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Anti-TNF Re-induction Is as Effective, Simpler, and Cheaper Compared With Dose Interval Shortening for Secondary Loss of Response in Crohn's Disease

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ABSTRACT

Background and Aims: The optimal duration of dose-intensified therapy following secondary loss of response [LOR] to anti-tumour necrosis factor [TNF] therapy remains unclear. Anti-TNF re-induction involves a finite period of intensified therapy and may be a cost-effective means of re-capturing response. This study aimed to compare the efficacy, durability, and cost of anti-TNF re-induction and dose interval shortening [DIS] for secondary LOR in Crohn's disease [CD].

Methods: This was a retrospective observational study in CD patients who developed secondary LOR to maintenance anti-TNF therapy, requiring subsequent re-induction and/or DIS. The primary outcome was treatment failure within 12 months. Secondary outcomes included factors associated with time to failure, disease activity, and incremental anti-TNF costs.

Results: Of 423 patients with CD on anti-TNF therapy, 80 [19%] developed secondary LOR, with 33 and 55 patients undergoing subsequent anti-TNF re-induction and DIS, respectively. There was no significant difference in the incidence of treatment failure at 12 months following re-induction and DIS, respectively [$p = 0.27$]. Factors predictive of a longer time to failure included a higher baseline serum albumin, male sex, and thiopurine co-therapy [each $p < 0.05$], whereas higher baseline faecal calprotectin was associated with shorter time to failure. There was no significant difference in clinical remission or objective disease activity across both groups. The median incremental cost of re-induction and DIS was AUD 4 838 and AUD 13 190, respectively.

Conclusions: In patients with CD who develop secondary LOR, re-induction may represent an effective and less expensive first-line strategy, reserving dose intensification strategies such as DIS for non-responders.

Key Words: Crohn's disease; anti tumour necrosis factor; re-induction; shortening of dosing interval; secondary loss of response; dose intensification

1. Introduction

Secondary loss of response [LOR] remains a potential barrier to the long-term efficacy of anti-tumour necrosis factor [TNF] therapy in Crohn's disease, occurring in up to 61% of anti-TNF naive patients with ongoing therapy.[1,2] Therapeutic options following secondary LOR include the addition of glucocorticoids or immunomodulator therapy, surgery, switching anti-TNF agents, or anti-TNF dose intensification by either shortening the interval between anti-TNF doses or increasing the baseline anti-TNF dose while maintaining the dosing interval.[3–5] While there is evidence to support shortening of the dose interval as a successful dose intensification strategy,[6–11] with up to two-thirds of patients regaining response in studies with short term follow-up,[3,12] doubling the baseline anti-TNF dose rather than shortening the interval between doses has also demonstrated efficacy.[3] Further, the European evidence-based consensus statement concluded that increasing the dose of anti-TNF and shortening the dosing interval are equivalent strategies [EL4].[13]

Amid growing scrutiny regarding the cost and resource implications of anti-TNF therapy, the need to minimise unnecessary or excessive periods of dose intensification has become increasingly important.[14] Although the optimal duration of dose intensification following secondary LOR remains unclear, observational studies have demonstrated that patients can recapture response using the more cost- and resource-effective strategy of fixed-duration dose intensification.[15] This highlights the need to further explore the relative merits of shorter fixed-duration rather than longer-term or ongoing dose intensification regimens.

Anti-TNF re-induction presents a model of fixed-duration dose intensification that is currently available as an Australian Government-subsidised means of dose intensification following secondary LOR in Crohn's disease. It involves transient dose intensification in a manner identical to anti-TNF induction therapy. Thus, infliximab [IFX] 5 mg/kg intravenously at Weeks 0, 2, and 6, or adalimumab [ADA] subcutaneously, 160 mg at Week 0 and 80 mg at Week 2, are administered before returning to standard maintenance dosing of 8-weekly IFX or fortnightly ADA. The rationale for re-induction is that secondary LOR may often represent a transient phenomenon that may be successfully overcome by a short-term increase in serum anti-TNF drug levels. Similar to many other countries, clinicians in Australia can also access dose interval shortening as an alternate dose intensification strategy to re-capture response following secondary LOR to anti-TNF therapy.

The relative efficacy of fixed-duration dose intensification regimens such as re-induction have yet to be directly compared with more established longer-term dose intensification strategies such as dose interval shortening. It follows that the contemporaneous use of anti-TNF re-induction and dose interval shortening to overcome secondary LOR in Crohn's disease within Australia presents a unique opportunity to compare both therapeutic approaches in a 'real-world' setting. Hence, this study aimed to compare the efficacy of anti-TNF re-induction with dose interval shortening, determine factors associated with durability of response following either strategy, and compare the relative cost and safety of both therapeutic approaches.

2. Methods

2.1. Patients and study design

This retrospective observational study included consecutive adult patients on maintenance anti-TNF therapy for confirmed Crohn's disease based on standardised clinical, endoscopic, histological, and radiological criteria,[13] who attended the tertiary inflammatory bowel disease [IBD] services at Eastern Health or Alfred Health in Melbourne, Australia, between January 2006 and August 2016. All patients had received standard maintenance IFX dosing [5 mg/kg] via intravenous infusion every 8 weeks after three induction doses at Weeks 0, 2, and 6, or standard maintenance fortnightly ADA [40 mg] subcutaneously following initial induction doses of 160 mg and 80 mg at Weeks 0 and 2. Those patients who subsequently developed secondary LOR to maintenance anti-TNF therapy and underwent subsequent re-induction and/or dose interval shortening were identified as the subgroup of interest. Patients who had been off maintenance anti-TNF therapy for more than 3 months immediately preceding re-induction or dose interval shortening were excluded.

Anti-TNF re-induction was administered as described above, and dose interval shortening was undertaken as either 5 mg/kg 6-weekly IFX or 40 mg weekly ADA. The decision and timing of when to undertake anti-TNF re-induction or dose interval shortening was at the discretion of the treating clinician, and was independent of the study investigators.

2.2. Data collection

Review of case notes and IBD database records was undertaken to determine patient demographics, smoking status, disease-related surgical history, Montreal disease classification, presence of extra-intestinal manifestations, anti-TNF treatment history, and immunosuppressive co-therapy, while laboratory data were extracted to assess serum anti-TNF drug levels and objective measures of disease activity including C-reactive protein [CRP], endoscopic activity, faecal calprotectin, and Harvey-Bradshaw Index [HBI], each at multiple time points where available.

2.3. Study outcomes

The primary outcome measure of the study was anti-TNF failure [defined below] within 12 months of re-induction or dose interval shortening. Secondary outcome measures included factors associated with or predictive of a longer time to anti-TNF failure, rates of clinical remission and objective disease activity following re-induction and/or dose interval shortening, and incremental anti-TNF drug cost of dose interval shortening relative to re-induction. Adverse outcomes including death, serious infections requiring admission or treatment de-escalation, and malignant diagnoses following re-induction or dose interval shortening, were also recorded.

2.4. Study definitions

Treatment failure following re-induction or dose interval shortening was defined as one of: Crohn's disease-related abdominal surgery; anti-TNF cessation; or switching to another anti-TNF or biologic agent. The need to dose-escalate the same anti-TNF following re-induction or dose interval shortening was not considered treatment failure unless anti-TNF therapy was changed or Crohn's disease-related abdominal surgery was undertaken. The time to treatment failure was defined as the time from the date of re-induction or dose interval shortening commencement until the date of treatment failure.

Cost estimates in Australian dollars [AUD] pertaining to anti-TNF re-induction and dose interval shortening were based on Australian Pharmaceutical Benefits Scheme pricing of ADA 40 mg [AUD 839.68] and IFX 5 mg/kg [AUD 604.86 per 100 mg] doses [as of 31 May, 2016], and did not include infusion centre-related or other consumable costs associated with administering each dose.

Time to secondary LOR was defined tangibly as the duration between the commencement of maintenance anti-TNF therapy through to the date of re-induction or dose interval shortening of the same agent, in the setting of both objective evidence of active disease and documented clinical suspicion of secondary LOR.

Clinical disease activity was retrospectively calculated using the HBI based on documented case notes, with clinical remission defined as a HBI score of less than 5. Patients with a stoma were excluded from HBI measurements. Objective evidence of active Crohn's disease was considered to be present when at least one of: faecal calprotectin ≥ 100 µg/ml, CRP ≥ 5 mg/L or endoscopic activity were present.

Anti-TNF drug levels were all performed using the Matrix ELISA assay in one laboratory, with 'subtherapeutic' serum ADA and IFX levels defined as less than 5 µg/ml and 3 µg/ml respectively. Immunomodulator co-therapy referred to either concomitant use of a thiopurine or methotrexate, and optimised thiopurine therapy was defined as therapy that achieved a 6-thioguanine [6-TGN] level greater than 235 pmol/8 x 10^8 erythrocytes.[16]

2.5. Statistical analysis

Data assessed descriptively and according to ShapiroWilk tests were found to be non-parametric; thus medians are presented throughout [with minimum and maximum ranges]. Continuous data were compared with Mann-Whitney tests or Spearman's correlation coefficients, and proportions were expressed as percentages and compared using two-sided Fisher's exact tests. Continuous data were kept in original form where possible.

Further bivariate analyses were performed, including Kaplan-Meier survival curves to compare the time to failure of re-induction versus dose interval shortening stratifying by anti-TNF agent, with differences assessed by log-rank tests. In order to ascertain factors associated with longer time to treatment failure, patients who underwent anti-TNF re-induction and/or dose interval shortening were combined to maximise discriminative power. Subsequent multiple linear regression analysis was then performed, incorporating factors identified as potentially associated or trending towards time to treatment failure after anti-TNF re-induction or dose interval shortening. Linear regression was found to provide the best fit for these multivariate models. A p-value < 0.05 was considered significant throughout this study.

2.6. Ethics

This study was approved by the human research ethics committees at both Eastern Health and Alfred Health. Individual patient consent was not obtained, given the retrospective, observational audit-based data collection.

3. Results

Of 423 patients with Crohn's disease on anti-TNF therapy, 80 [19%] patients developed secondary LOR to IFX [n = 45, 56%] and ADA [n = 35, 44%], with 33 undergoing subsequent anti-TNF re-induction and 55 having their dosing interval shortened.

3.1. Baseline patient and disease characteristics

There were no significant differences in patient or disease characteristics between patients who underwent re-induction or dose interval shortening, apart from a significantly higher proportion of current and ex-smokers at the time of anti-TNF initiation in the re-induction group [p < 0.01]. The majority of patients had an ileocolonic [L3] distribution of Crohn's disease, with no significant difference in the rates of perianal [p = 0.66] or stricturing [p = 1.00] disease across both groups.

Although fewer patients underwent therapeutic drug monitoring [TDM] before re-induction [p < 0.01], the majority of patients who underwent TDM demonstrated subtherapeutic serum anti-TNF drug levels before re-induction or dose interval shortening. One patient had an anti-TNF anti-body titre > 1.0 µg/ml associated with undetectable anti-TNF drug levels before re-induction, while two patients demonstrated similar findings before dose interval shortening. The median time to secondary LOR was 2.1 years, with a median time to re-induction or dose interval shortening of 1.8 years and 2.5 years, respectively [p = 0.79]. The median CRP before re-induction and dose interval shortening was 8.0 mg/L and 7.0 mg/L, respectively. Although at least 75% of patients were on combination therapy with a thiopurine or methotrexate at the time of initial re-induction [25/33] or dose interval shortening [49/55], we did not re-assess changes to co-immunomodulator therapy [starting or stopping] following initial dose escalation. Further characteristics and baseline comparisons of relevant variables between the two groups are shown in Table 1.

3.2. Treatment outcomes following re-induction and dose interval shortening

The median duration of follow-up across both groups was 1.8 years, with a median duration of follow-up after re-induction and dose interval shortening of 3.5 years and 1.5 years, respectively [p < 0.01]. There was no significant difference in the rates of treatment failure at 12 months [8 vs 8, p = 0.27] and 24 months [10 vs 11, p = 0.31]

Table 1. Baseline patient and disease characteristics before re-induction [RI] and dose interval shortening [DIS].

	RI *n* [%]	DIS *n* [%]	Total *n* [%]	*p*-Value
No. of patients	33 [38]	55 [63]	88 [100]	
Females	17 [52]	25 [45]	42 [48]	0.66
Smoker [including ex-smoker]	16 [48]	10 [18]	26 [30]	< 0.01
Previous surgery	14 [42]	26 [47]	40 [45]	0.83
Complicated disease[a]	29 [88]	51 [93]	80 [91]	0.47
Prior anti-TNF exposure	9 [27]	21 [38]	30 [34]	0.36
Infliximab	22 [67]	29 [53]	51 [58]	0.27
Methotrexate or thiopurine co-therapy	25 [76]	49 [89]	74 [84]	0.13
Therapeutic drug monitoring [TDM] undertaken	12 [36]	47 [85]	59 [67]	< 0.01
Median HBI score before RI or DIS	6	5	6	0.06
Median age at RI or DIS [y]	35.0	37.0	36.6	0.36
Median disease duration at RI or DIS [y]	8.2	10.2	9.4	0.08
Median time to secondary LOR [y]	1.8	2.5	2.1	0.79

TNF, tumour necrosis factor; HBI, Harvey-Bradshaw Index; y, years; LOR, loss of response.

[a]Complicated disease refers to perforating or stricturing Crohn's disease.

following anti-TNF re-induction or dose interval shortening, respectively. However, a greater number of patients demonstrated treatment failure more than 24 months after re-induction [n = 6] relative to dose interval shortening [n = 2]. This difference accounted for significantly more treatment failures following re-induction over the duration of the study [p = 0.02].

A similar proportion of patients treated with IFX demonstrated treatment failure following either dose escalation strategy at both 12 months [p = 1.00] and 24 months [p = 1.00], although there was a trend towards more IFX-associated treatment failure following re-induction relative to dose interval shortening beyond 24 months of follow-up. In contrast, a greater proportion of patients undergoing ADA re-induction demonstrated treatment failure relative to those who underwent dose interval shortening at both 12 months [p = 0.16] and 24 months [p = 0.09], with this trend reaching significance beyond 24 months of follow-up [p = 0.04].

Twenty-six patients switched or discontinued their anti-TNF agent following re-induction (n = 13, after a median 1.7 years, range [0.1, 4.4]) and dose interval shortening (n = 13, after a median 0.8 years, range [0.4, 3.4]) respectively. Four patients in the re-induction group required surgery [p < 0.01] after a median duration of 1.0 years [range 0.4, 2.7]. Further treatment outcomes following re-induction and dose interval shortening are shown in Table 2.

The rates of clinical remission [HBI < 5] at latest clinical review in patients who avoided treatment failure at end of the follow-up period were 65% [11/17] and 60% [25/42] following re-induction and dose interval shortening, respectively [p = 0.78]. Of patients who did not demonstrate treatment failure at the end of study follow-up, 86% [6/7] and 88% [22/25] had therapeutic drug levels following re-induction and dose interval shortening, respectively [p = 1.00]. The median CRP following re-induction and dose interval shortening was 6.0 mg/L and 5.0 mg/L, respectively.

Ten patients underwent anti-TNF re-induction followed by dose interval shortening, including two patients who underwent dose interval shortening immediately following re-induction. In this subgroup, the median duration between re-induction and subsequent dose interval shortening was 0.9 years [range 0.2, 2.9]. Four patients underwent anti-TNF re-induction twice.

3.3. Factors associated with longer time to failure following re-induction and dose interval shortening

As per Kaplan-Meier survival analyses shown in Figure 1, there was no significant difference in the time to failure using either approach [log rank test, p = 0.27]. Immunomodulator co-therapy was associated with a significantly longer time to failure relative to anti-TNF monotherapy [log rank test, p < 0.03] [Figure 2]. Although thiopurine co-therapy demonstrated a positive association [log rank test, p < 0.01], methotrexate co-therapy did not exhibit a significant effect on time to failure [log rank test, p = 0.26].

Positive and negative correlations with time to failure following re-induction and dose interval shortening [Table 3] were also demonstrated with serum albumin [r = 0.26] and faecal calprotectin [r = –0.80] respectively, the latter when controlling for sex and disease duration. Subsequent multiple linear regression analyses [Table 4] revealed factors predictive of a longer time to failure. These included a higher baseline serum albumin, male sex, and thiopurine co-therapy [each p < 0.05]. There was also a trend towards a longer time to failure following dose-intensified IFX relative to ADA, although this did not quite reach statistical significance [p = 0.06]. Consistent with the findings on bivariate analyses, there was also a significant inverse relationship between baseline faecal calprotectin and time to anti-TNF failure. There was no significant association between time to anti-TNF failure and smoking status, duration on anti-TNF before dose escalation, or baseline serum CRP level.

3.4. Real-world cost comparison of re-induction and dose interval shortening

The relative anti-TNF drug costs of each approach were compared incorporating the actual dosage [mg], duration of therapy [to the earlier of treatment failure or end of follow-up], and dosing frequency of re-induction and/or dose interval shortening performed for each individual patient in the cohort [Figure 3]. Relative to standard anti-TNF

Table 2. Treatment outcomes following re-induction [RI] and dose interval shortening [DIS]

	RI *n* [%]	DIS *n* [%]	Total *n* [%]	*p*-Value
Treatment failure ≤ 12 months	8 [24]	8 [15]	16 [18]	0.27
Infliximab	4 [18]	5 [17]	9 [18]	1.00
Adalimumab	4 [36]	3 [12]	7 [19]	0.16
Treatment failure ≤ 24 months	10 [30]	11 [20]	21 [24]	0.31
Infliximab	5 [23]	7 [24]	12 [24]	1.00
Adalimumab	5 [45]	4 [15]	9 [24]	0.09
Total treatment failure	16 [48]	13 [24]	29 [33]	0.02
Infliximab	10 [45]	9 [31]	19 [37]	0.38
Adalimumab	6 [55]	4 [15]	10 [27]	0.04
Median time to treatment failure [y]	1.0	0.8	0.9	0.56
Required surgery before anti-TNF change	4 [12]	0 [0]	4 [5]	0.02
Median follow-up following RI or DIS [y]	3.5	1.5	1.8	< 0.01
Therapeutic drug monitoring [TDM] undertaken	15 [45]	38 [69]	53 [60]	0.04
Therapeutic [anti-TNF] trough levels	7 [47]	25 [66]	32 [60]	0.23
DIS performed following RI	10 [30]		10 [11]	
Median time to DIS following RI [y]	0.9			
Median HBI score following RI or DIS	3	4	3	0.73
Developed non-Crohn's related infection requiring admission or de-escalation	1 [3]	7 [13]	7 [8]	0.25
Death following RI or DIS	1 [3]	0 [0]	1 [1]	0.38

TNF, tumour necrosis factor; HBI, Harvey-Bradshaw Index; y, years.

Table 3. Bivariate analyses of relevant variables and their associations with longer time to failure of same anti-TNF agent following re-induction [RI] and dose interval shortening [DIS].

Continuous variable[a]	r = [b]	*p*-Value
Age [y]	-0.07	0.54
BMI [kg/m^2]	0.04	0.87
Duration since IBD diagnosis [y]	-0.15	0.16
HBI score	-0.12	0.28
Serum CRP [mg/L]	-0.13	0.25
Serum albumin [g/L]	0.26	0.01
Faecal calprotectin [µg/ml]	-0.80	< 0.01

Categorical variable[a]	Median time to failure [y][c][+ vs -]	*p*-Value
Male sex	2.6 vs 1.5	0.30
Smoker before RI or DIS	1.5 vs 1.7	1.00
Inflammatory [B1][d] phenotype	1.8 vs 1.5	0.73
Extra-intestinal manifestation[s] present at RI or DIS	1.3 vs 1.7	1.00
Bowel resection[s] before RI or DIS	1.4 vs 1.7	0.69
Endoscopic activity before RI or DIS	1.5 vs 1.7	0.31
Sub-therapeutic [anti-TNF] trough before RI or DIS	1.6 vs 1.8	0.08
Anti-TNF indication: luminal vs perianal fistulising disease	1.7 vs 1.5	0.71
Previous exposure to alternative anti-TNF agent	2.0 vs 1.5	0.40

TNF, tumour necrosis factor; HBI, Harvey-Bradshaw Index; y, years; BMI, body mass index; CRP, C-reactive protein.

[a]At time of RI or DIS unless otherwise stated.

[b]Spearman's correlations shown, except for faecal calprotectin where r shown for partial correlation controlling for sex which was strongly correlated with calprotectin [r = 0.6, $p < 0.05$].

[c]Medians shown for categorical variables [positive vs null] in each case, Mann-Whitney tests used.

[d]As per Montreal classification of Crohn's disease.

dosing across the same duration of therapy, anti-TNF re-induction and dose interval shortening required an extra 2.0 doses [range 2.0, 4.0] and 6.5 doses [range 1.0, 78.0], respectively. This equated to a median incremental drug cost of AUD 4 838 [range 3 359, 7 258] and AUD 13 190 [range 2 330, 65 495] for re-induction and dose interval shortening, respectively [Mann-Whitney tests, each $p < 0.001$]. Therefore, the median incremental cost of anti-TNF re-induction was significantly less than that of dose interval shortening, demonstrating a 'real-world' cost saving of 63.3%, (95% CI [84.0, 92.0]) across this patient cohort.

Comparing the relative cost of ADA [range 2 512, 65 495] and IFX [range 2 330, 20 814] using each approach, demonstrated the median incremental cost of ADA dose interval shortening [AUD 29 488] relative to re-induction [AUD 3 359] was AUD 26 129, while the median incremental cost of IFX dose interval shortening [AUD 6 645] relative to re-induction [AUD 4 839] was AUD 1 806. This highlights the significant cost burden conferred by dose interval shortening of ADA.

3.5. Safety and adverse events

There were no significant differences in the incidence of infusion-related or other adverse reactions following either approach, and there were no more serious infections requiring hospitalisation or treatment de-escalation following dose interval shortening relative to re-induction [$p = 0.25$]. Two cases of malignancy occurred in the dose interval shortening cohort using ADA; these were melanoma and lymphoproliferative disorder of the rectum [1.0 and 1.1 years following dose interval shortening, respectively]. Finally, one patient died following medical complications in the postoperative period 0.4 years following IFX re-induction.

Table 4. Multiple linear regression analysis of relevant variables potentially associated with longer time to failure of the same anti-TNF agent following re-induction [RI] and dose interval shortening [DIS]: final conditional regression model shown.

Variable[a]	b coefficient [95% CI]	t score[b]	*p*-Value
Serum albumin [g/L]	0.05 [0.03, 0.07]	4.46	< 0.01
Sex	0.57 [0.07, 1.08]	2.25	0.03
Thiopurine co-therapy	0.51 [0.01, 1.00]	2.04	0.04
IFX used for RI or DIS [vs ADA]	0.48 [-0.02, 0.99]	1.90	0.06
Duration on same anti-TNF before RI or DIS [y]	0.06 [-0.09, 0.21]	0.76	0.45
Smoker	-0.12 [-0.71, 0.47]	-0.41	0.68
Serum CRP [mg/L]	-0.004 [-0.01, 0.01]	-0.75	0.46
Faecal calprotectin [µg/ml]	-0.003 [-0.01, 0.00]	-2.22	0.03

TNF, tumour necrosis factor; CRP, C-rective protein; y, years; IFX, infliximab; ADA, adalimumab; CI, confidence interval.

[a]At time of RI or DIS unless otherwise stated.

[b]In descending order of magnitude of effect size as per t-score shown.

4. Discussion

Two broad regimens have been applied in patients with Crohn's disease who develop secondary LOR to maintenance anti-TNF therapy. This is the first study to compare the efficacy, safety, and cost of anti-TNF re-induction as an alternative dose intensification strategy. In spite of having the limitations of retrospective data, the findings indicate that anti-TNF re-induction presents an effective and significantly less expensive fixed-dose approach to secondary LOR.

Our study demonstrated that rates of clinical remission [HBI < 5] were similar following either approach among patients who did not demonstrate treatment failure at the end of study follow-up [$p = 0.78$]. Further, there was no significant difference in the median time to failure [$p = 0.56$], or rates of treatment failure at 24 months [$p = 0.31$] following either approach. There was also no significant increase in infections requiring hospitalisation or treatment de-escalation following dose interval shortening relative to anti-TNF re-induction.

Although the median duration of follow-up after re-induction was more than 2-fold longer than that following dose interval shortening [$p < 0.01$], it remains important to consider that the therapeutic benefits of anti-TNF re-induction may not be as durable as ongoing dose interval shortening across all patients. This was reflected by higher rates of treatment failure across the re-induction cohort relative to the dose interval shortening cohort beyond 24 months of follow-up, likely accounting for more treatment failures following re-induction over the duration of study follow-up.

Our study also demonstrated that relative to IFX, a greater proportion of patients treated with ADA demonstrated treatment failure following re-induction relative to dose interval shortening across all measured time periods. This may suggest that ADA re-induction is not as durable as weekly ADA in preventing or

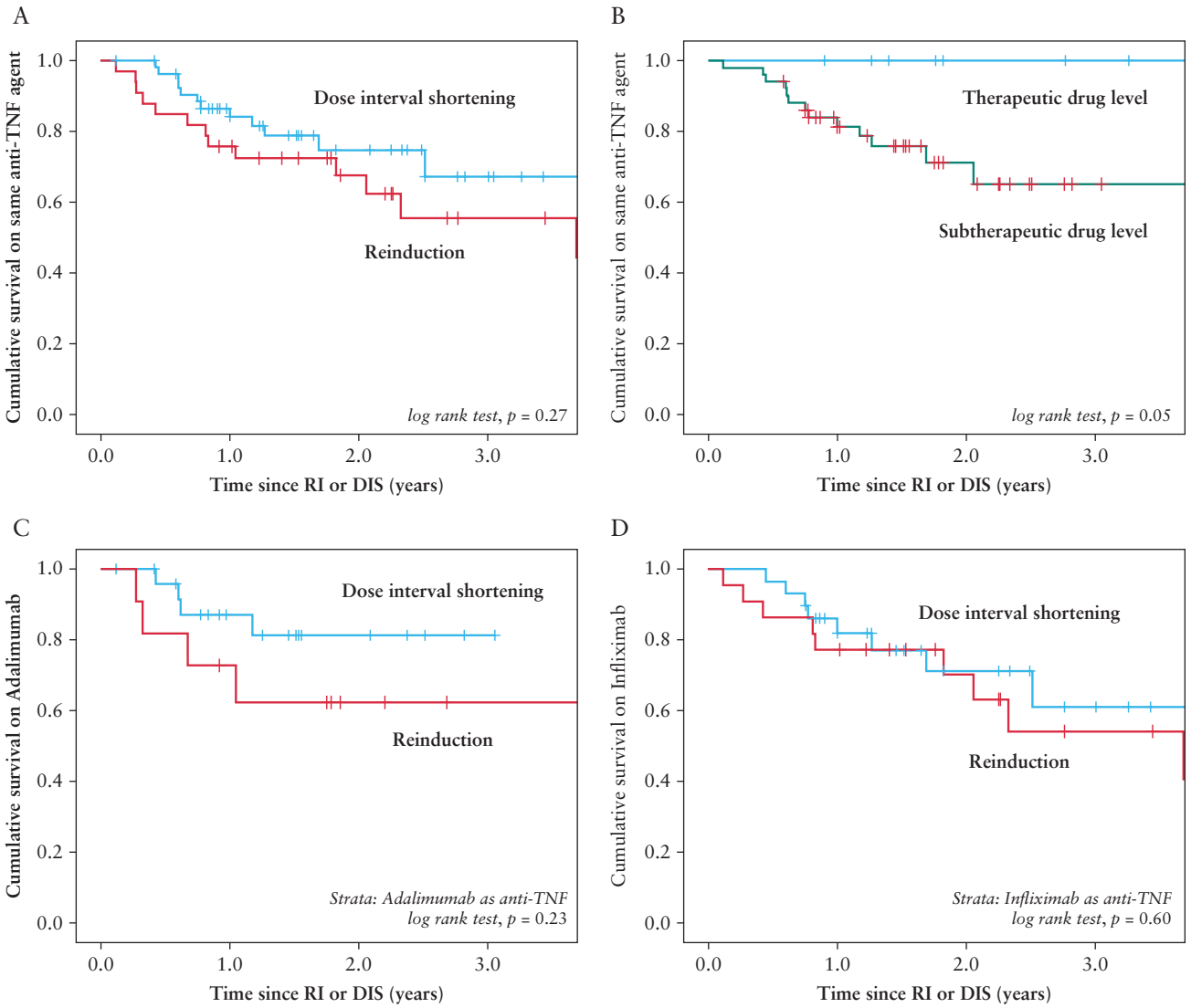

Figure 1. Kaplan-Meier survival plots depicting: [A] time to failure following re-induction [RI] vs dose interval shortening [DIS] showing no significant difference; [B] those with therapeutic drug levels at RI or DIS were more likely to have longer time to failure; [C, D] no significant differences in time to survival when stratifying by which anti-tumour necrosis factor [TNF] agent used for RI or DIS.

deferring treatment failure, particularly over a period of 24 months or more when these differences demonstrated significance. One possible explanation for this discrepancy is that unlike IFX, the number of extra doses received following ADA dose interval shortening relative to ADA re-induction becomes substantial over a much shorter period.

Multiple linear regression analysis identified that a higher baseline serum albumin was positively associated, whereas higher baseline calprotectin was negatively associated, with time to anti-TNF treatment failure. This may suggest that patients with a greater inflammatory burden are less likely to demonstrate a sustained response to either method of dose escalation. Interestingly, other putatively important co-factors such as smoking and serum CRP were not significantly associated with durability of response. This further underlines the need for prospective evaluation of anti-TNF re-induction and dose interval shortening, with particular emphasis on identifying patient and disease characteristics predictive of a favourable response to either approach.

Although the mechanistic explanation for the durability of response following short-term fixed-duration therapy [re-induction] relative to ongoing dose intensification [dose interval shortening] is uncertain and supportive data remain scarce, a retrospective study by Schnitzler *et al.* demonstrated that anti-TNF re-induction used in combination with or without temporary dose intensification can successfully regain treatment response.[15] While dose intensification can overcome low anti-TNF trough levels and anti-TNF antibodies, patients may not always require long-term dose intensification to regain and maintain response, given that anti-TNF antibodies are often transient.[17–21] In fact, Baert *et al.* demonstrated that among a large cohort of ADA-treated Crohn's disease patients who were dose escalated to weekly therapy, de-escalation back to fortnightly dosing was successful in 63% of patients in whom it was attempted.[11] Interestingly, Baert *et al.* did not find any predictors of successful de-escalation on multivariate analysis, further highlighting the lack of evidence-based de-escalation strategies to guide clinicians in this endeavour.

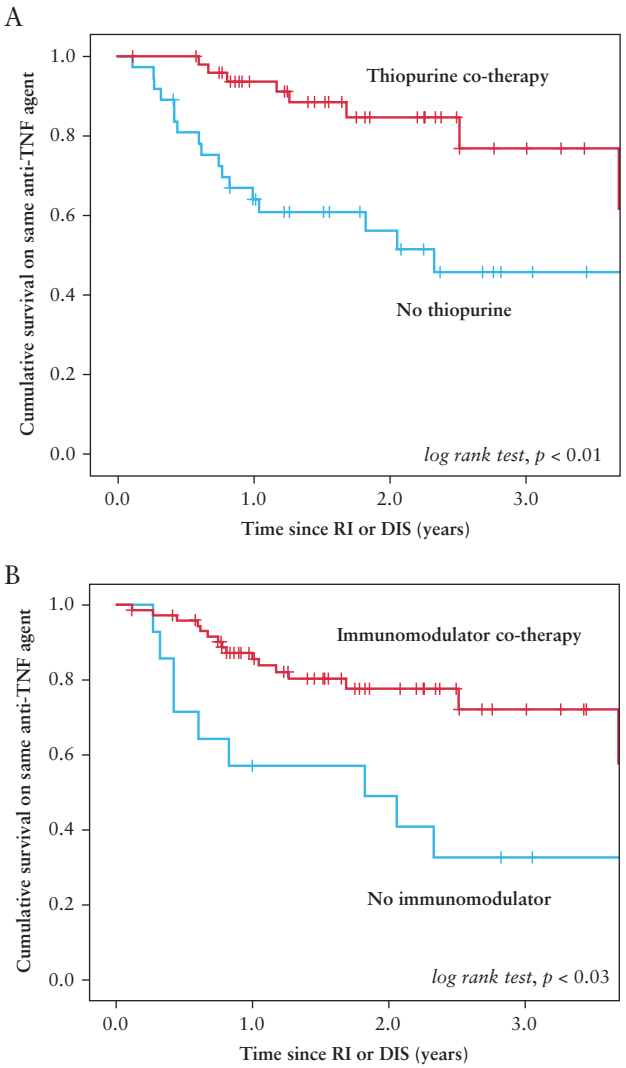

Figure 2. Kaplan-Meier survival plots showing significant impact of: [A] thiopurine co-therapy; or [B] immunomodulator co-therapy; on time to survival on same anti-tumour necrosis factor [TNF] agent following re-induction [RI] and dose interval shortening [DIS].

Two-thirds of patients who underwent TDM following dose interval shortening subsequently demonstrated therapeutic anti-TNF trough levels, whereas 47% of patients who underwent TDM following re-induction demonstrated therapeutic drug levels. Overall, 60% [32/53] of patients who underwent TDM following either method of dose-escalation, demonstrated therapeutic anti-TNF trough levels, with 70% [28/40] of these patients not demonstrating treatment failure over the duration of follow-up. This suggests that therapeutic anti-TNF trough levels following re-induction or dose interval shortening are associated with a more favourable response, highlighting the clinical utility of TDM in the period following dose escalation.

Dose interval shortening is clearly effective and thus widely used to overcome secondary LOR in a durable manner, but the cost implications of this approach relative to anti-TNF re-induction remain significant [Figure 3]. Hence, this study suggests that re-induction could be considered a first-line intervention in the setting of secondary LOR to anti-TNF therapy in Crohn's disease, reserving existing and more expensive dose intensification strategies such as dose interval shortening for those who fail to respond. Although we acknowledge the need for prospective studies, this approach also potentially addresses the clinical tendency to 'set' [dose escalate] and 'forget' [to re-assess for remission and de-escalate], particularly given the current lack of definitive, evidence-based de-escalation strategies. We can also be reassured that first-line re-induction does not impact on the efficacy of subsequent dose interval shortening, given that all 10 patients in our cohort who underwent initial re-induction for secondary LOR, and subsequently underwent dose interval shortening, did not exhibit treatment failure within 24 months of dose interval shortening.

Additional doses required for dose interval shortening to accommodate weekly ADA and 6-weekly IFX regimens were sourced exclusively through compassionate access from pharmaceutical companies. This limited access and ability to escalate to more intensive IFX regimens such as 4-weekly dosing. We acknowledge that the use of a 4-weekly rather than 6-weekly intensified IFX regimen may have proven more effective; however, a study by Kopylov *et al.* demonstrated that dose interval shortening to 6-weekly IFX was at least as effective as doubling the dose to 10 mg/kg or halving the infusion intervals to 4-weekly, in the setting of secondary LOR.[12] In view of the incremental costs associated with 4-weekly relative to 6-weekly IFX dosing, we believe that our practice of dose interval shortening to 6-weekly IFX presents important data regarding the relative efficacy of an affordable and more accessible means of IFX dose escalation relative to IFX re-induction.

The current study has several limitations, including the inability to attribute causality, given its retrospective, observational design. The dose escalation strategy undertaken for each patient was at the discretion of the treating clinician rather than based on standardised criteria. Access and availability to anti-TNF re-induction relative to dose interval shortening also likely influenced the therapeutic approach chosen to address secondary LOR across our patient cohort. Dose interval shortening represents a relatively recent therapeutic approach to secondary LOR in Australia, with anti-TNF re-induction over-represented within our cohort across earlier years. The availability and application of both therapeutic approaches are reflected in the significantly longer duration of median follow-up after re-induction, relative to dose interval shortening. It is also plausible that in view of fewer second-line biologic agents during earlier periods, changing biologic agents may have been deferred for longer periods, thereby indirectly increasing the collective time to treatment failure across the re-induction cohort.

Baseline patient and disease characteristics were similar across both groups. There were however, a greater proportion of current and ex-smokers in the re-induction group, the effect of which would, if anything, potentially worsen outcomes and comparisons of this group. Also, the use of tangible, objective criteria to define secondary LOR and anti-TNF failure in the absence of consensus definitions highlights one of the inherent strengths of our study. As is the case in many countries, access to and availability of anti-TNF TDM varied over the study period; hence routine TDM was not performed across our patient cohort. Finally, our cost analysis under-estimated the cost of IFX administration, as we did not include ancillary treatment costs such as those associated with staff and consumables related to the actual infusion. However, if these additional costs were included, the cost differential between IFX re-induction and dose interval shortening would have been even greater.

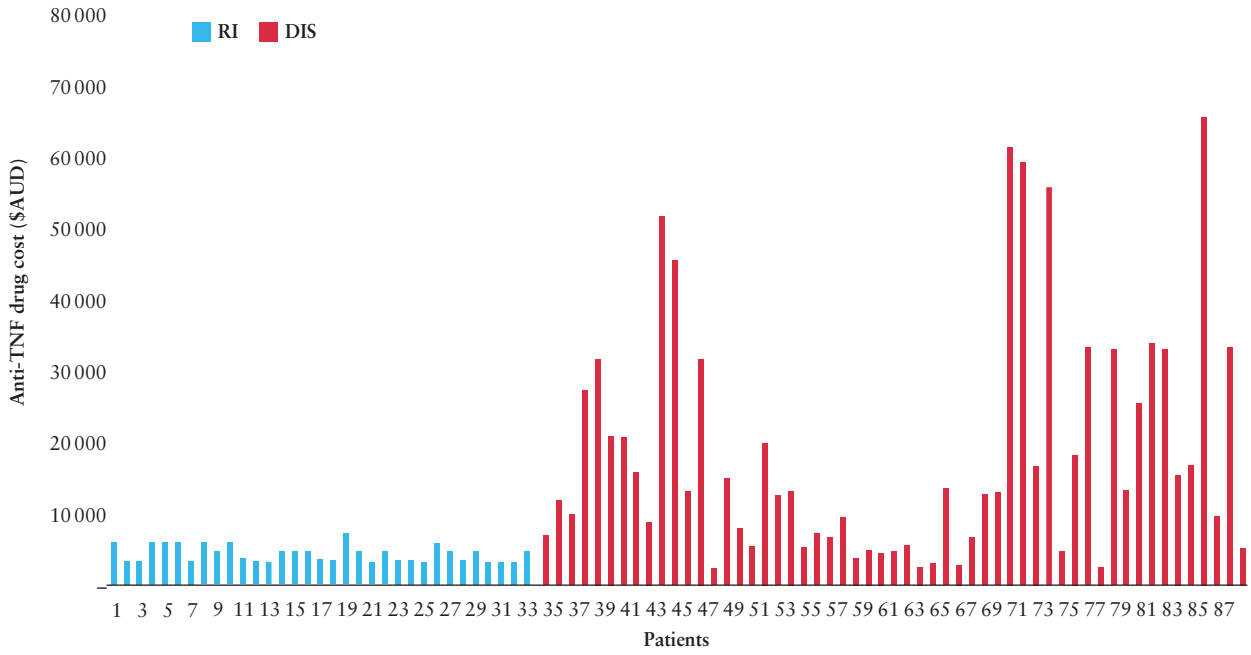

Figure 3. Difference in anti-tumour necrosis factor [TNF] drug costs across individual patients associated with re-induction [RI] and dose interval shortening [DIS]; Australian dollars [AUD].

5. Conclusions

These 'real world' data suggest that, in the setting of objectively defined secondary LOR to anti-TNF therapy in Crohn's disease, the strategy of re-induction as a first-line approach should be considered over the strategy of shortening the dosing interval for three reasons. Firstly, the efficacy of both approaches in successfully maintaining patients on their anti-TNF therapy at 12 and 24 months is similar. Secondly, re-induction confers a significant cost advantage relative to dose interval shortening. Finally, patients who do not achieve adequate longer-term response to anti-TNF re-induction can undergo subsequent dose interval shortening without apparent compromise to recapturing response. This type of rational approach to biologic therapy is of potential benefit to patients and payers alike, particularly in an era where clinicians are expected to be increasingly cognisant of both. Prospective randomised comparative evaluation of these strategies is warranted to validate the findings of the current study.

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Conflict of Interest

MPS receives educational grants and research support from Ferring and Orphan. MPS has also received fees to speak from Janssen, Abbvie, Ferring, Takeda, and Hospira, and is on the advisory boards of Janssen, Takeda, Pfizer, Celgene, Abbvie, and MSD. PRG has served as a consultant or advisory board member for AbbVie, Ferring, Janssen, Merck, Nestle Health Science, Danone, Allergan, Pfizer, Celgene, and Takeda. His institution has received speaking honoraria from AbbVie, Janssen, Ferring, Takeda, Mylan, Danone, and Pfizer. PRG has also received research grants for investigator-driven studies from AbbVie, Janssen, Danone, and A2 Milk Company. His Department financially benefits from the sales of a digital application and booklets on the low FODMAP diet. PRG has also published an educational/recipe book on diet. DVL has served as a speaker and/or received travel support from Takeda, Ferring, and Shire. He also has consultancy agreements with Abbvie, Janssen, and Pfizer and has received research funding grants for investigator-driven studies from Ferring, Shire, and AbbVie.

Author Contributions

AS, AV, and DVL reviewed the literature and prepared the manuscript. AS, AV, DVL, and AM contributed to the collection and analysis of data to AS, AV, DVL, MPS, and PRG revised the manuscript critically. AS, AV, and DVL prepared the final version of the manuscript. All authors approved the final draft before submission.

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