. Results

3.1. Baseline patient characteristics

Patient demographics are summarized in Table 1. 218 CD patients met study inclusion criteria. 117/218 patients (53.7%) were treated with infliximab and 101/218 patients (46.3%) with adalimumab. Overall proportions of patients receiving infliximab or adalimumab from 2003 to 2008 compared to those from 2009 to 2013 were similar. All patients treated with infliximab were naïve to anti-TNF therapy, whereas 38/101 (37.6%) patients treated with adalimumab were naïve to anti-TNF therapy. Median duration of follow-up was 170.0 weeks (range 21.4–435.4 weeks) for infliximab and 122.0 weeks (range 27.7–501.0 weeks) for adalimumab ($p = 0.61$).

Confirming similarity of disease phenotype, patients in both cohorts were similar with respect to age, Montreal Classification for age at diagnosis, disease location, and disease behavior, and presence of perianal disease (Table 1). Furthermore, at anti-TNF induction, median HBI score was similar between patients on infliximab (7, IQR 5–13) and adalimumab naïve to anti-TNF therapy (9, IQR 7–11, $p = 0.19$) or adalimumab with previous anti-TNF exposure (10, IQR 7–12, $p = 0.13$). While most patients had previously been treated

Table 1 Baseline patient demographics.

	Infliximab	Adalimumab	Adalimumab	p-Value [a]
	TNF naïve	TNF naïve	Previous anti-TNF	
n (%)	117 (53.7)	38 (17.4)	63 (28.9)	
Date of induction therapy (%)				
2003–2008	48 (60.0)	17 (21.3)	15 (18.8)	
2009–2013	69 (50.0)	21 (15.2)	48 (34.8)	
Gender				$p_1 = 0.95$
Male (%)	53 (45.3)	17 (44.7)	26 (41.3)	$p_2 = 0.60$
Female (%)	64 (54.7)	21 (55.3)	37 (58.7)	$p_3 = 0.73$
Median age (years, IQR)	38.8 (29.9–51.7)	39.8 (29.5–51.2)	41.3 (34.9–54.5)	$p_1 = 0.82$
				$p_2 = 0.35$
				$p_3 = 0.90$
Montreal classification — Age at diagnosis (%)				
A1	28 (23.9)	4 (10.5)	16 (25.4)	$p_1 = 0.19$
A2	71 (60.7)	26 (68.4)	37 (58.7)	$p_2 = 0.97$
A3	18 (15.4)	8 (21.1)	10 (15.9)	$p_3 = 0.19$
Montreal classification — Location (%)				
L1	48 (41.0)	17 (44.7)	20 (31.7)	$p_1 = 0.36$
L2	35 (29.9)	7 (18.4)	16 (25.4)	$p_2 = 0.17$
L3	34 (29.1)	14 (36.8)	27 (42.9)	$p_3 = 0.41$
Montreal classification — Behavior (%)				
B1	39 (33.3)	17 (44.7)	21 (33.3)	$p_1 = 0.13$
B2	19 (16.2)	9 (23.7)	11 (17.5)	$p_2 = 0.97$
B3	59 (50.4)	12 (31.6)	31 (49.2)	$p_3 = 0.22$
Perianal disease (%)	34 (29.1)	9 (23.7)	22 (34.9)	$p_1 = 0.52$
				$p_2 = 0.42$
				$p_3 = 0.24$
Previous azathioprine or methotrexate (%)	100 (85.5)	31 (81.6)	60 (95.2)	$p_1 = 0.57$
				$p_2 = 0.05$
				$p_3 = 0.03$

[a] p values: p_1 for comparison of infliximab to adalimumab naïve to anti-TNF therapy, p_2 for comparison of infliximab to adalimumab with previous anti-TNF exposure, and p_3 for comparison of adalimumab naïve to anti-TNF therapy to adalimumab with previous anti-TNF exposure.

with azathioprine or methotrexate, only approximately 60% of patients were on concurrent immunomodulation at anti-TNF induction for both adalimumab and infliximab; patients discontinued concomitant therapy mainly due to adverse effects or intolerability.

3.2. Secondary loss of response and dose escalation

Secondary loss of response is summarized in Table 2. The proportion of patients with secondary loss of response was similar for infliximab-treated — 51.3% (60/117) compared to adalimumab patients naïve to anti-TNF therapy — 60.5% (23/38) (p = 0.32), and adalimumab patients with prior anti-TNF exposure — 65.1% (41/63) (p = 0.08).

In secondary analysis, we stratified loss of response by year of induction therapy (2003–2008 vs. 2009–2013). There was no statistically significant difference in the proportion of patients experiencing secondary loss of response for adalimumab patients naïve to anti-TNF therapy (p = 0.25) or for adalimumab patients with prior anti-TNF exposure (p = 0.88), regardless of year of induction therapy (Table 2). However, a higher proportion of infliximab-treated patients receiving induction therapy from 2003 to 2008 experienced a secondary loss of response compared to those receiving induction therapy from 2009 to 2013 (62.5% vs. 43.5%, p = 0.04). Among IFX treated patients, a higher proportion of patients received concurrent immunomodulation from 2009 to 2013 (78.3% vs. 58.3%, p = 0.02) but there were no significant differences in gender, Montreal Classification, presence of perianal disease, previous immunomodulation, or disease activity by HBI when the two time periods were compared (data not shown).

Median time to secondary loss of response and dose escalation was significantly longer for infliximab patients (99.3 weeks, IQR 55.7–168.5 weeks) compared to that for both adalimumab patients who were either naïve to anti-TNF therapy (58.9 weeks, IQR 29.0–85.7 weeks) (p = 0.03) or who had prior anti-TNF exposure (52.7 weeks, IQR 20.1–85.0 weeks) ($p < 0.001$).

Kaplan–Meier analysis of time to secondary loss of response is shown in Fig. 1. Statistically significant difference in time to secondary loss of response requiring dose escalation was observed between the infliximab and adalimumab groups (both adalimumab naïve to anti-TNF and adalimumab previously exposed to anti-TNF therapy) ($p < 0.01$). Although adalimumab patients previously treated with anti-TNF agents trended towards earlier loss of response compared to anti-TNF naïve patients treated with adalimumab, this was statistically similar (p = 0.195).

Table 2 Anti-TNF dose escalation.

	Infliximab	Adalimumab	Adalimumab	p-Value [a]
	TNF naïve	TNF naïve	Previous anti-TNF	
n (%)	117 (53.7)	38 (17.4)	63 (28.9)	
Age at TNF induction (years) median (IQR)	33.0 (25.6–46.7)	35.5 (24.8–48.5)	37.6 (30.7–50.3)	$p_1 = 0.82$ $p_2 = 0.12$ $p_3 = 0.90$
Median Harvey Bradshaw Index at induction (IQR) [b]	7 (5–13)	9 (7–11)	10 (7–12)	$p_1 = 0.19$ $p_2 = 0.13$ $p_3 = 0.92$
Concurrent azathioprine or methotrexate (%)	82 (70.1)	23 (60.5)	37 (58.7)	$p_1 = 0.27$ $p_2 = 0.13$ $p_3 = 0.86$
Secondary loss of response (%)	60 (51.3)	23 (60.5)	41 (65.1)	$p_1 = 0.32$ [d]
2003–2008 [c]	30 (62.5)	12 (70.6)	10 (66.7)	$p_2 = 0.08$ [d]
2009–2013 [c]	30 (43.5)	11 (52.4)	31 (64.6)	$p_3 = 0.65$ [d]
Median time to secondary loss of response (weeks, IQR)	99.3 (55.7–168.5)	58.9 (29.0–85.7)	52.7 (20.1–85.0)	$p_1 = 0.03$ $p_2 < 0.001$ $p_3 = 0.85$

[a] p values: p_1 for comparison of infliximab to adalimumab naïve to anti-TNF therapy, p_2 for comparison of infliximab to adalimumab with previous anti-TNF exposure, and p_3 for comparison of adalimumab naïve to anti-TNF therapy to adalimumab with previous anti-TNF exposure.
[b] Harvey Bradshaw Index at induction of anti-TNF therapy available for 107 patients (56 infliximab, 51 adalimumab).
[c] Secondary loss of response stratified by date of induction therapy.
[d] p values presented for overall proportion of secondary loss of response (2003–2013); p values stratified by date of induction therapy comparing each treatment subgroup are also non-statistically significant (>0.05).

3.3. Risk factors for secondary loss of response and dose escalation

Univariate unadjusted and multivariate adjusted odds ratios for risk factors predicting secondary loss of response requiring dose escalation are summarized in Table 3. Concurrent immunomodulation with azathioprine or methotrexate significantly reduced the risk of loss of response in both univariate (OR 0.27, 95% CI 0.15–0.50) and multivariate (aOR 0.32, 95% CI 0.11–0.91) analysis. This was significant for both infliximab and adalimumab (result not shown). Moderate to severe disease activity (HBI $\geq$ 7 compared to mild disease HBI < 7) at time of induction also increased risk of loss of response by approximately 3-fold (Table 3). Previous treatment with azathioprine or methotrexate, anti-TNF agent, disease behavior by Montreal Classification, and presence of perianal disease did not significantly increase risk for loss of response. By Kaplan–Meier analysis (Fig. 2), concurrent immunomodulation significantly prolonged time to secondary loss of response and dose escalation, regardless of anti-TNF agent or previous anti-TNF exposure ($p < 0.01$). However, baseline immunomodulation was not associated with prolonged time to secondary loss of response.

Using the Cox proportional hazards model, hazard ratio for secondary loss of response was significantly higher for patients treated with adalimumab with previous anti-TNF exposure compared to infliximab (HR 1.98, 95% CI 1.03–3.82). Hazard ratios were similar for anti-TNF naïve patients treated with adalimumab regarding HBI at induction, Montreal Classification for disease location or behavior, perianal disease, or concurrent or previous immunomodulation (data not shown). Patients missing baseline HBI at induction were excluded from the multivariate logistic regression and Cox proportional hazards models. However, baseline patient characteristics, anti-TNF induction, and secondary loss of response outcomes were similar for the full cohort (Supplemental Table 1).

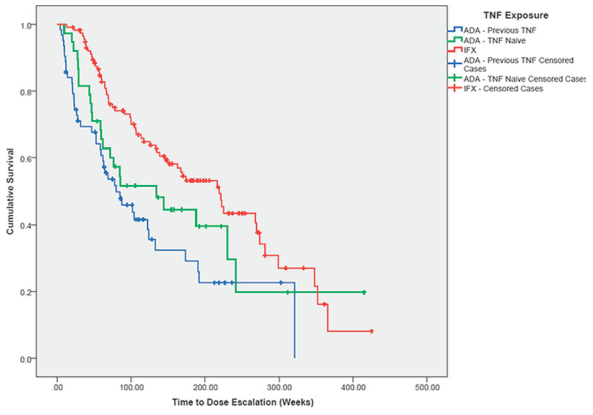

Figure 1 Kaplan–Meier survival curves of secondary loss of response during maintenance therapy requiring dose escalation for infliximab (red) versus TNF naïve adalimumab (green) and adalimumab with prior anti-TNF exposure (blue). Hashed lines indicate censored cases (maintained response to last follow-up). $p < 0.01$ for infliximab compared to either adalimumab group. $p = 0.195$ for adalimumab with previous anti-TNF exposure compared to adalimumab naïve to anti-TNF therapy.

Table 3 Univariate and multivariate logistic regression analysis of risk factors associated with secondary loss of response requiring dose escalation.

Risk factor	Univariate unadjusted odds ratio [95% CI]	Multivariate adjusted odds ratio [95% CI] [a]
Anti-TNF exposure		
Infliximab	1.00	1.00
Adalimumab — TNF naïve	1.46 [0.69–3.07]	1.96 [0.52–7.46]
Adalimumab — TNF exposed	1.77 [0.94–3.33]	2.00 [0.72–5.51]
Disease activity at induction		
HBI < 7 (mild)	1.00	1.00
HBI ≥ 7 (moderate/severe)	3.02 [1.29–7.04]	3.15 [1.17–8.49]
Montreal classification for age		
A1 — ≤16 years	1.00	1.00
A2 — 17–40 years	1.48 [0.76–2.87]	1.79 [0.57–5.39]
A3 — >40 years	1.25 [0.53–2.98]	0.69 [0.13–3.59]
Montreal classification for disease location		
L1 — ileal	1.00	1.00
L2 — colonic	1.63 [0.83–3.21]	2.92 [0.87–9.85]
L3 — ileocolonic	1.91 [1.01–3.60]	1.78 [0.58–5.47]
Montreal classification for disease behavior		
B1 — non-stricturing, non-penetrating	1.00	1.00
B2 — structuring	1.02 [0.47–2.22]	1.46 [0.42–5.11]
B3 — penetrating	1.36 [0.75–2.48]	2.99 [0.77–11.67]
Perianal disease		
Absent perianal disease	1.00	1.00
Present perianal disease	1.44 [0.79–2.61]	0.50 [0.13–2.01]
Concurrent immunomodulation		
No azathioprine or methotrexate	1.00	1.00
Concurrent azathioprine or methotrexate	0.27 [0.15–0.50]	0.32 [0.11–0.91]
Previous immunomodulation		
No previous azathioprine or methotrexate	1.00	1.00
Previous azathioprine or methotrexate	0.90 [0.39–2.03]	1.61 [0.33–7.96]

CI — confidence interval.
HBI — Harvey Bradshaw Index.
[a] Multivariate logistic regression model based on analysis of 107 patients (see Supplemental Table 1, patients with missing baseline disease activity were excluded from analysis)

4. Discussion

Infliximab and adalimumab have revolutionized the management of refractory Crohn's disease. However, the initial therapeutic benefit can be lost over time, representing a secondary loss of response. Dose escalation is often used to regain clinical response in this group of patients. Therapeutic escalation strategies described in the CD literature vary widely, reported outcomes are equally heterogeneous, and comparison of long-term outcomes in CD outpatients treated with adalimumab compared to infliximab has not been well evaluated.

In this study we examined secondary loss of response requiring therapeutic dose escalation of anti-TNF agents in a large, retrospective cohort of real-life CD outpatients, demonstrating that more than 50% of patients will require dose escalation irrespective of the anti-TNF administered. Nevertheless, patients treated with infliximab had a significantly longer time to secondary loss of response and therapeutic dose escalation compared to patients treated with adalimumab. Furthermore, concurrent immunosuppressive therapy with azathioprine or methotrexate reduced the risk of secondary loss of response.

In our cohort, similar rates of secondary loss of response were observed between infliximab and adalimumab. This is in keeping with the evidence from previous randomized controlled trials, including the ACCENT I study which demonstrated that approximately 50% of CD patients who responded to infliximab at week 2 were unable to maintain response to week 54.[2] Similar findings were corroborated by Sands et al. in the ACCENT II trial[3] evaluating infliximab for fistulizing CD and by Colombel et al. in the CHARM trial evaluating adalimumab for maintenance therapy in CD.[1] In the open label cohort literature, the incidence of secondary loss of response varies. In smaller cohorts, as few as 15% of patients lose response to infliximab,[22] but in larger cohorts with longer follow-up, secondary loss of response has been reported in approximately half of patients.[8,23] In non-randomized studies of adalimumab, the incidence of secondary loss of response requiring dose escalation is also variable. Two large prospective trials, ACCESS[24] (n = 304) and CHOICE[25] (n = 673), found that secondary loss of response and dose escalation were required in approximately one third of patients. While we report higher incidence of secondary loss of response in our cohort, this likely reflects the longer duration of follow-up.

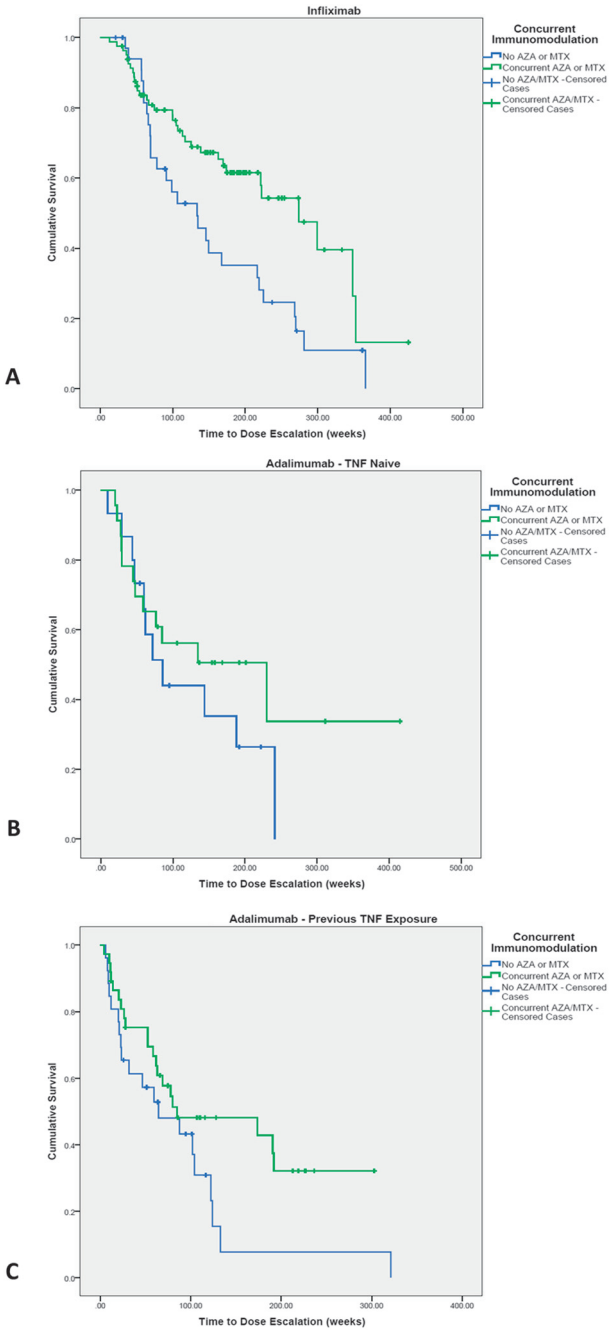

Figure 2 Kaplan–Meier survival curves of secondary loss of response requiring dose escalation for infliximab (A), TNF naïve adalimumab (B), and adalimumab with previous anti-TNF exposure (C), stratified by concurrent immunomodulation with azathioprine or methotrexate (green). Hashed lines indicate censored cases (maintained response to last follow-up). $p < 0.01$ for A, B, and C.

Most open label studies report outcomes at or before one year of treatment, but we followed anti-TNF therapy to a mean of greater than three years. Over time, a greater proportion of patients will lose response and require dose escalation; these late secondary non-responders were likely not captured in previous studies.

Among secondary loss of responders, varying times to dose escalation have been reported. Randomized trials have found median times to loss of response ranging from 38 weeks (ACCENT I, infliximab 5 mg/kg every 8 weeks) to 54 weeks (CHARM, adalimumab 40 mg every other week).[1,2] Not surprisingly, further heterogeneity is present among the open label cohort studies.[6,8,9,26–29] Several authors have reported single-center experiences where mean time to dose escalation occurs as quickly as two months.[7,30] Even in larger open label cohorts, dose escalation occurred rapidly; for instance, in a national Belgian cohort of 605 CD patients who responded to initial adalimumab therapy, Baert et al. reported that 34% of patients required dose escalation after a median of 7 months to maintain clinical response.[31]

We found the time to dose escalation in our cohort was significantly longer than what has been previously described in the literature, particularly for patients on infliximab, despite similar overall rates of secondary loss of response. We found median time to dose escalation was 99.3 weeks for infliximab, which is nearly twice as long as previously reported. The reason for this difference in time to dose escalation remains to be determined; however, one possible explanation relates to local protocolled standard of care optimization. In our clinic, anti-TNF induction therapy is optimized and typically consists of "triple therapy" with a defined corticosteroid taper and whenever possible, maintenance with concomitant immunosuppressives. Indeed, a higher proportion of patients in our cohort were on concurrent azathioprine or methotrexate, even in comparison to previous large prospective trials.[24] However, the optimal duration of combination therapy with immunomodulation and anti-TNF agents cannot be derived from this study.

Additionally, the approach to dose escalation in our clinic is protocolled to incorporate clinical, serological, and radiographical evidence of disease recurrence. In contrast, most previous studies that examined dose escalation did not have these protocolled approaches to induction, maintenance and loss of response.[6,8,9,26–29] The decision to intensify anti-TNF therapy is complex and while achieving symptomatic control is important, treatment options are limited after failure on one of the anti-TNF agents. Thus, dose escalation, without confirming disease activity, can result in the erroneous declaration of loss of response.

In our cohort, concurrent use of azathioprine or methotrexate significantly reduced risk of secondary loss of response (Table 3) and prolonged time to secondary loss of response and dose escalation (Fig. 2), regardless of anti-TNF agent and previous anti-TNF exposure. We hypothesize that this may be due to prevention of anti-drug antibody formation. Presence of anti-infliximab[32] and anti-adalimumab[7] antibodies has been associated with reduced serum trough drug levels and increased risk of loss of response. In the SONIC randomized controlled trial, Colombel et al. demonstrated that combination azathioprine and infliximab was superior to single agent therapy for reducing anti-infliximab antibody formation, achieving corticosteroid free remission at weeks 26 and 50, and improving mucosal healing.[33] Furthermore, in secondary analysis, we found a higher proportion of infliximab-treated patients receiving induction therapy from 2003 to 2008 experienced secondary loss of response compared to those receiving induction therapy from 2009 to 2013 (62.5% vs. 43.5%, $p = 0.04$). This may be related to increased concurrent

immunomodulator use in patients receiving induction from 2009 to 2013 (78.3% vs. 58.3%, p = 0.02), although this may also be confounded by length time bias wherein late secondary loss of responders in the 2009–2013 subgroup have not yet been captured due to shorter duration of follow-up.

The evidence supporting concurrent immunomodulation in patients treated with adalimumab is less clear. In a cohort of 168 CD patients, Karmiris et al. found that concurrent immunosuppressive therapy did not significantly reduce anti-adalimumab antibody formation, loss of response, or need for dose escalation. However, similar to our cohort, Karmiris et al. did demonstrate that concurrent immunomodulation prolonged time to dose escalation (17.0 weeks [12.0–27.5] for combination therapy vs. 12.0 weeks [8.0–22.0] for adalimumab alone, p = 0.008).[7] Unfortunately, our study was not able to assess the effect of immunogenicity as routine measurement of anti-drug antibody and serum trough drug levels was not available at our institution during the study period. This likely does impact treatment decisions in secondary loss of responders as patients who relapse in the setting of low serum trough drug levels may have greater clinical response to dose escalation compared to those losing response after developing anti-drug antibodies. This may be challenging to distinguish in real-life clinical practice as routine measurements of anti-drug antibodies and serum trough drug levels may not be available.

Previous anti-TNF therapy was not an independent predictor of loss of response in our cohort, but patients treated with adalimumab who had previous anti-TNF exposure trended towards earlier loss of response requiring dose escalation. Sample size likely limited our statistical power, as previous studies have found that this cohort of patients failing infliximab tends to have poorer outcomes compared to patients who are anti-TNF naïve. For instance, in the ACCESS trial, Panaccione et al. found patients with moderate-to-severe CD treated with adalimumab who had previously failed infliximab had lower rates of clinical remission (53% vs. 36%) and fistula healing (60% vs. 28%) at week 24 compared to patients who were anti-TNF naïve. Other authors have also suggested that infliximab failure predicts increased risk for adalimumab dose escalation.[34] This cohort of CD patients failing prior anti-TNF therapy may have TNF-resistant disease phenotype or severe underlying disease requiring aggressive medical and surgical intervention.

There are several other limitations to our study. Primarily, this was a retrospective evaluation. Due to the study design, certain factors that may affect maintenance of anti-TNF response including endoscopic disease severity, smoking status, and body weight were inconsistently available. Retrospective review also introduces the possibility of recall bias. However, our findings are in keeping with the previous literature on anti-TNF dose escalation and the study design allowed analysis of a large cohort of patients followed long-term, which was one of the major strengths of this study. Retrospective analysis does not allow strict protocolled assessment of response and although this may confound comparison to previous studies, it also may more accurately reflect clinical based practice. Secondly, the initial decision for adalimumab versus infliximab therapy was non-randomized in our cohort, and was decided at the discretion of the patient and attending gastroenterologist. Although this introduces the possibility of bias in choice of anti-TNF for patients with more severe disease, baseline disease activity, disease characteristics, and presence of perianal disease was similar in all treatment groups. Thirdly, baseline HBI was unavailable for a proportion of patients in the cohort, excluding them from the multivariate logistic regression and Cox proportional hazard models. However, the patient baseline characteristics, anti-TNF induction, and loss of response outcomes in this group of patients are similar to that of the total cohort (see Supplemental Table 1) and thus, these results remain generalizable. Fourthly, our sample size is limited, particularly for the anti-TNF-naïve adalimumab-treated subgroup of patients, and conclusions in this subgroup should be interpreted as exploratory.

Finally, a limitation to any study of anti-TNF therapy in the outpatient setting is evaluation of adherence to medical therapy, which is difficult to assess and has an important impact on clinical outcomes. In the Crohn's disease population, a recent meta-analysis has suggested that adherence with adalimumab is poor[35] and our finding that time to secondary loss of response to infliximab is longer compared to adalimumab should be interpreted cautiously with this in consideration. In our clinic, during the study period, the protocolled bi-monthly follow up from IBD nurse specialist for patients on adalimumab, and coordinator follow-up for those on infliximab, attempts to decrease medication non-adherence or differences in potential non-adherence between biologics. However, medication non-compliance is a universal challenge in the treatment of nearly all chronic diseases, and efficacy of medical therapy in this setting should be reflected by real-life studies.

In conclusion, over half of CD patients in this large retrospective cohort demonstrated a secondary loss of response requiring anti-TNF dose escalation in long-term follow-up, irrespective of the anti-TNF agent. However, an earlier time to secondary loss of response and dose escalation was seen among patients treated with adalimumab compared to infliximab. The time to secondary loss of response was prolonged by concurrent use of immunosuppressive therapy with azathioprine or methotrexate, regardless of anti-TNF agent or previous anti-TNF exposure. Further investigation will be needed to determine whether long-term response to dose escalation is sustained.

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Conflicts of interest

RNF, KIK, and LAD have served as speakers and consultants for Abbvie Canada Inc and Janssen Canada Inc. The remaining authors have no conflict relative to this study.

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RNF is acting as the article guarantor and contributed to study design, data collection, data analysis, and manuscript drafting and editing. CM and DF contributed to data

collection, data analysis and manuscript drafting and editing. VH contributed to data analysis, and manuscript drafting and editing. KIK, LAD, BPH contributed to manuscript editing. All authors have approved the final version of the manuscript.

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