

Time of infliximab therapy initiation and dose escalation in Crohn's disease

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34.8 ± 14.8 years. Of the 68 patients, 19% initiated infliximab within 2 years of diagnosis, and 51% had concurrent immunosuppressant therapy at the time of therapy initiation. Fifty percent of patients required dose escalation and the median time from therapy initiation to dose escalation was 10 mo (interquartile range: 5.3-14.8). There was a statistically significant higher probability of requiring dose escalation in patients who initiated biologic therapy within 2 years of diagnosis, without concurrent immunosuppressant therapy ($P < 0.01$).

CONCLUSION: Those who receive infliximab within 2 years of CD diagnosis require more intense immunosuppressant therapy than those who received infliximab later.

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Key words: Crohn's disease; Infliximab; Dose escalation

Abstract

AIM: To determine if early initiation of anti-tumor necrosis factor therapy affects the need for dose escalation.

METHODS: This was a retrospective review of patients receiving infliximab therapy for Crohn's disease (CD) at two outpatient gastroenterology clinics during July 2009 to October 2010. All patients included in the study were biologic agent naïve and had moderate to severe CD (Harvey Bradshaw index > 8). Patients were divided into groups based on length of time between diagnosis to therapy initiation and concurrent immunosuppressant therapy. Kaplan-Meier survival analysis was used to compare the time to dose escalation for the four groups.

RESULTS: There were 68 patients, 51% female and 49% male, with an average age at diagnosis of 24.7 ± 11.9 years. The average age at infliximab initiation was

Core tip: Crohn's disease patients who required infliximab therapy earlier (< 2 years) probably have a higher inflammatory burden of disease than those who require infliximab therapy later. Our results show that those who receive infliximab within 2 years of diagnosis require more intense immunosuppressant therapy to avoid dose escalation. This finding supports the importance of concurrent immunosuppressant therapy while on infliximab, as previously described by the SONIC trial.

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INTRODUCTION

Tumor necrosis factor (TNF)- α is a proinflammatory cytokine that has an important role in the pathogenesis of Crohn's disease (CD)^[1-4]. Serum and intestinal mucosa TNF- α levels are increased in CD, and disease activity is reduced by TNF- α -blocking agents^[5,6]. Several meta-analyses have shown that anti-TNF- α agents are effective in induction and maintenance therapy, as well as in the treatment of fistulizing CD^[7-13]. Moreover, the SONIC trial demonstrated that combination of azathioprine and infliximab is the most potent therapy to achieve steroid-free remission in CD patients^[14].

Unfortunately, about 50% of patients receiving anti-TNF agents lose some or all of their initial therapeutic response, requiring dose escalation by increasing dosage or by shortening interval between infusions. Factors that influence dose escalation for anti-TNF therapy in CD are largely unknown. Gisbert *et al.*^[15] showed in a systematic review that CD treated with infliximab results in a 37% loss of response rate, requiring dose intensification, equivalent to an annual risk for loss of infliximab response at 13% per patient-year. The etiology for this loss of response is unclear because immunogenicity data do not suggest a correlation with clinical response^[16,17]. Several studies have demonstrated that dose escalation by increasing dosage of infliximab (from 5 to 10 mg/kg), or shortening the interval between infusions from 8 to 6 wk is effective in reacquiring disease remission^[16].

The factors that influence infliximab response duration are largely unknown. Our hypothesis is that early initiation of infliximab when disease is more likely to be inflammatory in its phenotype incurs a longer duration of response and requires less need for dose escalation.

The aim of the present study was to determine the relationship between time of infliximab initiation from disease diagnosis to the time of infliximab initiation to dose escalation.

MATERIALS AND METHODS

This was a retrospective review of patients treated with infliximab for CD at two outpatient tertiary inflammatory bowel disease gastroenterology clinics from July 2009 to July 2010. Inclusion criteria were anti-TNF-naïve patients with moderate to severe CD as determined by Harvey Bradshaw Index (HBI) > 8 at the time of infliximab initiation, as assessed by individual gastroenterologists^[18]. Patients receiving infliximab for treatment of fistulizing disease were excluded. Infliximab induction protocol was 5 mg/kg at 0, 2 and 6 wk, and every 8 wk thereafter. The decision for dose escalation was based on persistent HBI > 8 at three infusions or later in therapy to treat disease exacerbation.

Univariate and multivariate analyses were performed on five predetermined variables that were thought to have the most impact on infliximab response. These were sex, age at diagnosis (< 17 , 17-40 and > 40 years), years

between diagnosis and infliximab initiation ($<$ or ≥ 2 years), behavior of disease, and concurrent immunosuppressant therapy (azathioprine, 6-mercaptopurine or methotrexate). Disease behavior was described using the Montreal classification^[19]. Fisher's exact test and logistic regression were used to examine the impact of these variables on the proportion of patients requiring dose escalation within 12 mo. Patients who discontinued therapy before 12 mo or who were followed for < 12 mo without dose escalation were treated as unknown in terms of dose escalation for this analysis. The impact of these variables on the timing of dose escalation was further examined through Kaplan-Meier survival curve and Cox proportional hazards model. Patients who discontinued therapy before dose escalation were censored in the survival analysis.

RESULTS

Ninety patients were receiving infliximab during July 2009 to July 2010. Sixty-eight patients met the inclusion criteria. The following were excluded: seven patients with prior exposure to biologics; 13 with ulcerative colitis; and two with missing essential historical data. Forty-nine percent of patients were male, with an average age at diagnosis of 24.7 ± 11.9 years, and average age at infliximab initiation of 34.8 ± 14.8 years. Of the 68 patients, 19% initiated infliximab within 2 years of diagnosis, and 51% had concurrent immunosuppressant therapy at the time of therapy initiation. Fifty percent of patients required dose escalation and the median time from therapy initiation to dose escalation was 10 mo (interquartile range: 5.3-14.8) (Table 1). Four patients discontinued therapy before 12 mo without dose escalation (2 were due to poor response, 1 was concerned with side-effect profile, and 1 had emergency colectomy), and 10 patients were followed up for < 12 mo; these patients were excluded from analysis. Seven patients discontinued therapy between 12 and 24 mo after therapy initiation: four were due to poor or loss of response to therapy (as defined by persistent symptoms based on assessment by a gastroenterologist); one had emergency colectomy secondary to obstruction; one had elective colectomy; and one discontinued due to concerns regarding side effects.

In the multivariate analysis (Table 2), only the variables "years between diagnosis and infliximab initiation" and "concurrent immunosuppressant therapy" were suggestive of possible impact on the probability of dose escalation within 12 mo or on the timing of dose escalation ($P = 0.11$ and $P = 0.09$, respectively). The four groups being compared were: " < 2 years between diagnosis and infliximab initiation with concurrent immunosuppressant therapy"; " < 2 years between diagnosis and infliximab initiation without concurrent immunosuppressant therapy"; " ≥ 2 years between diagnosis and infliximab initiation with concurrent immunosuppressant therapy"; and " ≥ 2 years between diagnosis and infliximab initiation without concurrent immunosuppressant therapy".

Table 1 Baseline clinical characteristics of cohort *n* (%)

Variable	All patients (<i>n</i> = 68)
Male	33 (49)
Age at diagnosis ¹ (yr)	18 (27)
< 17	43 (64)
17-40	6 (9)
> 40	
Age at diagnosis ¹ (yr)	24.7 ± 11.9
Past and current smoking ²	17 (25)
Age at first infliximab infusion (yr)	34.8 ± 14.8
Disease behavior ³	29 (44)
Non-stricturing, non-penetrating	12 (18)
Stricturing	12 (18)
Penetrating	13 (20)
Penetrating (perianal)	
Years between diagnosis and therapy initiation ¹	7.0 (2.0-14.5)
Years between diagnosis and therapy initiation ¹	13 (19)
< 2 yr	54 (81)
≥ 2 yr	
Concurrent immunosuppressant therapy ¹	34 (51)
Concurrent prednisone therapy ³	8 (12)
< 20 mg/d	10 (15)
≥ 20 mg/d	
Dose escalation	34 (50)
Mean time to dose escalation (mo)	10.0 (5.3-4.8)

Continuous data are reported as mean ± SD, or median and IQR when not normally distributed. ¹Data for one patient are missing; ²Data for two patients are missing; ³Data unknown for 12 patients. Past smokers defined as those who had quit smoking at least 6 mo prior to first infliximab dose or those who smoked < 5 cigarettes/d. Current smokers defined as those who smoke at least 5 cigarettes/d for at least 6 mo prior to the first dose of infliximab.

Fisher's exact test was conducted on the four groups depending on the time from diagnosis to initiation of infliximab and exposure to immunosuppressants (Table 3). Although there were no significant differences between these groups individually ($P = 0.19$), the proportion of patients that needed dose escalation within 12 mo was substantially higher for those starting infliximab within 2 years of diagnosis and not on concurrent immunosuppressant therapy than the other three groups combined ($P = 0.05$). Kaplan-Meier survival curves in Figure 1 showed a similar result ($P = 0.01$). The median time to dose escalation was 5 mo for those who started infliximab within 2 years of diagnosis and not on concurrent immunosuppressant, and 19 mo for the other three groups combined (Log rank, $P < 0.01$).

DISCUSSION

Several associations have been postulated to explain infliximab dose escalation requirements, including development of neutralizing antibodies, augmented clearance, concomitant drug interactions, and genetic factors^[20]. Although several studies have shown poor correlation of clinical response and immunogenicity, more recent data suggest that immunosuppression with infliximab increases efficacy, and the pathophysiology likely stems at least in part from a reduction in anti-infliximab antibody formation^[14,21]. Several studies have demonstrated that there

Table 2 Univariate and multivariate analysis of clinical variables on infliximab

Variable	<i>n</i>	Requiring dose escalation within 12 mo	Fisher's exact test <i>P</i> value	Log-rank test <i>P</i> value
Sex			0.58	0.91
Male	24	41.7%		
Female	30	33.3%		
Age at diagnosis			1.00	0.72
< 17 yr	11	36.4%		
17-40 yr	36	36.1%		
> 40 yr	6	33.3%		
Disease behavior			0.91	1.00
Non-stricturing, non-penetrating	24	37.5%		
Stricturing	9	44.4%		
Penetrating	9	33.3%		
Penetrating (perianal)	11	27.3%		
Years between diagnosis and therapy initiation			0.31	0.11
< 2 yr	12	50.0%		
≥ 2 yr	41	31.7%		
Concurrent immunosuppressant therapy			0.16	0.09
No	27	48.1%		
Yes	26	26.9%		

Table 3 Patients requiring dose escalation within 12 mo of therapy initiation

Years between diagnosis and therapy initiation	< 2 yr		≥ 2 yr	
On concurrent immunosuppressant therapy	No	Yes	No	Yes
Proportion of subjects	4/5 = 0.80	2/7 = 0.29	8/21 = 0.38	5/19 = 0.26
needed dose escalation within 12 mo				

is a significant benefit in steroid-free remission and mucosal healing in early combination immunosuppression and biologic therapy compared to immunosuppression alone^[22-24]. Support for the immunogenicity phenomenon was also observed in this study cohort.

All patients had moderate to severe CD (HBI > 8). Five factors were preselected for analysis: concurrent immunosuppressant therapy; years between diagnosis and infliximab initiation; disease behavior; age at diagnosis; and sex. There was a significantly higher probability of requiring dose escalation in the group of patients in whom therapy was initiated within < 2 years and not on immunosuppressant therapy ($P < 0.01$) than in the other three groups combined. Trough levels of serum infliximab were not available at our center. Despite the small sample size, these data support the importance of concurrent immunosuppressant therapy while on infliximab as previously described by the SONIC trial^[14]. Being a retrospective cohort study, we were not able to collect all the variables necessary to prove our hypothesis, however, our suspicion is that those who required infliximab therapy earlier (< 2 years) than the rest of the cohort had a higher inflammatory burden of disease. If this assumption is true, it would explain why concomitant immuno-

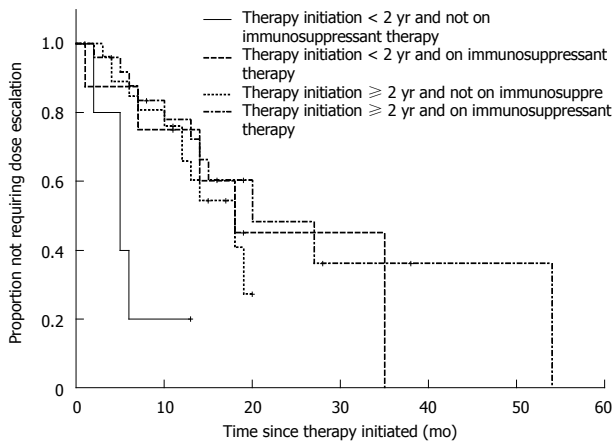


Figure 1 Kaplan-Meier survival curves to compare the time to dose escalation for the subgroups.

suppression is so important in this clinical context. This may also suggest that concomitant immunosuppression is not as important when anti-TNF agents are used in scenarios where the inflammatory burden is less. This factor may in part explain the difference in the results from the SONIC study^[14] (mean duration of disease for patients on combination therapy: 2.2 years) and the COMMIT study^[25] (mean duration of disease for patients on combination therapy: 10.8 years).

Compared to patients diagnosed with CD > 2 years from initiating infliximab, those who receive infliximab within 2 years of diagnosis require more intense immunosuppressant therapy to avoid dose escalation. Further studies are required to determine optimal induction therapy for CD patients with a significant inflammatory burden. A broader question raised by this study is the importance of assessing a patient's inflammatory burden and how this may influence our choice of therapy.

COMMENTS

Background

Tumor necrosis factor (TNF)- α is a proinflammatory cytokine that has an important role in the pathogenesis of Crohn's disease (CD). Serum and intestinal mucosa TNF- α levels are increased in CD, and disease activity is reduced by TNF- α -blocking agents.

Research frontiers

Several studies have shown poor correlation of clinical response and immunogenicity. More recent data suggest that immunosuppression with infliximab increases efficacy, and the pathophysiology likely stems at least in part from the reduction of anti-infliximab antibody formation.

Innovations and breakthroughs

The present study determined the relationship between time to infliximab initiation from disease diagnosis to the time of infliximab initiation to dose escalation.

Applications

There was a significantly higher probability of requiring dose escalation in the group of patients in whom therapy was initiated within < 2 years and not on immunosuppressant therapy than in the other three groups combined.

Peer review

This is an interesting paper on the association of infliximab with immunosuppressive therapy in patients with inflammatory bowel disease. It could be better divided into the pertinent variables before making conclusions about the note of early vs late introduction of infliximab and the influence of immunogenicity.

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