

Inflammatory bowel disease patients are frequently nonadherent to scheduled induction and maintenance infliximab therapy: A Canadian cohort study

Christopher Ma MD*, Chad J Evaschesen MD FRCPC*, Grenvil Gracias MD, Vivian W Huang MD FRCPC, Darryl K Fedorak BSc, Karen I Kroeker MD FRCPC, Levinus A Dieleman MD PhD, Brendan P Halloran MD FRCPC, Richard N Fedorak MD FRCPC

C Ma, CJ Evaschesen, G Gracias, et al. Inflammatory bowel disease patients are frequently nonadherent to scheduled induction and maintenance infliximab therapy: A Canadian cohort study. *Can J Gastroenterol Hepatol* 2015;29(6):309-314.

BACKGROUND: Adherence to maintenance medication regimens in inflammatory bowel disease patients has traditionally been poor. Although infliximab has demonstrated efficacy in inducing and maintaining disease remission, adherence to regularly scheduled infliximab infusions is required to maintain therapeutic trough drug levels and prevent the development of anti-infliximab antibodies.

OBJECTIVES: To characterize patient adherence to regularly scheduled induction and maintenance infliximab infusions.

METHODS: A retrospective cohort study was conducted evaluating adult outpatients with Crohn disease or ulcerative colitis on an induction or maintenance regimen of regularly scheduled infliximab from 2008 to 2010 at the University of Alberta (Edmonton, Alberta). Nonadherence was defined by a discrepancy of >72 h between the scheduled date of infusion and the actual date of administration. Patients were defined as nonadherent if they received <80% of their infliximab infusions per schedule.

RESULTS: A total of 215 patients (173 Crohn disease, 42 ulcerative colitis) met the inclusion criteria. Patients received a median of 12.0 infliximab infusions (interquartile range 7.0 to 13.0) during the study period; 412 induction and 1837 maintenance infliximab infusions were administered. Of 140 patients, 109 (77.9%) were adherent to their infliximab induction regimen, while 68 of 215 (31.6%) were adherent to their infliximab maintenance regimen. One hundred ninety-eight of 215 (92.1%) patients received at least one delayed maintenance infliximab infusion and 20 (10.1%) received maintenance infusions, on average, >1 week late.

CONCLUSIONS: While three-quarters of patients are adherent to infliximab induction therapy, fewer than one-third remained adherent to their scheduled maintenance infliximab regimen.

Key Words: Adherence; Crohn disease; Inflammatory bowel disease; Infliximab; Ulcerative colitis

Crohn disease (CD) and ulcerative colitis (UC) are chronic relapsing and remitting inflammatory bowel diseases (IBD). Similar to many chronic illnesses, lifelong therapy is typically required to maintain patients in remission. However, adherence to medical therapy in this cohort has traditionally been quite poor; a systematic review involving 4322 IBD patients found widely varying rates of nonadherence to maintenance medication regimens, including some studies reporting nonadherence rates as high as 72% (1). Multiple variables contribute to poor adherence, including illness-

Souvent, les patients atteints d'une maladie inflammatoire de l'intestin ne respectent pas le traitement d'induction et d'entretien prévu à l'infliximab : une étude de cohorte canadienne

HISTORIQUE : En général, les patients atteints d'une maladie inflammatoire de l'intestin respectent peu leur traitement médicamenteux. Même si l'efficacité de l'infliximab à induire et maintenir une rémission est démontrée, il faut adhérer aux perfusions régulières d'infliximab afin de maintenir les taux thérapeutiques minimaux et de prévenir l'apparition d'anticorps anti-infliximab.

OBJECTIF : Caractériser l'adhérence des patients à des perfusions régulières d'induction et d'entretien à l'infliximab.

MÉTHODOLOGIE : Entre 2008 et 2010, des chercheurs de l'université de l'Alberta, à Edmonton, ont mené une étude de cohorte rétrospective pour évaluer des patients ambulatoires adultes atteints de la maladie de Crohn ou de la colite ulcéreuse suivant un traitement régulier d'induction ou d'entretien à l'infliximab. La non-adhérence au traitement était définie par un écart de plus de 72 heures entre la date de perfusion prévue et la date d'administration. Les patients étaient définis comme n'adhérant pas au traitement s'ils recevaient moins de 80 % de leurs perfusions d'infliximab par série.

RÉSULTATS : Au total, 215 patients (173 atteints de la maladie de Crohn, 42 de la colite ulcéreuse) respectaient les critères d'inclusion. Ils ont reçu une médiane de 12,0 perfusions d'infliximab (plage interquartile de 7,0 à 13,0) pendant la période de l'étude, soit 412 inductions et 1 837 traitements d'entretien. Des 140 patients, 109 (77,9 %) adhéraient au traitement d'induction à l'infliximab, et 68 sur 215 (31,6 %), au traitement d'entretien. Cependant, 198 des 215 patients (92,1 %) ont tardé avant de recevoir au moins une perfusion d'entretien à l'infliximab, dont 20 (10,1 %) avaient en moyenne une semaine de retard.

CONCLUSIONS : Les trois quarts des patients adhèrent au traitement d'induction à l'infliximab, mais moins du tiers continue d'adhérer au traitement d'entretien prévu.

treatment- and patient-related factors (2). Nonadherence in this population has been associated with poor outcomes and disease relapse (3); thus, compliance with therapy represents a critical component of the management plan.

Over the past decade, IBD patients with moderate-to-severe disease are increasingly being treated with biologic agents targeting tumour necrosis factor (TNF)-alpha, including infliximab. While infliximab has demonstrated efficacy in randomized controlled trials for the induction and maintenance of remission in both CD (4,5) and

*Authors who contributed equally to the work

Division of Gastroenterology, University of Alberta, Edmonton, Alberta

Correspondence: Dr Richard N Fedorak, University of Alberta, 2-14A Zeidler Building, Edmonton, Alberta T6G 2X8. Telephone 780-492-6941,

fax 780-492-8121, e-mail richard.fedorak@ualberta.ca

Received for publication March 24, 2015. Accepted May 9, 2015

UC (6), its 'real-life' clinical effectiveness may be hampered by poor adherence. Specifically, secondary loss of response during maintenance therapy is a common phenomenon encountered in more than one-half of IBD patients receiving anti-TNF agents (7), with development of antidrug antibodies playing a central role. In patients treated with infliximab, missing or delaying regularly scheduled infusions may contribute to drug immunogenicity (8), decreased serum trough drug levels (9) and, ultimately, adverse clinical outcomes. In fact, frequently missing or delaying infliximab infusions can mimic an episodic administration regimen, which compared with fixed scheduled infusion protocols in subgroup analysis of the A Crohn's Disease Clinical Trial Evaluating Infliximab in a New Long-Term Treatment Regimen (ACCENT I) trial resulted in increased likelihood of antidrug antibody development (28% versus 9%), reduced likelihood of mucosal healing (18% versus 44%), increased hospitalizations (38% versus 23%), and reduced clinical response and remission rates (10).

Several authors have evaluated adherence to infliximab therapy in patients with IBD. Recently, Lopez et al (11) reviewed 13 studies evaluating adherence in this cohort and demonstrated varying rates of adherence ranging from 36% to 96%. Nevertheless, there are several limitations to the results from these studies. Most findings are extrapolated from pharmacy refill data or administrative databases (12), medical insurance claims (13) or self-reported questionnaires (14), which are inherently subject to under-reporting, recall bias and coding inaccuracy. Furthermore, they may not reflect true medication adherence because these types of data do not capture administration of delayed or early infusions. Defining nonadherence is also particularly challenging and highly heterogeneous: previous authors have used the number of missed or delayed infusions, missing refill prescriptions, medication possession ratio <80% or inadequate total infusions over a defined time period; however, these are all surrogate measures for assessing medication adherence.

Thus, in the present study, we assessed the 'true' adherence to regularly scheduled infliximab induction and maintenance therapy using manually searched medical chart review of scheduled and administered infliximab infusions. We define the proportion of patients who were nonadherent to infliximab therapy, characterize the incidence of early and delayed infusions and describe the variance around scheduled infusions. In a secondary analysis, we examined risk factors predicting nonadherence to long-term maintenance infliximab therapy.

METHODS

Study design and setting

The present retrospective cohort study was performed using data collected from CD and UC outpatients receiving maintenance infliximab therapy from August 2008 to August 2010, at the University of Alberta (Edmonton, Alberta). Patients were identified from the Division of Gastroenterology inflammatory bowel disease electronic database.

Patient population

Patients were eligible for inclusion if they met the following criteria: adult (>17 years of age); diagnosis of CD or UC; receiving either initial induction regimen of infliximab 5 mg/kg at weeks 0, 2 and 6; or advanced onto a regularly scheduled maintenance outpatient infliximab regimen. Disease phenotype, infliximab dose escalation, concurrent medical therapy and duration of infliximab before the study were not contraindications to inclusion.

Outcomes and definitions

The primary objectives of the present study were to: determine the proportion of IBD patients who are adherent to a regularly scheduled infliximab infusion protocol; and to characterize the incidence of early and delayed infliximab administration. The secondary objective was to assess risk factors predicting infliximab nonadherence.

For the present study, nonadherence to a single infliximab infusion was defined as a discrepancy of >72 h between the scheduled date of infliximab infusion and the actual date of administered infusion. There is no previous widely accepted definition for adherence to an

individual infliximab infusion – a 72 h cut-off was decided on because this creates a six-day window for the patient to receive their infusion per protocol (three days before and three days after their scheduled infusion date). It was agreed that this was a sufficient time frame to accommodate statutory holidays, infusion clinic availability and minor personal reasons that may briefly delay or expedite the infusion schedule. A missed infliximab infusion was defined during maintenance therapy if the delay between administered infusions was >12 weeks.

Overall patient nonadherence was defined if <80% of infliximab infusions were received adherently. Thus, patients requiring a temporary delay in infliximab infusions due to infection, perianal disease, holidays, etc, were not deemed to be nonadherent to therapy. This cut-off was based on previous studies involving IBD patients in which definitions of nonadherence included medication possession ratio <80% and receiving <7 infliximab infusions in first year of therapy (seven infusions represents approximately 80% of the potential infusions for the first year of therapy, including three induction and six maintenance infusions) (15,16).

The scheduled date of infliximab infusion was determined by the patient's optimal infliximab infusion regimen (ie, the next scheduled infusion would be eight weeks from the previous administered infusion if the patients is receiving maintenance therapy every eight weeks). For induction therapy, the scheduled infusion dates were at weeks 0, 2 and 6. For maintenance therapy, the scheduled infusion dates were every eight weeks from the previous infusion. For patients requiring dose escalation during maintenance therapy and receiving infusions more frequently than every eight weeks, the scheduled date of infusion was adjusted accordingly.

Study follow-up time was defined from the date of first administered infusion to the date of last infusion received during the study inclusion period; total duration of infliximab therapy was determined from the date of first infliximab induction infusion.

Data collection

Data were extracted from official infliximab infusion records by two of the authors (CJE and GG) using a standardized case report form. These records included baseline patient demographic data, lifetime infliximab infusions received, infusion frequency (induction versus maintenance, maintenance infusion every eight weeks versus escalated/de-escalated schedule), actual date of administered infusion and previous medication exposure. Data were reviewed by two of the authors (CM and RNF).

Baseline patient data collected included sex, age, IBD diagnosis (CD versus UC), previous medical therapy (mesalamine or 5-aminosalicylate products, azathioprine or methotrexate) and total lifetime infliximab infusions received before inclusion. Subsequently, the scheduled infusion date was identified as described above and actual date of administered infliximab using the official infusion record. Clinical outcomes, including disease flares, hospital admissions and IBD-related surgeries, were not available in the infusion records (these outcomes were outside the scope of the present study).

Statistical methods

For continuous variables, mean, SD, median and interquartile range (IQR) were calculated. The variance in days between date of actual administered and date of scheduled infusion was calculated for each infusion.

A post hoc sensitivity analysis was performed. Because there is no consensus definition of nonadherence to an individual infliximab infusion, adherence to maintenance infliximab therapy was determined if the definition of adherence was relaxed to allow a discrepancy between scheduled and administered infusion of >7 days (from three days). A sensitivity analysis was also performed whereby patients receiving <6 maintenance infusions were excluded; this enhanced the power of the analysis to better account for temporary causes of nonadherence.

Univariate and multivariate logistic regression analyses were performed to examine the association between patient variables and

TABLE 1
Baseline patient demographics of 215 inflammatory bowel disease patients managed with induction or maintenance infliximab at the University of Alberta Inflammatory Bowel Disease Consultation and Research Clinic (Edmonton, Alberta) between 2008 and 2010

Characteristic	
Inflammatory bowel disease diagnosis	
Crohn disease	173 (80.5)
Ulcerative colitis	42 (19.5)
Infliximab dosing	
Induction dosing	140 (65.1)
Maintenance dosing	215 (100.0)
Infusion escalation during maintenance therapy	144 (67.0)
Sex	
Male	120 (55.8)
Female	95 (44.2)
Age, years, mean \pm SD	
At study inclusion	41.4 \pm 13.7
At infliximab induction	40.8 \pm 13.7
Previous medications	
Mesalamine or 5-ASA products	209 (97.2)
Immunomodulators (azathioprine or methotrexate)	197 (91.6)
Infliximab Infusions, median (IQR)	
Lifetime infusions	12.0 (7.0–19.5)
Infusions during the study period	12.0 (7.0–13.0)
Follow-up, weeks, median (IQR)	
Study follow-up duration	80.1 (38.7–100.9)
Total time on infliximab	80.1 (38.7–138.7)

Data presented as n (%) unless otherwise indicated. ASA Aminosalicylate; IQR Interquartile range

nonadherence, with results expressed as OR with 95% CI. Age (defined as >40 and ≤ 40 years), sex, IBD diagnosis (CD versus UC), previous medication exposure, requirement for infusion escalation and lifetime infliximab infusions (defined as ≤ 7 infusions, eight to 12 infusions and ≥ 13 infusions) were a priori included in the regression model. Fistulizing disease was not included in the logistic regression model because it would not apply to patients with UC.

Statistical analysis was performed using SPSS version 22.0 (IBM Corporation, USA).

RESULTS

Baseline patient characteristics

Patient demographics are summarized in Table 1. A total of 215 patients (173 CD, 42 UC) met the inclusion criteria. One hundred forty (65.1%) patients received infliximab induction dosing during the study period and all patients received at least one maintenance infusion of infliximab. Patients received a median of 12.0 infliximab infusions (IQR 7.0 to 19.5) lifetime and were followed for a median duration of 80.1 weeks (IQR 38.7 to 100.9 weeks) during the study.

Forty-one (23.7%) CD patients had fistulizing disease; 144 patients (67.0%) required dose escalation of infliximab to more frequent infusions than every eight weeks (escalations to maintenance infusion every four to seven weeks, depending on the clinical circumstances and clinician judgement). Almost all patients had previous exposure to mesalamine, azathioprine or methotrexate.

Adherence with infliximab induction therapy

Adherence to infliximab induction infusions (5 mg/kg at weeks 0, 2 and 6) is summarized in Table 2. One hundred forty patients received a mean (\pm SD) of 2.9 \pm 0.3 infliximab induction infusions. A total of 412 infliximab induction infusions were administered.

TABLE 2
Patient adherence* to infliximab (IFX) induction therapy and characteristics of early and delayed IFX induction infusions in 140 inflammatory bowel disease patients

Variable	
IFX induction, n	
Patients receiving IFX induction therapy	140
Total administered IFX induction infusions	412
Adherence to induction IFX	
Patients adherent to IFX induction, n (%)	109 (77.9)
Adherent IFX induction infusions per patient, mean \pm SD	2.7 \pm 0.6
Delayed induction infusions	
Patients receiving at least one delayed IFX infusion, n (%)	65 (46.4)
Late infusions per patient, mean \pm SD	0.5 \pm 0.6
Late days per infusion, mean \pm SD	1.5 \pm 1.8
Cumulative late days per patient, mean \pm SD	2.1 \pm 4.1
Early induction infusions	
Patients receiving at least one early IFX infusion, n (%)	67 (47.9)
Early infusions per patient, mean \pm SD	0.5 \pm 0.6
Early days per infusion, mean \pm SD	1.2 \pm 1.6
Cumulative early days per patient, mean \pm SD	1.1 \pm 2.8

*Defined as receiving $>80\%$ of induction infusions within 72 h of the regularly scheduled date of infusion at weeks 0, 2 and 6

TABLE 3
Patient adherence* to infliximab (IFX) maintenance therapy and characteristics of early and delayed IFX maintenance infusions in 215 inflammatory bowel disease patients

IFX maintenance	
Patients receiving IFX maintenance therapy, n	215
IFX maintenance infusions, median (IQR)	9.0 (4.0–13.0)
Total administered IFX maintenance infusions, n	1837
Adherence to maintenance IFX	
Patients adherent to IFX maintenance, n (%)	68 (31.6)
Adherent IFX maintenance infusions per patient, mean \pm SD	6.0 \pm 3.8
Total missed IFX infusions [†] , n (%)	32 (1.7)
Delayed maintenance infusions	
Patients receiving at least one delayed IFX infusion, n (%)	198 (92.1)
Late infusions per patient, mean \pm SD	3.5 \pm 2.5
Late days per infusion, days, mean \pm SD	3.3 \pm 4.6
Patients delaying infusions, on average, >7 days, n (%)	20 (10.1)
Early maintenance infusions	
Patients receiving at least one early IFX infusion, n (%)	171 (79.5)
Early infusions per patient, mean \pm SD	2.1 \pm 1.8
Early days per infusion, days, mean \pm SD	1.2 \pm 1.6

*Patient adherence defined as receiving $>80\%$ of maintenance infusions within 72 h of regularly scheduled date of infusion; [†]A maintenance infliximab infusion was considered to be missed if the delay between administered infusions was >12 weeks

Of 140 patients, 109 (77.9%) were adherent to their infliximab induction infusions and received, on average, 2.7 \pm 0.6 induction infusions with adherence. Sixty-five (46.4%) patients received at least one delayed induction infusion, but mean delay time was short (1.5 \pm 1.8 days). A similar number of patients received at least one early infliximab induction infusion (n=67 [47.9%]).

Adherence to infliximab maintenance therapy

Adherence to infliximab maintenance therapy is summarized in Table 3. Two hundred fifteen patients received a total of 1837 infliximab maintenance infusions. Over the two-year study period, patients received a median of 9.0 maintenance infusions (IQR 4.0 to 13.0).

Sixty-eight of 215 (31.6%) patients were adherent to $>80\%$ of their infliximab maintenance infusions. On average, patients were adherent

to 6.0 ± 3.8 maintenance infliximab infusions over the follow-up period and, on average, accumulated 25.8 ± 35.5 late days. Only 32 maintenance infliximab infusions were completely missed; however, nearly all (92.1% [198 of 215]) patients received at least one delayed maintenance infusion. Although the mean delay per infusion was 3.3 ± 4.6 days, 10% (20 of 198) of patients received delayed infusions, on average, >1 week late.

Mean variance from the scheduled infliximab maintenance infusion was 4.0 ± 4.6 days. As such, a patient would be expected to accrue a dropped infliximab maintenance infusion every 13.9 infusions (112.0 weeks) based on the standard maintenance regimen of infliximab infusion every eight weeks. Among the 20 patients experiencing a mean delay in administration of infliximab >7 days, a dropped infliximab maintenance infusion would be accrued every 33.3 weeks.

Sensitivity analysis

Exclusion of patients receiving <6 maintenance infusions in sensitivity analysis did not change overall adherence to therapy: only 46 of 145 (31.7%) patients in this cohort were adherent to their maintenance regimen. When the definition of nonadherence to an individual infliximab infusion was relaxed to allow a discrepancy between scheduled and administered infusion date of >7 days, 101 of 215 (46.5%) patients were adherent to $>80\%$ of their infliximab maintenance infusions.

Predictors of nonadherence during maintenance therapy

Univariate and multivariate ORs for risk factors predicting nonadherence to infliximab maintenance therapy are summarized in Appendix 1. Only male sex was associated with slightly increased risk for nonadherence in both univariate (OR 1.73 [95% CI 1.00 to 2.99]; $P=0.049$) and multivariate (OR 1.77 [95% CI 1.01 to 3.11]; $P=0.046$) regression analysis. No other factors reached statistical significance.

DISCUSSION

Infliximab has a central role in the management of patients with moderate-to-severe IBD and, although it has demonstrated efficacy in randomized clinical trials, real-life clinical effectiveness may be limited by poor adherence. Previous studies evaluating anti-TNF therapy compliance in this cohort have primarily used administrative data and surrogate markers of adherence such as medication possession ratio (15). While these measures capture substantial lapses in adherence, they lack the resolution to identify nonadherence on an infusion-to-infusion basis. Here, we present a large Canadian retrospective evaluation of 215 IBD patients treated with infliximab, and assess through detailed chart review, the true adherence to both induction and maintenance infliximab infusion regimens. We found that while 77.9% of patients were adherent to induction infusions, fewer than one-third of patients had sustained infusion adherence and 10% will experience delayed infusions, on average, >1 week from the ideal scheduled dosing protocol during maintenance therapy.

Adherence to infliximab was first examined by Kane et al (12) in 2006; they described 96% adherence to therapy after retrospectively reviewing 1185 infusions using administrative and pharmacy refill data. This incredibly high adherence rate relates to the use of 'no show' visits as the definition for nonadherence. Similarly, we found a very low incidence of completely missed infusions (1.7%). Other authors, using administrative database definitions for nonadherence including medication possession ratio $<80\%$ or <7 infusions during the first year of treatment, have also found varying rates of adherence, ranging from 57.1% to 79.8% (13,14,16).

In contrast to previous studies in which nonadherence was defined only by completely missed infusions, we believe that frequently delayed infliximab infusions are a reflection of poor patient compliance with the treatment regimen. Thus, we used a generous definition of adherence to both individual infusions (within six days of scheduled infusion)

as well as overall adherence (80% of infusions received per schedule) to describe patient adherence to infliximab therapy with greater resolution. Other authors have used similarly constructed composite definitions of nonadherence (17). Our definition for nonadherence accounts for common barriers to compliance including patient inconvenience or statutory holidays (patients can schedule their infusion for the next available business day if the scheduled infusion date falls on a weekend or holiday and still be considered adherent to therapy) as well as unpredictable or excusable reasons for delaying infliximab infusions such as personal emergencies, infections or drug adverse effects.

Overall, adherence to anti-TNF therapy, given its necessity for scheduled intravenous administrations, may be slightly better compared with adherence to oral maintenance therapies including 5-aminosalicylate products and immunomodulators. A systematic review of oral therapy compliance in IBD patients by Jackson et al (1) found that most studies report approximately 30% to 45% nonadherence rates. This disparity may reflect differences in disease activity (highly active disease requiring biologic therapy may prompt better adherence), route and schedule of administration (intravenous versus oral, every eight week maintenance versus daily therapy), and more frequent clinician follow-up and monitoring. However, it should be highlighted that even among patients on infliximab therapy, there exists a significant rate of nonadherence. Exploring reasons for nonadherence was outside the scope of the present study but has been evaluated elsewhere (18).

Few studies have directly evaluated delays to individual scheduled infliximab infusions and are predominantly reported in abstract form. In a small retrospective cohort of 82 IBD patients on infliximab, Duncan et al (19) found that infusions were postponed in 14 of 82 (17%) patients over 12-month follow-up. Similarly, another abstract by Angelucci et al (20) found that 19.1% of infusions were delayed, median delayed administrations per patient was three infusions, and the median delay was 9.6 days (range one to 35 days). Both authors cite 'technical' reasons, including patient forgetfulness, inconvenience and intentional nonadministration as the reason for delayed infusion in $>90\%$ of cases. In our cohort, we report even higher rates of delayed infusions, delayed infusions per patient and total accumulated late days, most likely related to our increased sample size and duration of follow-up. Specific indication for delayed infliximab administration is not part of our infliximab infusion record. However, medically appropriate indications for delaying infusions, such as adverse events or infections, are accounted for by our definition of nonadherence. These specific indications for delaying infusions would presumably only affect a minority of the patient's total infusions and, thus, they should still be able to receive $>80\%$ of their infusions with adherence. In fact, Angelucci et al (20) report that only 3.3% of nonadherent infusions were due to adverse events in their cohort.

Delays and nonadherence with infliximab therapy may have significant implications on clinical outcomes in patients with IBD. In particular, we hypothesize that nonadherence has a substantial impact on long-term maintenance of clinical response and secondary loss of response. In both prospective (10) and retrospective (21) cohorts, it has been shown that patients managed with regularly scheduled infliximab compared with episodically administered therapy have improved outcomes for mucosal healing, disease-related hospitalizations and surgeries, and maintained clinical response. While all patients in our cohort were on scheduled therapy, prolonged and recurrent delays to infusion can mimic a more episodic pattern of administration. Unfortunately, clinical outcomes, including hospitalizations, surgeries and disease flares, are not tracked in our infliximab infusion records. Thus, we are unable to correlate infliximab adherence with disease outcomes, although this should be evaluated in future studies.

The mechanism behind primary and secondary loss of response to infliximab is influenced by subtherapeutic serum trough drug levels predisposing to the formation of neutralizing anti-infliximab antibodies (22). Recently, in a post hoc analysis of the ACCENT trial,

Cornillie et al (23) found that CD patients with week-14 infliximab trough level ≥ 3.5 $\mu\text{g/mL}$ were 3.5 times more likely to achieve durable sustained response through week 54 of therapy (OR 3.5 [95% CI 1.1 to 11.4]). Similar evidence exists in UC, in which detectable serum infliximab drug levels are significantly associated with clinical remission and decreased risk for colectomy (24). We hypothesize that delayed and nonadherent infliximab infusions increase the time during which patients have subtherapeutic infliximab trough levels and are predisposed to forming antidrug antibodies. Therapeutic drug monitoring with infliximab trough levels and antibody prevalence was not clinically available during the time of the study in our jurisdiction. Future studies should evaluate the relationship between delays in administered infliximab, therapeutic drug monitoring and, ultimately, clinical outcomes.

Nonadherence to infliximab maintenance therapy also has significant implications on health care utilization (25). Using the Integrated Health Care Information Service claims database, Kane et al (16) found significantly increased health care utilization costs among non-adherent CD patients on infliximab, who were 2.5 times more likely to require CD-related hospitalization, had 90% greater CD-related medical costs and 115% greater hospitalization costs compared with infliximab-adherent patients. Wan et al (26) estimated treatment costs using propensity-weighted regression models and reported similar results. Although nonadherent patients had expectedly reduced infliximab drug costs (\$14,889 versus \$28,289; $P < 0.001$), they had substantially increased costs for hospitalizations (\$17,634 versus \$2,458; $P < 0.001$), outpatient visits (\$10,909 versus \$7,357; $P < 0.001$) and emergency room visits (\$458 versus \$236; $P < 0.001$).

Early infusions did occur in our cohort, although this was less common and patients accumulated fewer early days compared with delayed infusions (6.9 early versus 25.8 late days). Although earlier infusion is likely preferable to delayed infusion to ensure ongoing maintenance of clinical response, excessively early administration may result in elevated infliximab trough levels, which have been shown to be associated with adverse events including dermatological reactions (27).

Definitive predictors of infliximab adherence have not been consistently reported across multiple studies (11,28). Kane et al (12) previously found that female patients were more likely to be nonadherent to infliximab but interestingly, the opposite trend was observed in our cohort, and nonadherent behaviours have been well described in male patients by other authors (29,30). Whether this relates to differences in patient population, financial drug coverage, temporal trends in infliximab use or sampling error is unclear. Kane et al (12) also reported that patients were more likely to be nonadherent for an infusion > 18 weeks after induction; although not statistically significant in our regression analysis, the higher rate of adherence observed during induction therapy in our cohort compared with maintenance therapy suggests attrition of patient adherence behaviours over time. Additionally, we found that requirement for infusion escalation trended toward increased nonadherence; we hypothesize that common 'technical' reasons for delayed infusions such as forgetfulness and inconvenience are magnified in patients requiring more frequent infliximab infusions.

There were several limitations to the present study. First, although detailed review of infusion records enabled us to analyze infliximab drug adherence with more resolution than previous studies, we were limited in collecting other clinical parameters, including disease phenotype (particularly for CD), severity of disease and disease activity, clinical response and remission status, concurrent medical therapy and non-invasive biomarkers of inflammation (eg, C-reactive protein). This limited the power of our regression analysis for identifying predictors of

nonadherence. A second limitation was that reasons for nonadherence were not available based on the infusion record. Although previous authors have defined patient-related 'technical' factors as being the predominant reason for nonadherence, we are unable to confirm this here. Medical reasons for delaying infliximab infusions such as opportunistic infections could not be captured in our data set, but we have attempted to minimize this potential misclassification bias using a composite definition of nonadherence as described above. While the criterion for defining adherence to an individual infliximab infusion may appear strict (within 72 h of schedule), this actually creates a six-day window for the patient to receive their infusion per protocol. Even when the definition for adherence was extended to seven days in the sensitivity analysis, fewer than one-half of patients were adherent.

Third, data are available to 2010 but may be less generalizable because experience with infliximab has evolved. Additionally, there may be referral bias because the present study was conducted at a tertiary care centre. In less specialized community gastroenterology practices, adherence to therapy may be even worse, particularly if infusion sites are not centralized, potentially amplifying the effects of preventable reasons associated with poor compliance (eg, inconvenience).

Finally, although we recognize that therapeutic drug monitoring will become a critical component of IBD management moving forward, data regarding serum infliximab trough levels and antibodies to infliximab were not available in our jurisdiction at the time of the study. Furthermore, clinical outcomes relevant to patients with IBD, including hospitalization, surgery and disease flare, are not recorded in our infliximab infusion database. These are major outcomes of interest associated with anti-TNF therapy adherence but were outside the scope of the present study and should be evaluated in future studies.

CONCLUSION

Although three-quarters of IBD patients were adherent to infliximab induction therapy, only one-third sustained adherence during maintenance regimens. Frequently, patients on infliximab experience delays to infusion, and future studies should evaluate whether these delays result in altered drug immunogenicity, increased anti-infliximab antibody formation or adverse patient outcomes.

DISCLOSURES: RNF has served as a consultant and advisory board member for AbbVie Canada Inc and Janssen Canada Inc, and received clinical/basic research grants from AbbVie and Janssen. KIK, LAD and BPH have served as consultants and speakers for AbbVie and Janssen. The remaining authors have no financial disclosures or conflicts of interest to declare.

FUNDING: This study was funded, in part, by the Alberta Innovates Health Solutions, Alberta Inflammatory Bowel Disease Consortium, and the Centre of Excellence for Gastrointestinal Inflammation and Immunity Research (CEGIIR).

AUTHOR CONTRIBUTIONS: RNF is acting as the article guarantor and contributed to study design, data collection, data analysis and manuscript editing. CM contributed to data analysis, manuscript drafting, and editing. CJE contributed to study design, data collection and data analysis. GG contributed to data collection and data analysis. VH, DKE, KIK, LAD and BPH contributed to manuscript editing. All authors have approved the final version of the manuscript, including the authorship list.

APPENDIX 1
Univariate and multivariate logistic regression analyses of risk factors predicting nonadherence* to infliximab maintenance therapy in 68 adherent and 147 nonadherent inflammatory bowel disease (IBD) patients

Risk factor predicting non-adherence to maintenance infliximab therapy	OR (95% CI)	
	Univariate	Multivariate
IBD diagnosis		
Crohn disease	1.00	1.00
Ulcerative colitis	0.74 (0.37–1.46)	0.62 (0.29–1.29)
Male sex	1.73 (1.00–2.99)	1.77 (1.01–3.11)
Age >40 years	1.43 (0.77–2.66)	1.37 (0.71–2.64)
Previous mesalamine/5-ASA exposure	0.87 (0.17–4.39)	0.64 (0.11–3.54)
Previous azathioprine or methotrexate	0.67 (0.26–1.78)	0.64 (0.22–1.84)
Requirement for infliximab infusion escalation	1.54 (0.86–2.74)	1.40 (0.67–2.94)
Lifetime infliximab infusions		
≤7	1.00	1.00
8–12	1.52 (0.71–3.26)	1.44 (0.65–3.15)
≥13	0.81 (0.43–1.53)	0.93 (0.43–2.04)

*Nonadherence defined as receiving <80% of infliximab maintenance infusions within 72 h of scheduled date. ASA Aminosalicylate

REFERENCES

- Jackson CA, Clatworthy J, Robinson A, Horne R. Factors associated with non-adherence to oral medication for inflammatory bowel disease: A systematic review. *Am J Gastroenterol* 2010;105:525-39.
- Lopez-Sanroman A, Bermejo F. Review article: How to control and improve adherence to therapy in inflammatory bowel disease. *Aliment Pharmacol Ther* 2006;(24 Suppl 3):45-9.
- Kane S, Huo D, Aikens J, Hanauer S. Medication nonadherence and the outcomes of patients with quiescent ulcerative colitis. *Am J Med* 2003;114:39-43.
- Hanauer SB, Feagan BG, Lichtenstein GR, et al. Maintenance infliximab for Crohn's disease: The ACCENT I randomised trial. *Lancet* 2002;359:1541-9.
- Sands BE, Anderson FH, Bernstein CN, et al. Infliximab maintenance therapy for fistulizing Crohn's disease. *N Engl J Med* 2004;350:876-85.
- Rutgeerts P, Sandborn WJ, Feagan BG, et al. Infliximab for induction and maintenance therapy for ulcerative colitis. *N Engl J Med* 2005;353:2462-76.
- Ma C, Huang V, Fedorak DK, et al. 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. *J Crohn's Colitis* 2014;8:1454-63.
- Hanauer SB, Wagner CL, Bala M, et al. Incidence and importance of antibody responses to infliximab after maintenance or episodic treatment in Crohn's disease. *Clin Gastroenterol Hepatol* 2004;2:542-53.
- Maser EA, Vilella R, Silverberg MS, Greenberg GR. Association of trough serum infliximab to clinical outcome after scheduled maintenance treatment for Crohn's disease. *Clin Gastroenterol Hepatol* 2006;4:1248-54.
- Rutgeerts P, Feagan BG, Lichtenstein GR, et al. Comparison of scheduled and episodic treatment strategies of infliximab in Crohn's disease. *Gastroenterology* 2004;126:402-13.
- Lopez A, Billioud V, Peyrin-Biroulet C, Peyrin-Biroulet L. Adherence to anti-TNF therapy in inflammatory bowel diseases: A systematic review. *Inflamm Bowel Dis* 2013;19:1528-33.
- Kane S, Dixon L. Adherence rates with infliximab therapy in Crohn's disease. *Aliment Pharmacol Ther* 2006;24:1099-103.
- Carter CT, Leher H, Smith P, Smith DB, Waters HC. Impact of persistence with infliximab on hospitalizations in ulcerative colitis. *Am J Manag Care* 2011;17:385-92.
- Kitney L, Turner JM, Spady D, et al. Predictors of medication adherence in pediatric inflammatory bowel disease patients at the Stollery Children's Hospital. *Can J Gastroenterol* 2009;23:811-5.
- Carter CT, Waters HC, Smith DB. Effect of a continuous measure of adherence with infliximab maintenance treatment on inpatient outcomes in Crohn's disease. *Patient Prefer Adherence* 2012;6:417-26.
- Kane SV, Chao J, Mulani PM. Adherence to infliximab maintenance therapy and health care utilization and costs by Crohn's disease patients. *Adv Ther* 2009;26:936-46.
- Arranz EM, Arranz MDM, Herranz MJ, et al. Compliance to the scheduled treatment with infliximab. Experience in a tertiary care hospital. *J Crohn's Colitis* 2012;6:S156.
- Horne R, Parham R, Driscoll R, Robinson A. Patients' attitudes to medicines and adherence to maintenance treatment in inflammatory bowel disease. *Inflamm Bowel Dis* 2009;15:837-44.
- Duncan J, Sastrillo M, Baker J, et al. An audit of adherence to anti-TNF therapy in patients with inflammatory bowel disease. *Gut* 2011;60:A141-A2.
- Angelucci E, Galletti B, De Nitto D, et al. Adherence to anti-tumor necrosis factor alpha therapy in inflammatory bowel diseases: An Italian monocentric experience. *Gut* 2011;60:A410.
- Stein DJ, Ananthakrishnan AN, Issa M, et al. Impact of prior irregular infliximab dosing on performance of long-term infliximab maintenance therapy in Crohn's disease. *Inflamm Bowel Dis* 2010;16:1173-9.
- Ben-Horin S, Chowers Y. Loss of response to anti-TNF treatments in Crohn's disease. *Aliment Pharmacol Ther* 2011;33:987-95.
- Cornillie F, Hanauer SB, Diamond RH, et al. Postinduction serum infliximab trough level and decrease of C-reactive protein level are associated with durable sustained response to infliximab: A retrospective analysis of the ACCENT I trial. *Gut* 2014;63:1721-7.
- Seow CH, Newman A, Irwin SP, Steinhart AH, Silverberg MS, Greenberg GR. Trough serum infliximab: A predictive factor of clinical outcome for infliximab treatment in acute ulcerative colitis. *Gut* 2010;59:49-54.
- Carter CT, Waters HC, Smith DB. Impact of infliximab adherence on Crohn's disease-related healthcare utilization and inpatient costs. *Adv Ther* 2011;28:671-83.
- Wan GJ, Kozma CM, Slaton TL, Olson WH, Feagan BG. Inflammatory bowel disease: healthcare costs for patients who are adherent or non-adherent with infliximab therapy. *J Med Economics* 2014;17:384-93.
- Huang V, Dhami N, Fedorak DK, et al. Infliximab trough levels are correlated with infliximab-associated adverse events. *Gastroenterology* 2014;146:S-1.
- Fidder HH, Singendonk MM, van der Have M, Oldenburg B, van Oijen MG. Low rates of adherence for tumor necrosis factor-alpha inhibitors in Crohn's disease and rheumatoid arthritis: Results of a systematic review. *World J Gastroenterol* 2013;19:4344-50.
- Sewitch MJ, Abrahamowicz M, Barkun A, et al. Patient nonadherence to medication in inflammatory bowel disease. *Am J Gastroenterol* 2003;98:1535-44.
- Kaplan GG, Panaccione R, Hubbard JN, et al. Inflammatory bowel disease patients who leave hospital against medical advice: Predictors and temporal trends. *Inflamm Bowel Dis* 2009;15:845-51.