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The efficacy of shortening the dosing interval to once every six weeks in Crohn's patients losing response to maintenance dose of infliximab

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SUMMARY

Background
Patients treated with infliximab for Crohn's disease (CD) frequently require intensified dosage due to loss of response. There are scant data regarding the efficacy of shortening the dosing interval to 6 weeks.

Aim
We sought to investigate the efficacy of a once every 6 weeks' strategy compared with dose-doubling.

Methods
This work was a multicentre retrospective study of infliximab-treated CD patients who required dose escalation. The clinical outcome of patients treated by intensification to 5 mg/kg/6 weeks (6-week group) was compared with the outcome of patients whose infliximab was double-dosed (10 mg/kg/8 weeks or 5 mg/kg/4 weeks).

Results
Ninety-four patients (mean age: 29.8 years) were included in the study, 55 (59%) in the 6-week group and 39 (41%) in the double-dose group. Demographics and disease characteristics were similar between the two groups, although patients with re-emerging symptoms 5–7 weeks postinfusion were more likely to receive 5 mg/kg/6 weeks dosing (OR: 3.4, 95% CI: 1.4–8.8, $P < 0.01$). Early response to dose-intensification occurred in 69% of patients in the 6-week group and 67% in the double-dose group (P = N.S.). Regained response was maintained for 12 months in 40% compared with 29% of the patients respectively (P = N.S.).

Conclusion
In CD patients who lost response to standard infliximab dose, especially when symptoms re-emerge 5–7 weeks postinfusion, shortening the dosing interval to 6 weeks appears to be at least as effective as doubling the dose to 10 mg/kg or halving the infusion intervals to once in 4 weeks.

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INTRODUCTION

Crohn's disease (CD) is a disabling chronic inflammatory bowel disease. The anti-tumour necrosis factor alpha (TNF-α) infliximab is a monoclonal mouse-human chimeric immunoglobulin that was introduced in the late 1990s. It has since been demonstrated to be an effective treatment for both luminal and fistulizing disease.[1, 2] Scheduled therapy with infliximab is associated with an increased likelihood of maintaining remission, reduced likelihood of development of antibodies to infliximab (ATI), reduced number of hospitalisations and corticosteroid requirements.[3, 4]

Currently accepted regimen for scheduled administration of infliximab includes loading dose of 5 mg/kg at week 0, 2 and 6, followed by repeated infusions of 5 mg/kg every 8 weeks. However, 30–84% of the patents experience loss of response (LOR) to infliximab along the course of the treatment (1.4–7). It is advocated to try and induce regained response in these patients by either shortening the interval between the infusions or increasing the dose. The customary strategy and the only one reported in the framework of a controlled trial is doubling the dosage to 10 mg/kg every 8 weeks,[1] although shortening the dosing interval to 4 weeks is also common.[5–8] In the ACCENT 1 trial, this double-dosing policy has lead to regained response in 80–90% of patients.[1] However, rather than double-dosing, many physicians reduce the dosing interval to 6 weeks in those patients who experience a shortened duration of response.[9] Although this approach may be less costly and could be more convenient for the patients, requiring clinic visit every 6 weeks instead of every 4 weeks, there are sparse data to support this clinical practice or its efficacy.

Therefore, the aim of this retrospective multicentre study was to examine the efficacy of shortening the dosing interval of infliximab to every 6 weeks as compared with the conventional double-dose approach of halving the interval to every 4 weeks or escalating the dose to 10 mg/kg.

METHODS

Study design and population

This work was an observational retrospective study of infliximab-treated CD patients in the years 2000–2009 at the gastroenterology departments of the participating tertiary medical centres. The study population comprised patients who have lost response to maintenance infliximab infusions of 5 mg/kg every 8 weeks as per their treating physician's judgment. The patients were divided to those whose therapeutic regimen was intensified to 5 mg/kg every 6 weeks (group I) vs. those who received either 10 mg/kg every 8 weeks or 5 mg/kg every 4 weeks (group II). Patient files were reviewed by an investigator in the participating institution, and clinical and laboratory parameters were recorded. The clinical outcome of regained response at 4–8 weeks after the first intensified dose infusion (immediate response) and after 1 year (sustained response) was compared for patients in group I vs. group II.

The study was approved by the institutional ethics committee of the Sheba Medical Center and also approved or exempted by the local ethics committees of the participating centres.

Definitions

Maintenance dosing was defined as at least one 8-week-interval infusion of infliximab following the induction course and prior to any dose escalation. Immediate response to intensification was defined as improvement of the symptoms at the first clinic visit after dose intensification of infliximab as per the treating physician judgment, coupled with a decision to continue the intensified dose regimen without alterations. Long-term sustained response was defined as improvement of the symptoms on the intensified therapeutic regimen lasting at least 1 year without any further alterations of the therapeutic regimen. Failure of the intensified therapeutic regimen was defined by absence of improvement of the symptoms of disease and by a decision of the treating physician to increase the dose or shorten the dose interval of infliximab further, add immunomodulator or corticosteroids therapy, switch to another anti-TNF medication (Adalimumab/Certolizumab) or refer for CD-related surgery.

Statistical analyses

Continuous variables were analysed by two-tailed Student's *t*-test or Mann–Whitney *U*-test, as appropriate, and categorical variables were analysed by Fisher Exact test. On the basis of data from ACCENT 1,[1] we assumed 80% response for double dose and hypothesised a lessened response of 50% to the smaller dosing escalation of 5 mg/kg/6 weeks. To detect this difference with a power of 80% and with α-level of 5%, we computed that 72 patients (36 patients in each arm) would be required. All statistics were performed using MedCalc software (Mariakerke, Belgium). $P < 0.05$ was considered statistically significant.

RESULTS

Patient characteristics

Ninety-four patients were included in the study. Group I included 55 patients who were administered infliximab 5 mg/kg every 6 weeks. Group II included 39 patients whose dosing was intensified to either 10 mg/kg every 8 weeks (24 patients) or 5 mg/kg every 4 weeks (15 patients). The demographic and disease characteristics of the study cohort, stratified into the two groups are depicted in Table 1. Five patients were formerly treated by episodic infliximab, but the treatment was stopped prior to resumption by a complete loading and maintenance scheduled therapy. The clinical data analysed for these patients refer only to their scheduled treatment phase. In three patients in group I and two patients in group II, the therapeutic regimen was successfully down escalated following sustained response to the escalation after a median duration of intensified treatment of 6 ± 1.7 (range: 3–9) months. The clinical data for these patients were analysed as per escalated regimen of infliximab. Eighteen of 94 patients achieved immediate response with an escalated regimen of infliximab (10 from group I and eight from group II), but have had a duration of follow-up of <1 year. Thus, they were included in the outcome data analysis regarding the immediate response only.

Immediate clinical response

Overall, 64 of 94 (68%) study patients had short-term clinical response to intensified therapeutic regimen (Figure 1). Thirty-eight of 55 patients (69%) in group I experienced immediate short-term clinical response to shortening the therapeutic interval compared with 26/39 (67%) in the double-dose group II ($P > 0.9$). The median time to first visit after escalation when response was determined was 6 ± 2.2 (2–8) weeks.

Elevated CRP level before the escalation was present in 69 of 79 patients with available measurement, but was not predictive of greater response to escalation (data not shown). Sequential CRP level both before and after treatment intensification was available in 64 of the 94 patients, and was elevated above the upper normal limit in 56 of these 64 patients before escalation. Intensification of the therapeutic regimen resulted in normalisation of the CRP in 26 of these 56 (46%) patients. Immediate response to escalation occurred among 22/26 patients with CRP normalisation compared with 17 of 30 with persistent elevation of CRP (OR: 4.2, 95% CI: 1.2–15.2, $P = 0.03$).

Sustained clinical response

Twenty-seven (36%) of the 76 patients who completed follow-up period of at least 1 year had a sustained clinical response at 12 months after infliximab intensification (median follow-up: −1.9 years). The course and subsequent therapies employed for the individual study patients are shown in Figure 2. In group I, 18/45 (40%) patients with complete follow-up had sustained their response at 1 year compared with nine of 31 (29%) of patients in group II ($P = 0.65$). The median duration of sustained response was 16 ± 10.7 (range: 12–52,) months in group I and 17 ± 16.4 (range: 12–60) months in group II ($P = 0.99$). A Kaplan–Meier curve depicting the cumulative incidence over time for LOR to the intensified regimen for the two groups is shown in Figure 3. No demographic or clinical factor was found to be predictive for sustained response to escalation regimen of infliximab (Table 2).

We also divided patients to those with early postinfusion LOR (re-emerging symptoms <4 weeks postinfusion, $n = 27$) vs. those with late postinfusion LOR (symptoms occurring 5–7 weeks postinfusion, $n = 67$). This analysis showed that early postinfusion LOR patients were more likely to be double-dosed than to receive 5 mg/kg/6 weeks (17/39 vs. 10/55, OR: 3.4, 95% CI: 1.4–8.8, $P < 0.01$), whereas patients with late postinfusion LOR mostly received shortened 6 weeks' interval infusions (Table 1). In terms of efficacy, however, both strategies yielded comparable rates of sustained response among the 76 patients with complete follow-up: 15/36 patients with late postinfusion LOR treated by 5 mg/kg/6 weeks were still responding at 12 months compared with six of 18 patients with late LOR treated by double-dosed regimen (P = N.S.). Sustained response was also comparable for patients with early <4 weeks postinfusion LOR treated by either strategy, but the numbers of patients were smaller (3/13 vs. 3/9, for 5 mg/kg/6 weeks vs. double dose respectively).

Finally, we analysed the results for sustained clinical response at 1 year or at the end of follow-up by incorporating the 18 patients with <1 year of follow-up (mean follow-up duration of 0.6 years). There was no difference in the sustained response rate between group I and group II in this analysis as well (28/55 vs. 17/39 respectively, $P = 0.56$).

Second escalation of infliximab dosage

Forty-nine patients of the total cohort did not achieve sustained clinical response after the first escalation of

Table 1 | Demographic and clinical characteristics of the included patients

	Entire cohort (n = 94)		Group I (n = 55)		Group II (n = 39)		
	n	%	*n*	%	*n*	%	*P*
Age at diagnosis (years)							
<16	17	18	7	13	10	26	0.19
16–40	68	72	41	75	27	69	0.87
>40	9	10	7	13	2	5	0.31
Age at initiation of infliximab therapy (years)	29.8 ± 10.3		31.9 ± 10.6		27 ± 9.3		0.5
Duration of disease before initiation of IFX (years)	10.4 ± 6.8		10.7 ± 6.7		9.14 ± 6.3		0.79
Gender							
Male	44	47	25	45	19	49	0.85
Female	50	53	30	55	20	52	1
Location							
Upper	3	3	1	2	2	5	0.57
Small bowel	19	20	12	22	13	18	0.37
Colon	21	22	8	15	7	33	0.78
Ileocolonic	54	58	35	64	19	49	0.48
Disease phenotype							
Fistulizing	20	21	10	18	10	26	0.52
Stricturing	36	38	24	44	12	31	0.86
Perianal	38	40	20	36	15	39	0.49
Concurrent medications							
Thiopurines	50	53	27	49	23	59	0.43
Methotrexate	6	6	6	11	0	0	0.76
Budesonide	6	6	3	6	3	8	0.73
Systemic CS	1	1	0	0	1	3	1
5-ASA	15	16	4	7	11	28	0.12
Postinfusion time to LOR (time of re-emerging symptoms) response							
Early (≤4 weeks)	27	29	10	18	17	44	0.01
Late (>4 weeks)	67	71	45	82	22	56	0.01
Number of maintenance IFX infusions until LOR, median (range)	6 ± 6.6 (1–36)		6 ± 10.7 (1–36)		4 ± 5.7 (1–24)		0.85
CRP level							
Pre-escalation level available	79	84	44	80	35	90	
Elevated CRP before escalation	69	87	38	86	31	89	0.59

Group I patients were switched to infliximab 5 mg/kg/6 weeks. Group II patients were intensified to infliximab 10 mg/kg/8 weeks or 5 mg/kg/4 weeks (double dose).

IFX, infliximab; CS, corticosteroids; CRP, C-reactive protein; LOR, loss of response.

infliximab dosage. In 28/49 (57%) of these failing patients, a further dose escalation of infliximab was attempted. Eleven (39%) of the 28 patients responded to a second escalated infliximab dosage (mean follow-up time: −1.1 years). The clinical course of these patients and their breakdown to patients receiving second

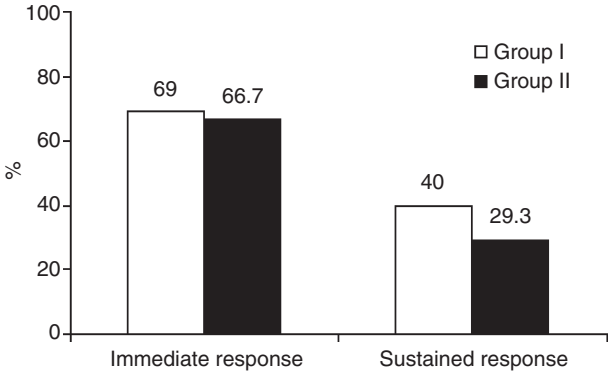

Figure 1 | Short- and long-term response to escalation regimen of infliximab. Group I patients were switched to infliximab 5 mg/kg/6 weeks. Group II patients were intensified to infliximab 10 mg/kg/8 weeks or 5 mg/kg/4 weeks (double dose).

escalation after previous 6 week regimen vs. previous double dose is described in Figure 1 and Table 3. Considered together, first and second escalations resulted in 38/76 (50%) of patients being in sustained clinical response at 12 months after initial LOR.

DISCUSSION

The present study evaluated the efficacy of shortening the dosing interval of infliximab to once in every 6 weeks in patients who lost response to standard maintenance regimen, in comparison to doubling the dose or halving the dosing interval to once in every 4 weeks. There are limited data pertaining to the rates of LOR and regain of response to intensified dose. In particular, data regarding the optimal dose intensification protocol in such patients are lacking.

In the ACCENT 1 study, 29% of the patients receiving scheduled infusions of infliximab experienced worsening of symptoms requiring dose increase.[1] Of these patients, 80–90% responded to the intensified dose, but the rate of 1 year sustained response to the escalated regimen was not reported due to the design of the study. Requeiro *et al.*[7] found that in a cohort of patients who received at

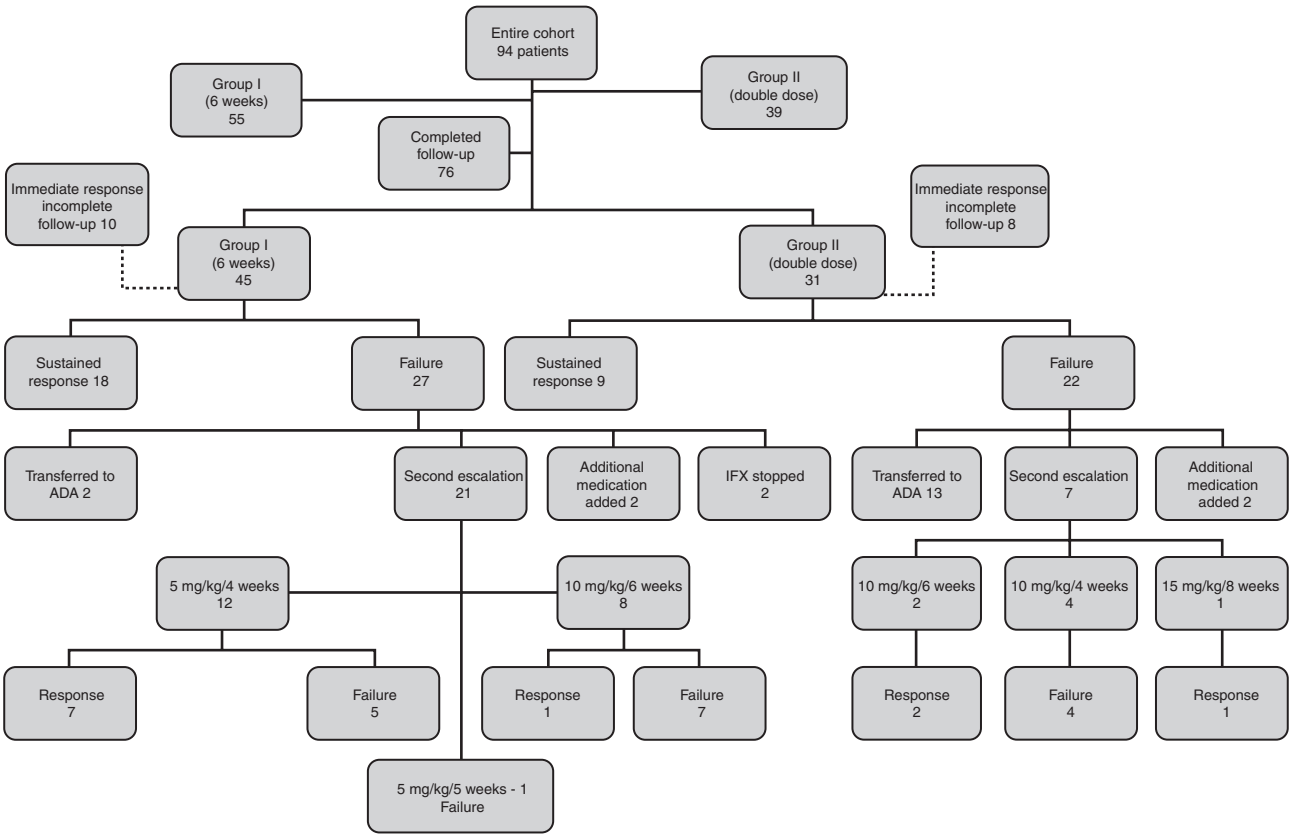

Figure 2 | The clinical course of the patients treated with escalated dose of infliximab (IFX). Group I patients were switched to infliximab 5 mg/kg/6 weeks. Group II patients were intensified to infliximab 10 mg/kg/8 weeks or 5 mg/kg/4 weeks (double dose). Additional medication – systemic corticosteroids or methotrexate. ADA, Adalimumab.

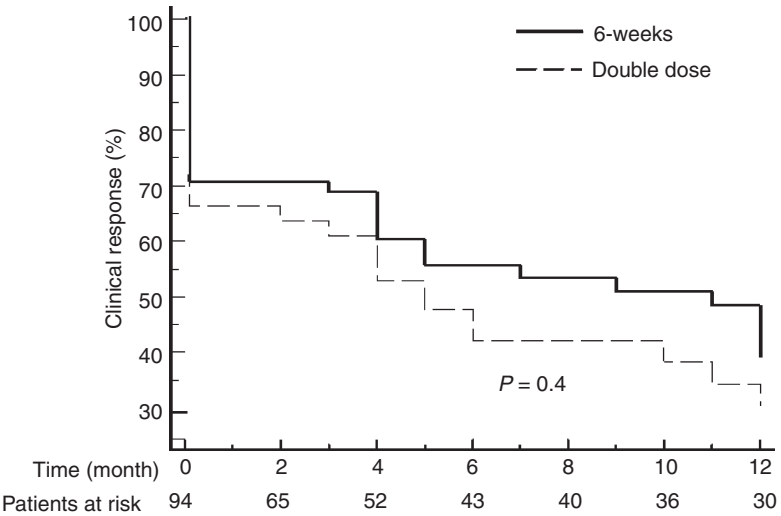

Figure 3 | Cumulative probability of loss of response over time for the two treatment groups. Group I patients were switched to infliximab 5 mg/kg/6 weeks. Group II patients were intensified to infliximab 10 mg/kg/8 weeks or 5 mg/kg/4 weeks (double dose).

least eight doses of infliximab (both scheduled and episodic), 31% of the patients required dose intensification after 12 months and 54% after 30 months. Overall, 76% of these patients remained under infliximab treatment at the conclusion of follow-up, but data regarding possible additional interventions in these patients and the 1-year response rate were not reported. In a cohort of 614 patients receiving either episodic or maintenance treatment with infliximab, 50% required some change of treatment regimen including switch from episodic to scheduled treatment, shortening of dosage interval or dose escalation.[5] However, data pertaining specifically to each of these policies, and the response at 12 months were not provided. Thus, to the best of our knowledge, this study is the first to assess specifically the sustained response to escalation at the clinically meaningful 12 months' time point.

There are few systematic data regarding the shortening of the dosing interval to once every 6 weeks rather than double dosing or halving the interval. A study by Seow *et al.*[10] in patients receiving maintenance infliximab therapy for ulcerative colitis demonstrated that in patients who had lost response to 5 mg/kg of infliximab every 8 weeks, shortening of the dosing interval to 6–7 weeks resulted in regained remission in 44% of the patients, whereas doubling the dose resulted in regained remission in 25% of the patients, but the duration of the regained remission was not reported. Magro *et al.*[9] found that shortening the dosing interval to 6 weeks was an efficient strategy for managing LOR in CD patients receiving maintenance treatment with infliximab. However, this was a small-scale retrospective study that included only 15 patients.

Infliximab has linear pharmacokinetics with elimination half-life of 12 days and no plasma level accumulation with multiple infusions,[11] so a 6-week-interval approach appears to be acceptable and safe from the pharmacological point of view. St Clair *et al.*[12] performed a pharmacokinetic modelling for escalation of infliximab based on the cohort of rheumatoid arthritis patients. This model concluded that shortening the dose interval to every 6 weeks would increase the median serum trough level 3.5-fold compared with 2.2-fold increase in trough level after a 50% increase in infliximab dose given every 8 weeks. However, the validity of these calculations was not confirmed by actual infliximab concentration measurements, and efficacy of shortened 6-week dosing intervals was not clinically evaluated in the study.

Arguably, shortening the dosing interval to 5 mg/kg every 6 weeks is appropriate for patients with shortened response to infliximab, whereas double dosing (or interval halving) should be reserved for patients with complete or early LOR to the last infusion.[8] Although this rationale is clinically sound, and has underlain physicians' therapeutic choices for a majority of patients in our study as well, the clinical outcomes of these differing policies have not been previously investigated. Thus, we believe this study is important for being the first to compare between these two management approaches. The results suggest that escalation of the therapeutic regimen to once every 6 weeks appears to be at least as effective as doubling the dose or halving the interval, especially for patients with late postinfusion LOR (re-emerging symptoms 5–7 weeks postinfusion). This preliminary evidence supporting the validity of the 5 mg/kg/6 weeks intensification policy is also important given the significant costs incurred by these escalation regimens. In fact, based on published U.S. costs of $662/100 mg infliximab and $193 per infusion,[13] keeping a 60-kg patient on 5 mg/kg/6w for 12 months would cost US$19 611 compared with US$24 990–26 148 for the double-dose

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Table 2 | Predictors of sustained (12 months) response to infliximab escalation

	Sustained response (n = 27)		Failure to achieve response (n = 49)		
	n	%	n	%	P-value
Age at diagnosis (years)	23.5 ± 9.4		26 ± 10.4		0.19
Age at initiation of infliximab therapy (years)	29.8 ± 10.2		31.1 ± 10.6		0.36
Duration of disease before initiation of IFX (years)	7.47 ± 6.7		5.26 ± 5.5		0.13
Female	11	59	23	47	0.67
Male	16	41	26	53	0.67
Location					
Upper	0	0	2	4	0.54
Ileocolonic	14	52	24	49	1
Small bowel	5	19	20	41	0.21
Colonic	5	19	5	10	0.48
Disease phenotype					
Fistulizing	8	30	10	20	0.59
Stricturing	8	30	17	35	0.81
Perianal	9	33	16	33	1
Concomitant medications					
Thiopurines	14	52	26	53	1
Methotrexate	2	7	3	6	1
Budesonide	2	7	4	8	1
5-ASA	7	26	5	10	0.2
Median number of maintenance IFX infusions until LOR (range)	9 ± 7.8 (0–25)		6 ± 8.9 (0–36)		0.49
Postinfusion time to LOR (time of re-emerging symptoms)					
Early (≤4 weeks)	6	27	16	73	0.14
Late (>4 weeks)	21	39	33	61	0.14
CRP above normal before first escalation*	19	82	37	80	0.8

IFX, infliximab; CS, corticosteroids; CRP, C-reactive protein; LOR, loss of response.

* Numbers are out of 63 CRP results available.

Table 3 | Number of patients receiving and responding to second escalation regimens of infliximab dose

Group	Failure of first escalation	Second escalation		5 mg/kg/ 4 weeks		10 mg/ kg/6 weeks		10 mg/ kg/4 weeks		15 mg/ kg/8 weeks		5 mg/kg/ 5 weeks	
		Total	Resp	Total	Resp	Total	Resp	Total	Resp	Total	Resp	Total	Resp
Group I	27	21	8	12	7	8	1	–	–	–	–	1	0
Group II	22	7	3	–	–	2	2	4	0	1	1	–	–
Total	49	28	11	12	7	10	3	4	0	1	1	1	0

Total, total number of patients in the subgroup; Resp, number of patients that responded to the escalation.

strategies, amounting to a $5379–6537 savings in cost per patient per annum.

The overall rate of primary nonresponse to the first escalation was 32%, and many of the responding patients subsequently lost response to the escalated regimen within <1 year of treatment. Nevertheless, an important observation of the study is that nearly 40% of patients without a sustained response to the first escalation (either primary or secondary nonresponders) may still regain response to a second elevation of infliximab dose or further shortening of the dosing interval. Taken together, dose-intensification policy (with either one or two dose increases) results in an approximately 50% rate of sustained response at 12 months after LOR to standard maintenance therapy.

A major limitation of this retrospective study is the absence of response criteria based on clinical scoring systems. However, from the practical point of view, the patient's report and the clinician's decision regarding continuation or change in the therapeutic regimen probably reflects the real-life assessment of the severity of the disease and the clinical decision making. Although the involvement of several centres could contribute to heterogeneity of the clinician's assessment of the patient's response, it also lends further support to the wider clinical relevance of the observations as they are derived from several tertiary centres rather than any single centre with a particular policy.

As alluded to above, another possible limitation stems from a basic difference between the two groups in the sense that physicians have opted to intensify the dose to once every 6 weeks in patients reporting shortened response of 5–7 weeks to the last infusion, whereas they tended to double dose in patients experiencing little effect of the infusion whatsoever. Nonetheless, upon subanalysing the efficacy of escalation strategies for patients with late postinfusion LOR, 5 mg/kg/6w was at least as effective as double dosing. The strategies were also comparable when applied for patients with early postinfusion LOR, albeit the numbers of patients in this subanalysis were small. Thus, the present results are clinically pertinent for substantiating that the two approaches are comparable, especially for patients with late postinfusion LOR (re-emerging symptoms 5–7 weeks postinfusion). Nonetheless, a cautionary note should be placed, as this study was not designed as a non-inferiority study, and can not definitively exclude the presence of a difference – albeit small – in the efficacy of the two policies.

Finally, infliximab drug level and presence or absence of ATI were previously shown to correlate with LOR[14–16] and to be helpful in directing therapy,[17] but were mostly unavailable for the present study patients. Colonoscopy findings before/after dose-adjustment were also unavailable. Although these shortcomings do not affect the validity of the observations, it would be important in the future to analyse the rates of regained response by different escalation protocols in association with drug level, ATI status and endoscopic mucosal healing.

In conclusion, in patients with CD and LOR to infliximab, escalation of the infliximab dosing to once every 6 weeks appears to be at least as effective as doubling the dose or halving the dosing interval to every 4 weeks, and results in sustained response in 40% of patients. However, these preliminary data should be corroborated by a larger scale and preferably a prospective controlled study comparing the regained response rate to 5 mg/kg/6w vs. the double-dose strategy in patients with LOR to infliximab, stratified by early or late postinfusion re-emergence of symptoms.

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