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Higher Rates of Dose Optimisation for Infliximab Responders in Ulcerative Colitis than in Crohn's disease

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Abstract

Background: Studies have demonstrated the benefit of dose optimisation in the setting of secondary loss of response to infliximab in inflammatory bowel disease.
Aim: The aim of our study was to retrospectively investigate the rates of dose optimisation in an inflammatory bowel disease cohort receiving maintenance infliximab therapy to determine if there are different rates of dose optimisation between CD and UC cases and what impact this has on the durability of treatment effect.
Methods: Cases receiving infliximab for treatment of IBD between January 2008 and February 2014 were identified from an infusion centre database. Cases receiving ≥ 4 infusions were included in the study. Details of infusion dosing and timing were obtained. A dose increase from 5 mg/kg to 10 mg/kg or a reduction in the dosing interval was considered a dose optimisation.
Results: A total of 412 cases were included in the study; 52.7% required at least one dose optimisation. Dose optimisation was more common in UC than in CD cases [67.2% vs 46.3%, $p = 0.00006$]. The median time to dose optimisation was 7 months (95% confidence interval [CI] 4.8–9.2) for UC cases and 27 months [95% CI 7.3–46.7] for CD cases, $p = 0.00003$.
Conclusions: Here we have shown that dose optimisation is required more frequently in UC than in CD, with a significantly shorter time to dose optimisation for UC cases than CD cases. The majority of cases responding to induction therapy with infliximab will have a sustained response to therapy, but over 50% will require a dose optimisation during their treatment.

Keywords: Infliximab; dose optimisation; dose escalation; inflammatory bowel disease

1. Introduction

Infliximab is a monoclonal antibody against tumour necrosis factor alpha [TNFα], effective in the treatment of luminal and fistulising Crohn's disease [CD] and ulcerative colitis [UC].[1,2,3,4] Clinical trials have mainly focused on efficacy and safety over the first year of treatment and as a result there is a lack of data on the durability of treatment with infliximab for periods longer than 12 months. The majority of patients started on infliximab will be continued on it as long as they are responding, in part due to high rates of relapse associated with drug discontinuation in a number of studies, particularly in Crohn's disease.[5,6,7,8,9] In those maintained on infliximab in the long term, the annual risk for loss of infliximab response was calculated to be 13% per patient-year in a previous review.[10]

Studies have demonstrated the benefit of dose optimisation through dose increase or interval reduction, in the setting of secondary loss of response to infliximab or reduction in duration of response to therapy. Regueiro *et al.* found that 31% of CD patients required dose intensification at 12 months, and the need for intensification rose to 54% over a 30-month period.[11] Further, a Spanish study reported that over half of patients who were dose-optimised in the setting of secondary loss of response regained full remission.[12] The aim of our study was to investigate the rates of dose optimisation in an inflammatory bowel disease cohort receiving maintenance infliximab therapy, to determine whether there are different rates of dose optimisation between CD and UC cases; and what impact this has on the durability of treatment effect. We hypothesise that the larger inflammatory burden associated with UC results in higher infliximab dosing requirements.

2. Materials and Methods

All cases receiving infliximab for treatment of IBD between January 2008 and February 2014 at our institution were included. Data were retrospectively collected. Cases receiving four or more infusions were included, that is cases who responded to an induction regimen of three doses, typically at 0, 2, and 6 weeks. Details of infusion dosing and timing were obtained from a central infusion centre database. A dose increase from 5 mg/kg to 10 mg/kg or a sustained reduction in the dosing interval to less than 8 weeks was considered a dose optimisation. Increases in dose to account for an increase in body weight was not included as part of the definition of dose optimisation. This was a retrospective study and dose optimisation was made at the treating physicians' discretion. Usual clinical practice at our institution mandates that patients with a loss of response requiring dose optimisation are identified by an increase in clinical symptoms in addition to evidence of disease activity based on laboratory, endoscopic or radiological disease activity. All included cases were under the care of two experienced inflammatory bowel disease [IBD] physicians.

Baseline characteristics of cases were obtained from a central database or chart review where necessary. Where available, results of infliximab level testing for trough infliximab level [TLI] and antibodies to infliximab [ATI] were evaluated using a homogeneous mobility shift assay [Prometheus Laboratories]. The range for reported drug levels was < 1 µg/ml to > 34 µg/ml; therefore for analysis 34 µg/ml was used as a maximum serum trough level. The timing of drug level procurement was at the discretion of the treating physician. A drug level was considered to be a trough level if taken within 7 days of the next scheduled infusion.

Discrete variables were compared using χ^2 statistics. Non-parametric tests [Mann–Whitney] were used for comparison of infliximab levels between groups. An independent t test was used to compare normally distributed continuous variables. Only cases receiving their first dose of infliximab after January 2008 were included in time to event analysis [n = 252]. Kaplan-Meier curves were used to assess survival differences between groups. SPSS software was used for all statistical analysis [IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp.].

The study was approved by the institutional ethics review board of Mount Sinai Hospital, Toronto.

3. Results

A total of 412 cases were included in the study; 287 had a diagnosis of CD and 125 of UC. The average age at diagnosis was 21 years and 49% of cases were male. Baseline characteristics are shown in Table 1. The median year of diagnosis was 2002; 52.7% of cases required at least one dose optimisation. By the end of the study period, 66% of cases [n = 272] were on ongoing maintenance infliximab therapy. The average number of infusions received during the study period was 25 [range 4–68] with a mean cumulative dose of infliximab of 10 690mg. An increase in infliximab dose was made in 85 cases and a reduction in interval in 199 cases, with 67 cases requiring both a dose increase and interval reduction. Dose optimisation was more common in UC than in CD cases [67.2% vs 46.3%, p = 0.00006]. Both dose increase and interval reduction were more common within the UC cohort; 33.6% vs 15.0%, p = 0.00003 and 60.8% vs 42.9%, p = 0.001, respectively. Within the CD cohort, there was no difference in the rates of dose optimisation when broken down by disease behaviour or location, see Table 2. There was no difference in rates of dose optimisation in UC cases based on disease extent. CD cases required 4.37 mg/kg/month of infliximab vs 5.26 mg/kg/month for UC cases, p = 0.00003.

Table 1. Baseline characteristics.

	n [%]
Diagnosis	CD 287 [69.7] UC 125 [30.3]
Gender	Male 202 [49] Female 210 [51]
Age at diagnosis overall	Mean 21.1 years [SD 9.84]
CD	19.3
UC	25.0[a]
Age at first infliximab infusion overall[a]	Mean 29.9 years [SD 11.2]
CD	29.0
UC	31.5
Disease duration at first infliximab infusion[b]	Median 71.5 months [IQR 22.2–146.5]
CD	86.5 [IQR 32.5–157.5]
UC	43.5 [IQR 11–118.75]
Disease location CD	L1 32 [11.1]; L3 137 [47.7] L2 83 [28.9]; L4 35 [12.2]
UC	Pancolitis 104 [83.2], left-sided 21 [16.8]
CD disease behaviour[c]	B1 132 [46.8] B2 81 [28.7] B3 69 [24.5]

CD, Crohn's disease; UC, ulcerative colitis; IQR, interquartile range.
[a]CD vs UC, $p < 0.005$.
[b]252 cases commencing infliximab therapy after January 2008.
[c]Data available on 282 CD cases.

Table 2. Rates of dose optimisation [dose increase or interval reduction] broken down by disease type and location and behaviour.

	Any dose optimisation %	χ^2 *p-value*
CD	46.3	0.00006
UC	67.2	
CD B1	44.7	0.822
CD B2	46.9	
CD B3	49.3	
CD ileal involvement	47.1	0.702
CD colonic only	44.6	

CD, Crohn's disease; UC, ulcerative colitis.

A total of 252 cases were included in a survival analysis determining the cumulative probability of continued infliximab use and dose optimisation-free survival. The median time from diagnosis to infliximab therapy was 71.5 months [interquartile range 22.25–146.5]. The average time from diagnosis to infliximab therapy was longer for CD than for UC cases [113.89 vs 76.15 months, $p = 0.003$]; 78% continued on infliximab 12 months after commencing therapy, with 60% continuing beyond 3 years, see Figure 1. There was no difference in the time to infliximab discontinuation between UC and CD cases, see Figure 2. Nor was there a difference in time to discontinuation between those dose-optimised and those who remained on a standard dosing regimen, $p = 0.114$.

The median time to dose optimisation was 16 months [95% CI 8.3–23.7] with 46% of cases requiring a dose optimisation by 1 year and 61% by 3 years. Time to dose optimisation was statistically significantly shorter for UC than CD cases, log rank $p = 0.00003$, Figure 3. The median time to dose optimisation was 7 months [95% CI 4.8–9.2] for UC cases and 27 months [95% CI 7.3–46.7] for CD cases. Following dose optimisation there was no difference in the time to drug discontinuation between UC and CD cases, $p = 0.768$. Data on immunomodulator use was available in a subgroup of 187 [75%] cases included in this analysis. The difference in time to dose optimisation between the UC and CD groups remained statistically significant, log rank $p = 0.001$, when adjusted for immunomodulator use, Figure 4. Age at diagnosis, disease duration at infliximab initiation, and immunomodulator use were not significantly associated with a time to dose optimisation in a Cox regression analysis. For UC cases, there was no difference in time to dose optimisation for those with left-sided disease vs pancolitis, $p = 0.35$. Taking all cases together; those with isolated small bowel disease had a longer time to dose optimisation compared with those with colonic involvement [UC or colonic CD], $p = 0.012$.

Trough infliximab levels were available on 107 cases: 70 CD and 37 UC cases. There was no difference in the mean level between the two groups: 8.85 µg/ml vs 10.72 µg/ml, $p = 0.318$. The levels before any dose optimisation were lower in UC cases [$n = 6$] than in CD cases [$n = 13$], 1.98 µg/ml [SD +/- 2.5] vs 6.26 µg/ml [SD +/- 9.9], $p = 0.317$, though numbers in each group were low. ATI were present on at least one occasion in 26% of cases with available drug levels.

4. Discussion

Here we show, in a retrospective study with detailed analysis of infliximab dosing schedules, that UC patients require more frequent dose optimisation than CD cases. This resulted in similar rates of drug discontinuation and, in a subgroup, similar trough infliximab levels between the two groups: 46% of cases in this study required a dose optimisation within the first year of therapy. Data on rates of infliximab dose 'intensification' in UC compared with CD patients are limited.[13,14] We hypothesised that a higher inflammatory burden associated with UC explains this increased need for dose optimisation. Rapid drug clearance rates have been demonstrated in acute severe UC.[15] In addition, improved outcomes have been demonstrated in acute severe UC with an accelerated induction regimen.[16] A higher inflammatory burden could potentially result in a slower response to therapy; therefore, to negate the influence of a partial response to induction therapy requiring an early dose optimisation, we also performed analyses excluding those with a dose optimisation within the first 3 months and 6 months, and the difference seen between UC and CD cases was maintained [data not shown].

A Spanish study including 309 CD cases reported an annual risk of loss of response to infliximab of 12% per patient-year of treatment; of those who received an escalation of their infliximab therapy following loss of response, 56% re-achieved remission and 40% had a partial response.[12] The authors reported that the concurrent use of an immunomodulator is associated with a significant improvement in the maintenance of infliximab response, unlike in Regueiro's study where no difference was observed.[11,12] Other studies have reported the concomitant use of an immunosuppressant to be associated with higher infliximab [IFX] levels and lower rates of ATI formation.[17–19] However, this finding has not been consistent across all studies[20] and, when episodic and maintenance therapy have been compared, the use of concomitant immunosuppression appears to be of greater

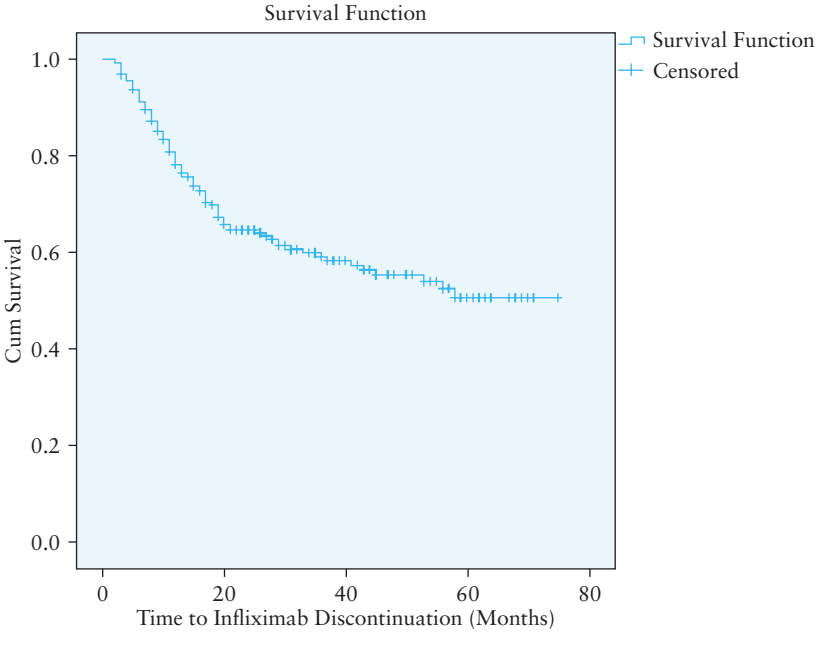

Figure 1. Time to infliximab discontinuation overall in the cohort of 252 cases.

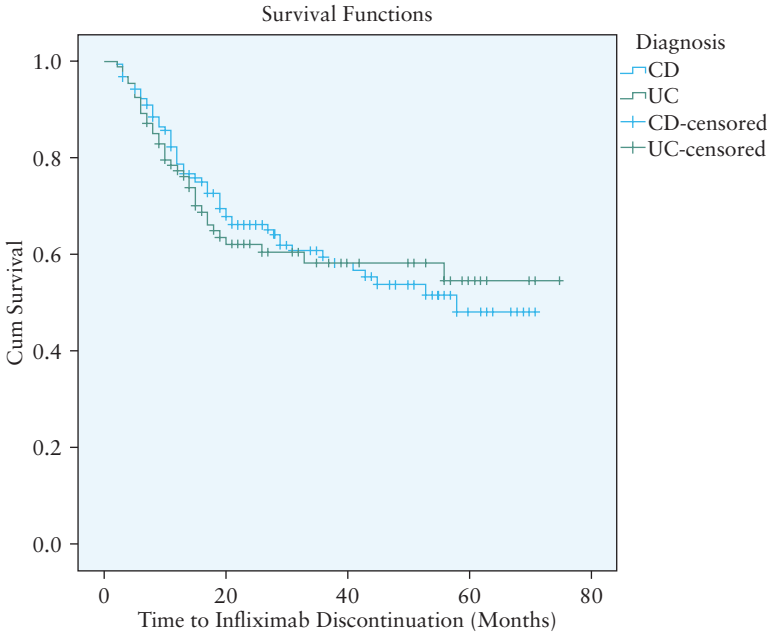

Figure 2. Time to infliximab discontinuation by diagnosis, broken down by disease type; Crohn's disease versus ulcerative colitis.

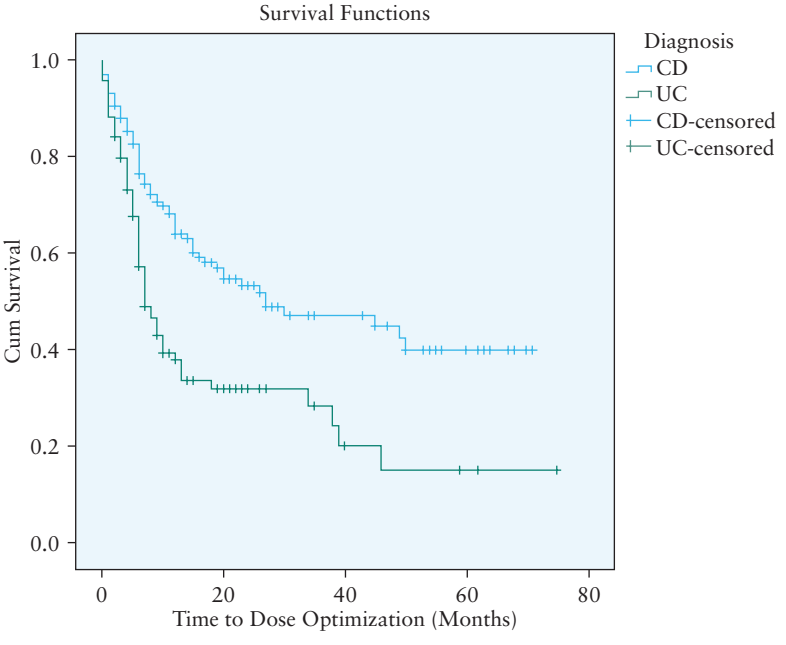

Figure 3. Time to dose optimisation; dose optimisation-free survival, comparing ulcerative colitis cases with Crohn's disease cases.

value in those receiving episodic treatment.[21,22,23] An early report on the long-term follow up of IBD cases treated with infliximab, with the majority having CD and receiving episodic therapy, found an annual dropout rate of only 7.1% among those receiving scheduled therapy and 10.7% in those receiving episodic therapy; however, 50% of the overall cohort required at least one dose intervention.[24] All cases in our study received infliximab as scheduled maintenance therapy and therefore the impact of concomitant immunomodulator therapy may not have been as great within our patient population. Indeed, the time to dose optimisation was not affected by concomitant immunosuppressant use in a subgroup analysis. While Sokol *et al.* found that infliximab doses [g/kg/semester] were significantly lower during immunosuppressant therapy, recent data from the Leuven group found no difference in the rates of dose optimisation in those on infliximab monotherapy vs combination therapy.[25,26] Appropriate dosing to ensure adequate trough levels, particularly during the induction period, may be a superior strategy to prevent ATI formation and may prolong durability of infliximab response without dose escalation.

Low trough infliximab levels have been associated with less favourable outcomes in both UC and CD in many studies.[18,20,21,23,27] Low or undetectable trough IFX levels can occur in the presence and absence of antibody to infliximab. ATI lead to the formation of drug-antibody complexes with higher clearance rates, but there are

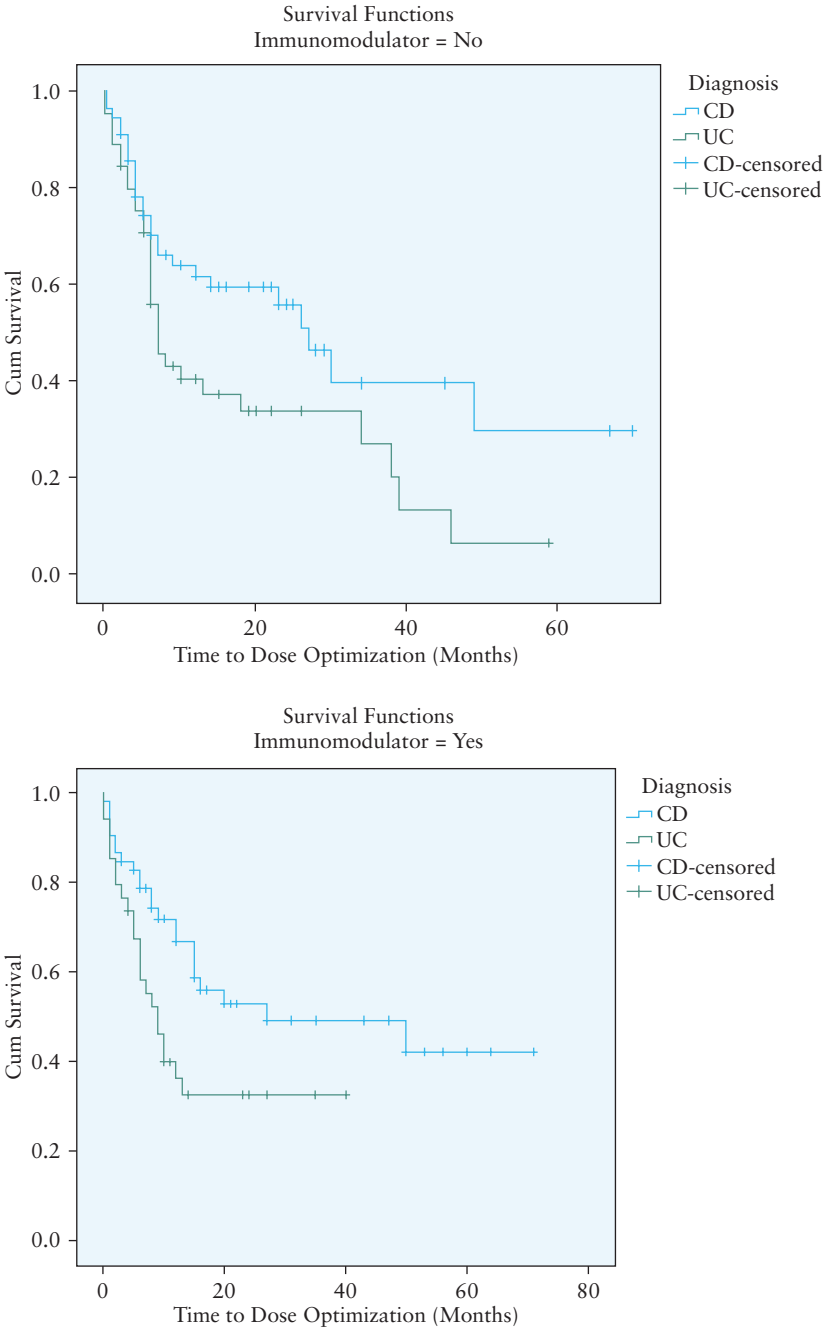

Figure 4. Time to dose optimisation; dose optimisation-free survival for ulcerative colitis [UC] cases vs Crohn's disease [CD] cases, stratified by immunomodulators use.

multiple factors which affect the pharmacokinetics of infliximab.[28,29] Indeed, newer assays have demonstrated that loss of response with low infliximab trough levels occurs in the absence of ATI.[30,31] More severe inflammation may result in more rapid clearance via a number of mechanisms,[28] including enteric losses as demonstrated by the detection of infliximab in the stool of those with severe inflammation.[32] In a study investigating the kinetics of ATI formation in both UC and CD patients, it was observed that patients with transient and sustained ATI had significantly higher C-reactive protein [CRP] levels at the start of infliximab therapy compared with those who remained ATI-negative during the study period.[30] The authors hypothesised that this may reflect the fact that those with a higher CRP have more severe disease and therefore require higher induction doses of infliximab in order to achieve good infliximab trough levels. This parallels our results, in that UC patients required more frequent dose optimisations, perhaps due to an increased inflammatory burden associated with the pancolonic inflammation frequently observed in UC.

Various assay-based algorithms on managing secondary loss of response with dose optimisation or change to an alternative agent have been developed.[31,33,34] A decision-analysis model found that after a CD patient has lost response to 5 mg/kg of infliximab, dose escalation to 10 mg/kg will yield more quality-adjusted life-years compared with switching to adalimumab; however, the cost was considerable.[35] Whether the dose is increased or the interval reduced does not appear to effect efficacy of the strategy to dose-optimise in

the setting of a secondary loss of response.[36] Dose increase may be more cost effective and more attractive to patients, as more frequent infusions carry higher costs and more patient inconvenience.

Our study has some limitations, the primary one being that this is a retrospective analysis and therefore dose optimisation was made at the discretion of individual treating physicians at our institution and not in a protocolised fashion. However, all cases were under the care of just two experienced physicians and therefore there was consistency in the approach to secondary loss of response. Equally, as this is a retrospective analysis, outcome measures were not recorded at consistent time points. We feel that ongoing infliximab therapy is a good surrogate marker of treatment response. Decision-making in real-world clinical practice is more often based on patient-reported symptoms than on therapeutic drug monitoring or assessment of mucosal healing, and therefore our results are more reflective of this. Data on immunomodulator use were not available for all cases. However, data were available for 75% of the cases that were included in the time to dose optimisation analysis, and the finding that dose optimisation was required earlier in the course of therapy in UC cases remained significant after adjusting for immunomodulator use. Although we do hypothesise that the differences in rates of dose optimisation between UC and CD may reflect differences in inflammatory burden, we did not see statistically significant difference in time to dose optimisation between those classified as pancolitis vs left-sided colitis. This may be due to small numbers of cases with left-sided colitis having a dose optimisation [$n = 9$]. Alternatively is also possible that, even with left-sided UC, there is more surface involved than in many cases of CD and therefore possibly more rapid loss of drug into the gut.

5. Conclusion

Here we have shown that whereas the majority of IBD cases responding to induction therapy with infliximab will have a sustained response to therapy, over 50% will require a dose optimisation during their treatment. The time to dose optimisation is significantly shorter for UC cases than CD cases, likely reflecting a higher inflammatory burden in UC than CD cases or some other as yet unknown difference between the two diseases. Optimisation of treatment regimens is essential to ensure a durable response to treatment, particularly in UC.

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Conflict of Interest

Hillary Steinhart has served as a speaker, a consultant, and an advisory board member for Abbvie, Actavis, Aptalis, Forrest Pharmaceuticals, Janssen, Pharmascience, Shire, and Takeda, and has received research funding from Amgen, Abbvie, Pfizer, and Takeda. Mark Silverberg has served as a speaker, a consultant, and an advisory board member and has received research funding from Janssen, Abbvie, Takeda, Aptalis, and Prometheus. Sarah O'Donnell and Joanne Stempak have no conflicts of interest.

Author Contributions

Sarah O`Donnell was involved with the study design, and performed the literature search, data collection, data analysis, data interpretation, and manuscript writing. Joanne Stempak performed data collection, and data interpretation. Hillary Steinhart and Mark Silverberg were involved in the study design and performed data analysis, data interpretation, and manuscript writing.

Conference presentation

Digestive Disease Week 2014, Chicago, IL, USA—poster presentation.

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