

## Accelerated infliximab infusions for inflammatory bowel disease improve effectiveness

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### Abstract

**AIM:** To study the safety and effectiveness associated with accelerated infliximab infusion protocols in patients with inflammatory bowel disease (IBD).

**METHODS:** Original protocols and infusion rates were developed for the administration of infliximab over 90-min and 60-min. Then the IBD patients on stable maintenance infliximab therapy were offered accelerated infusions. To be eligible for the study, patients needed a minimum of four prior infusions. An initial infusion of 90-min was given to each patient; those

tolerating the accelerated infusion were transitioned to a 60-min infusion protocol at their next and all subsequent visits. Any patient having significant infusion reactions would be reverted to the standard 120-min protocol. A change in a patient's dose mandated a single 120-min infusion before accelerated infusions could be administered again.

**RESULTS:** The University of Virginia Medical Center's Institutional Review Board approved this study. Fifty IBD patients treated with infliximab 5 mg/kg, 7.5 mg/kg and 10 mg/kg were offered accelerated infusions. Forty-six patients consented to participate in the study. Nineteen (41.3%) were female, five (10.9%) were African American and nine (19.6%) had ulcerative colitis. The mean age was 42.6 years old. Patients under age 18 were excluded. Ten patients used immunosuppressive drugs concurrently out of which six were taking azathioprine, three were taking 6-mercaptopurine and one was taking methotrexate. One of the 46 study patients used corticosteroid therapy for his IBD. Seventeen of the patients used prophylactic medications prior to receiving infusions; six patients received corticosteroids as pre-medication. Four patients had a history of distant transfusion reactions to infliximab. These reactions included shortness of breath, chest tightness, flushing, pruritus and urticaria. These patients all took prophylactic medications before receiving infusions. 46 patients (27 males and 19 females) received a total of fifty 90-min infusions and ninety-three 60-min infusions. No infusion reactions were reported. There were no adverse events, including drug-related infections. None of the patients developed cancer of any type during the study timeframe. Total cost savings for administration of the both 90-min and 60-min accelerated infusions compared to standard 120-min infusions was estimated to be \$53 632 (\$116 965 vs \$63 333,  $P = 0.001$ ). One hundred and eighteen hours were saved in the administration of the accelerated infusions (17 160 min vs 10 080 min,  $P = 0.001$ ). In the study popula-

tion, overweight females [body mass index (BMI) > 25.00 kg/m<sup>2</sup>] were found to have statistically higher BMIs than overweight males (mean BMI 35.07 ± 2.66 kg/m<sup>2</sup> vs 30.08 ± 0.99 kg/m<sup>2</sup>, *P* = 0.05), finding which is of significance since obesity was described as being one of the risk factors for Crohn's disease.

**CONCLUSION:** We are the first US group to report substantial cost savings, increased safety and patient satisfaction associated with accelerated infliximab infusion.

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**Key words:** Infliximab; Accelerated infusion; Crohn's disease; Ulcerative colitis; Obesity

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## INTRODUCTION

Crohn's disease (CD) and ulcerative colitis (UC) represent two classes of progressive inflammatory diseases of the gastrointestinal tract that can present with life-threatening episodes and complications over the course of a patient's life. The use of infliximab, a chimeric monoclonal antibody against tumor necrosis factor (TNF), has changed the management of inflammatory bowel disease (IBD) through its ability to improve both short- and long-term outcomes in patients.

The Food and Drug Administration approved infusion time for infliximab in the United States is 120-min<sup>[1]</sup>. Given the need for repeated infusions of the drug, it would be preferable for patients and health care providers alike to be able to improve the speed of this administration process. There are several European studies showing that the incidence of adverse reactions to infliximab are comparable whether it is given over the standard 120 min or over a shorter time period<sup>[2-5]</sup>. A Canadian study has demonstrated that faster infusions of the drug result in fewer infusion reactions than the standard 120-min administration<sup>[2]</sup>. However, no United States studies have been conducted showing the safety of a rapid infusion protocol and the vast majority of publications on this topic used a standard dose between 3 and 5 mg/kg<sup>[6]</sup>.

With the passing of the Affordable Care Act, new measures for health care quality improvement have been developed. These measures include incentives for utilizing hospital resources more efficiently and improving

patient satisfaction scores<sup>[7]</sup>. Given the time savings to the patients, the resultant cost savings to the hospital, and the reduced rate of infusion reactions, accelerated infusions of infliximab in United States patients may help improve these metrics. This study aims to be the first United States study investigating the safety and cost-effectiveness associated with the use of an accelerated infusion protocol for infliximab in patients receiving variable doses of the drug.

## MATERIALS AND METHODS

In 2011, the Digestive Health Center at the Medical Center of the University of Virginia introduced a new clinical protocolized management of infliximab administration. The new practice introduced an optional choice for the patients interested in receiving accelerated infliximab infusions. An infusion was considered to be accelerated if it was administered over 90 min and/or over 60 min. Concomitantly, original infusion rates were developed for the accelerated infusions (Table 1).

A prospective cohort of consecutive patients were then assessed and recruited for this protocol. From August 2011 to March 2012, 50 IBD patients on stable dosing of infliximab, with at least four prior infusions, were offered the accelerated protocol. Initially, patients were only included if they did not use pre-medications and if they had no history of any infusion reactions. Later, patients who used pre-medications became eligible for the accelerated protocol. Eventually, patients with a remote history of infusion reactions were also made eligible. Patients under age 18 were excluded.

Doses of infliximab included 5 mg/kg, 7.5 mg/kg, and 10 mg/kg. Patients included in the study followed the protocol seen in Figure 1. Patients were initially transitioned to a 90-min infusion protocol; those that tolerated this infusion were subsequently given 60-min infusions at all future visits.

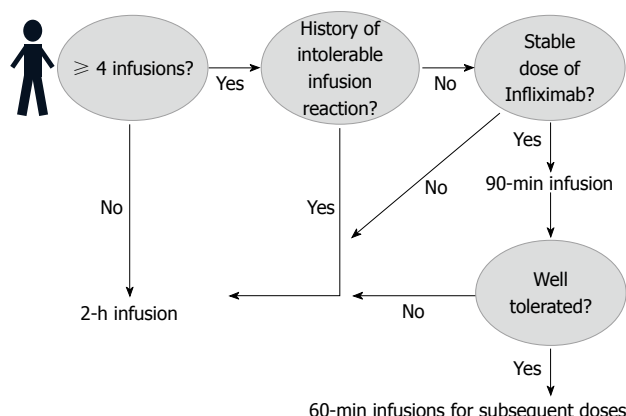
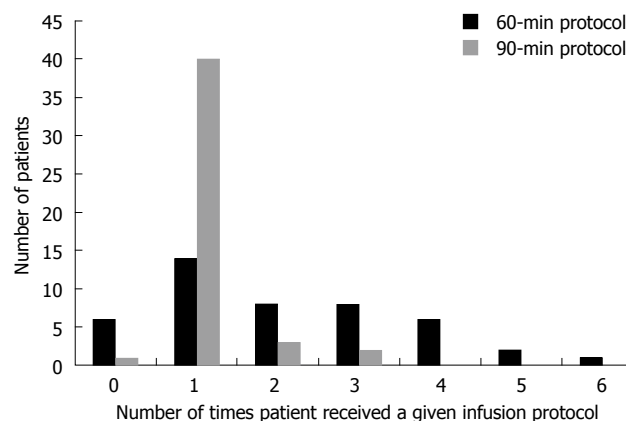
## RESULTS

The University of Virginia Medical Center's Institutional Review Board (IRB) approved this study (IRB No. = 15928). Fifty IBD patients were offered accelerated infusions and 46 patients consented to participate in the study. Nineteen (41.3%) were female, five (10.9%) were African American and nine (19.6%) had UC. The mean age was 42.6 years old. Complete demographics and other characteristics of the study population are shown in Tables 2 and 3.

Of the 46 patients consenting to participate, one withdrew immediately prior to receiving the first accelerated infusion. The remaining 45 subjects were given at least one 90-min infusion and 39 subjects were given at least one 60 min infusion. In total, fifty 90-min infusions and ninety-three 60-min infusions were given. No infusion reactions of any type were noted. The distribution of the number of accelerated infusions of each type can be seen in Figure 2.

**Table 1** Protocols developed for standard and accelerated infliximab infusions

Standard infliximab infusions		Accelerated infliximab infusions							
120 min, 250 mL		90 min, 250 mL		60 min, 250 mL		90 min, 500 mL		60 min, 500 mL	
Rates (mL/h)	Dose (mL)	Rates (mL/h)	Dose (mL)	Rates (mL/h)	Dose (mL)	Rates (mL/h)	Dose (mL)	Rates (mL/h)	Dose (mL)
10	2.5	10	2.5	20	2.5	20	5	50	5
20	5	20	5	40	5	40	10	100	10
40	10	40	10	80	10	80	20	350	40
80	20	80	20	160	20	300	40	500	80
150	75	500	190	300	75	700	420	750	350
250	135			550	135				


**Figure 1** Protocol for assigning infusion times to patients consenting to participate in the study.

**Figure 2** Number of accelerated infusions given to each patient in the study.

There were also no patient-reported infections or hospitalizations among the patients in the study. None of the patients developed cancer of any type during the study timeframe. Reasons for giving 90-min infusions multiple times to the same patient included change in infliximab dose, concerns about a specific patient's blood pressure control, and physician preference. One patient experienced a local reaction at the infusion site during a 60-min infusion, which was due to catheter placement rather than a true infusion reaction; nevertheless this patient requested a 90-min infusion at the next visit. However, when the patient came for her next infusion, she opted to continue receiving it over 60 min. The prior local reaction was not replicated by the subsequent infusions. Thus, both the patient and the provider concluded that the previous reaction was induced by intravenous catheter malfunction.

Ten patients used immunosuppressive drugs concurrently out of which six were taking azathioprine, three were taking 6-mercaptopurine and one was taking methotrexate. One of the 46 study patients used corticosteroid therapy for his IBD. Six patients received corticosteroids as pre-medication.

Four patients had a remote history of infusion reactions to infliximab therapy. These reactions included shortness of breath, chest tightness, flushing, pruritus and urticaria. These patients all took prophylactic medications before receiving infusions. Other patients receiving pre-medications took them because of treatment re-ini-

tiation or because of physician preference. Prophylactic medications included acetaminophen, loratadine, famotidine, cetirizine, hydrocortisone and diphenhydramine.

Hospital cost savings were calculated by estimating the cost required to deliver infusions over 120-min *vs* using the accelerated infusion times. In this study, 118 h of infusion time and \$53 632 were saved by using the accelerated protocols. Using a Mann-Whitney *U* test, these savings were found to be statistically significant: \$116 965 *vs* \$63 333 ( $P < 0.001$ ).

Body mass index (BMI) data for all patients were obtained. Thirteen of 46 patients (28.2%) fell under the definition of obese with a BMI  $> 30$  kg/m<sup>2</sup>. Numerous BMI comparisons were made between subpopulations of patients in the study. In the subpopulation of overweight (BMI  $> 25.0$  kg/m<sup>2</sup>) females *vs* males, females had statistically higher BMIs. Their mean BMI was 35.07 kg/m<sup>2</sup>, SD = 8.83, SE = 2.66 kg/m<sup>2</sup> *vs* 30.08 kg/m<sup>2</sup>, SD = 4.11, SE = 0.99,  $P < 0.05$ . The distribution of BMIs among these two populations is shown in Figure 3. Other subpopulation comparisons were not found to be significantly different, including comparisons between data of Caucasians and African Americans, patients receiving regular doses (5 mg/kg) and higher doses (7.5 mg/kg and 10 mg/kg) and males and females as a whole.

Though no systematic surveying of the study patients was performed, all study patients expressed increased satisfaction associated with the accelerated protocol *vs* the standard 120-min infusions. As a result, three patients,

**Table 2** Characteristics of study participants

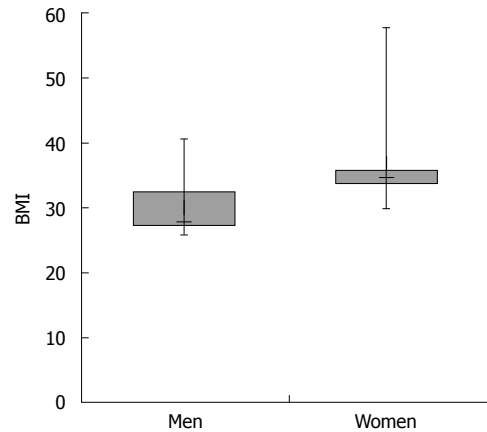
Characteristics	Data (%)
Gender	Female: 19/46 (41.3) Male: 27/46 (58.7)
Race	African American: 5/46 (10.9) Caucasian: 41/46 (89.1)
Age, yr	Mean: 42.6 Median: 41.5 Range: 21-89
Disease type	Ulcerative colitis: 9/46 (19.6) Crohn's: 37/46 (80.4)
Use of premedications	17/46 (37.0)
On corticosteroid therapy	1/46 (2.2)
On immunosuppressive therapy	10/46 (21.7)
Dose	5 mg/kg: 25/46 (54.3) 7.5 mg/kg: 5/46 (10.9) 10 mg/kg: 16/46 (34.8)
Number of infusions prior to accelerated protocol	Mean: 27.4 Median: 22 Range: 4-65
Body mass index	Normal (18.5-25.0): 19/46 (41.3) Low (< 18.5): 1/46 (2.2) High (> 25.0): 26/46 (56.5)

who had initially declined to participate, expressed the desire at a later date to receive accelerated infusions.

## DISCUSSION

The current paradigm of infusing infliximab over 120 min was based on clinical trial data showing a tolerable incidence of side effects at this rate. A number of studies have shown that infusing at rates faster than the current practice is safe<sup>[2-5]</sup>. Accelerated infusions of infliximab were safe in the population of patients in this study. There were no infusion reactions observed after delivering a total of 143 accelerated infusions over the course of this study. Only one patient had to revert to a 120-min infusion after receiving accelerated infusions. This instance was due to an increase in the infliximab dose, which mandated a subsequent 120-min infusion per the study protocol. Several patients repeated the intermediate rate infusions for various reasons; however, these reasons did not include suspected infusion reactions. Similar to prior studies<sup>[2-5]</sup>, this study provides further evidence that accelerated infusions of infliximab in IBD patients are well-tolerated regardless of dose, diagnosis, history of infusion reactions or treatment frequency.

Prior studies of faster infusion times have had different study populations. Our study is the first to use a dose of 7.5 mg/kg at faster rates and the largest number of patients receiving 10 mg/kg ( $n = 16$ , 34.78% of the study population). Noticeably, there is only one prior study that included patients who received a 10 mg/kg dose ( $n = 5$ , 2.8% of the study population)<sup>[5]</sup>. Our study population is also notable for containing a majority of patients not receiving prophylaxis; among those getting pre-medications, there were a number of reasons for the prophylaxis. Some of our patients had a remote history of infusion



**Figure 3** Distribution of body mass index scores for overweight patients in the study. Data is presented as a box and whisker plot showing quartiles and ranges. BMI: Body mass index.

reactions, while others had had treatment re-initiations; these patients all received pre-medications and none had infusion reactions with the accelerated protocol. Compared to other studies, our patient population also had a larger percentage of UC (19.6%) and overweight patients (56.5%).

This diversity in our patient population helps to broaden the evidence for safe administration of infliximab at faster rates. Higher doses of infliximab may be used and patients with prior infusion reactions or treatment re-initiations may still safely receive their treatments with a faster protocol.

The need for anti-TNF therapy is increasing. Several studies have suggested that a more aggressive “top-down” approach to CD, such as involving early adoption of regular doses of infliximab, is more effective than the traditional “step up” method of treatment<sup>[8]</sup>. Using early aggressive therapy has been shown to decrease the need for surgery and reduce hospitalizations in patients with CD<sup>[8]</sup>, and prompt induction therapy in UC has been shown to promote mucosal healing, an important prognostic factor<sup>[9]</sup>. The active ulcerative colitis trials 1 and 2, which investigated using infliximab as maintenance therapy for UC, demonstrated significant improvements in clinical response to treatment among patients with moderate-to-severe UC receiving infliximab, when compared to patients receiving conventional therapy<sup>[10]</sup>. Whether the use of infliximab can reduce the rate of colectomy for UC patients is not currently known, but current data is promising<sup>[11]</sup>.

With the improvement in treatment options over the last decade comes the sobering fact that hospitalizations and inpatient charges for IBD, especially CD, have increased substantially: from 1998 to 2004, the hospitalization rate for CD-related health issues increased by 4.3% and total charges increased from \$762 million to \$1.33 billion<sup>[12]</sup>. Considering the proven effectiveness of anti-TNF therapy and the rising incidence of IBD, it is likely that the number of patients on maintenance infliximab regimens will increase in the future. With rising health



**Table 3** Data for each individual study participant

No	Patient	Age (yr)	BMI	Dose <sup>1</sup>	Date		Diagnose	Diagnosis
					90 min infusion	60 min infusion <sup>3</sup>		
1	Male: Caucasian	37	170lbs (77 kg) BMI = 21.83 kg/m <sup>2</sup>	22 infusions 5 mg/kg per 8 wk	12/16/2011	02/20/2012	Ulcerative colitis	Tylenol 650 mg Claritin 10 mg Solucortef 100 mg
2	Male: Caucasian	56	202lbs (91 kg) BMI = 28.98 kg/m <sup>2</sup>	13 infusions 7.5 mg/kg per 8 wk	04/02/2012		Crohn's disease	
3	Male: Caucasian	39	146lbs (66 kg) BMI = 19.80 kg/m <sup>2</sup>	50 infusions 10 mg/kg per 7 wk	12/19/2011	02/09/2012 03/29/2012	Crohn's disease	Hydrocortisone 100 mg
4NI	Female: African-American <sup>2</sup>	50	198lbs (89 kg) BMI = 31.01 kg/m <sup>2</sup>	22 infusions 5 mg/kg per 7 wk Hb = 12.3 g/dL			Crohn's disease	
5	Male: Caucasian	28	203lbs (92 kg) BMI = 29.17 kg/m <sup>2</sup>	38 infusions 5 mg/kg per 8 wk	09/27/2011	11/22/2011 01/23/2012 03/20/2012	Crohn's disease	
6	Male: Caucasian	30	115lbs (52 kg) BMI = 15.60 kg/m <sup>2</sup>	6 infusions 5 mg/kg per 8 wk			Crohn's disease	
7	Female: Caucasian	53	300lbs (136.5 kg) BMI = 57.78 kg/m <sup>2</sup>	42 infusions 5 mg/kg per 8wk	08/08/2011	10/11/2011 12/21/2011 02/13/2012	Crohn's disease (fistulizing)	
8	Female: Caucasian Moved to Germany Dec 2011	21	121lbs (55 kg) BMI = 22.18 kg/m <sup>2</sup>	12 infusions 5 mg/kg per 8wk	08/22/2011	10/17/2011 12/12/2011	Crohn's disease	
9	Male: Caucasian	50	179lbs (81 kg) BMI = 27.25 kg/m <sup>2</sup>	8 infusions 5 mg/kg per 6 wk	08/23/2011	10/04/2011 11/15/2011 12/27/2011 02/07/2012 03/21/2012	Crohn's disease	
10	Male: Caucasian	47	195.8lbs (89 kg) BMI = 28.96 kg/m <sup>2</sup>	15 infusions 10 mg/kg per 6 wk	11/08/2011	12/27/2011 02/06/2012 03/21/2012	Crohn's disease	
11	Female: Caucasian	58	157lbs (71 kg) BMI = 23.87 kg/m <sup>2</sup>	62 infusions 7.5 mg/kg per 7 wk	11/07/2011 12/29/2011 02/03/2012	04/02/2012	Crohn's disease	
12	Female: Caucasian Moved to another hospital	55	200lbs (90 kg) BMI = 34.16 kg/m <sup>2</sup>	50 infusions 7.5 mg/kg per 8 wk	09/26/2011	11/21/2011	Crohn's disease	
13	Male: Caucasian	29	154lbs (70 kg) BMI = 21.50 kg/m <sup>2</sup>	40 infusions 5 mg/kg 400 mg per 6 wk Hb = 15.6g/dL	01/03/2012	02/14/2012 03/30/2012	Crohn's disease	
14	Female: Caucasian	36	248lbs (113 kg) BMI = 35.87 kg/m <sup>2</sup>	16 infusions 5 mg/kg 600-7.5 mg/kg shortened infusion D/C	09/02/2011 10/28/2011 Normal infusion time 01/27/2012 (after dose increase)	03/23/2012	Ulcerative colitis	
15	Female: Caucasian	34	167lbs (76 kg) BMI = 29.80 kg/m <sup>2</sup>	9 infusions 5 mg/kg 400 mg per 6-8wk Hb = 12.1g/dL	07/28/2011	09/16/2011 11/02/2011 12/20/2011 02/09/2012 03/22/2012	Crohn's disease	
16	Female: Caucasian	54	121lbs (54 kg) BMI = 20.14 kg/m <sup>2</sup>	48 infusions 5 mg/kg per 8 wk	03/05/2012		Crohn's disease	
17	Female: African-American	68	191lbs (87 kg) BMI = 33.71 kg/m <sup>2</sup>	30 infusions 10 mg/kg per 4 wk	11/23/2011	12/22/2011 01/16/2012 02/17/2012 03/16/2012	Crohn's disease	
18	Female: Caucasian	25	146lbs (66 kg) BMI = 22.87 kg/m <sup>2</sup>	Since 2005 5 mg/kg per 8 wk	01/05/2012 03/01/2012		Crohn's disease	
19	Female: Caucasian	56	145lbs (66 kg) BMI = 22.87 kg/m <sup>2</sup>	51 infusions 10 mg/kg per 5 wk	10/21/2011	12/02/2012 01/13/2012 02/17/2012 03/30/2012	Crohn's disease	

20	Female: Caucasian	26	143lbs (65 kg) BMI = 23.85 kg/m <sup>2</sup>	10 infusions 5 mg/kg per 7 wk	07/25/2011	09/23/2011 11/10/2011 01/05/2012 02/23/2012	Crohn's disease
21	Male: Caucasian	47	199lbs (90 kg) BMI = 22.75 kg/m <sup>2</sup>	48 infusions 10 mg/kg per 6 wk	12/20/2011	01/31/2012 02/12/2012	Ulcerative colitis
22	Female: Caucasian	36	232lbs (105 kg) BMI = 35.28 kg/m <sup>2</sup>	5 infusions 10 mg/kg, 1100 mg in 500 mL per 6 wk	01/13/2012 02/24/2012	04/06/2012	Crohn's disease
23	Male: Caucasian	21	202 lbs (91 kg) BMI = 27.40 kg/m <sup>2</sup>	4 infusions 5 mg/kg per 8 wk	01/23/2012	03/21/2012	Crohn's disease
24	Female: Caucasian	41	126lbs (57.5 kg) BMI = 19.86 kg/m <sup>2</sup>	14 infusions 10 mg/kg per 8 wk	02/22/2012	04/12/2004	Crohn's disease
25	Male: Caucasian Transferred receives remicade locally (01/31/12)	34	212lbs (96.8 kg) BMI = 32.46 kg/m <sup>2</sup>	24 infusions 5 mg/kg per 8 wk	08/11/2011	10/07/2011 12/02/2011	Ulcerative colitis
26	Male: Caucasian	41	196lbs (88 kg) BMI = 32.62 kg/m <sup>2</sup>	21 infusions 10 mg/kg per 6 wk	04/04/2012		Crohn's disease
27	Male: Caucasian	63	176lbs (80 kg) BMI = 26.76 kg/m <sup>2</sup>	61 infusions 5 mg/kg 400 mg	09/08/2011	11/29/2011 01/27/2012 03/14/2012	Crohn's disease
28	Male: Caucasian	38	149lbs (67.5 kg) BMI = 22.00 kg/m <sup>2</sup>	10 infusions 10 mg/kg per 6 wk	12/08/2011	01/20/2012 03/06/2012	Crohn's disease
29	Female: Caucasian	42	259lbs (117.5 kg) BMI = 41.80 kg/m <sup>2</sup>	46 infusions 10 mg/kg 1200 mg in 500 mL	02/13/2012	04/02/2012	Crohn's disease
30	Male: Caucasian	40	192LBS (87 kg) BMI = 27.55 kg/m <sup>2</sup>	65 infusions 7.5 mg/kg per 8 wk	12/13/2011	02/07/2012	Crohn's disease
32	Male: Caucasian	49	154LBS (70 kg) BMI = 23.42 kg/m <sup>2</sup>	49 infusions 10 mg/kg 700 mg per 8wk	12/19/2011	02/10/2012	Crohn's disease
33	Male: Caucasian	23	131lbs (59.5 kg) BMI = 18.83 kg/m <sup>2</sup>	15 infusions 10 mg/kg per 8 wk	01/11/2012	03/09/2012	Ulcerative colitis
34	Male: Caucasian	26	208lbs (94.5 kg) BMI = 26.71	7 infusions 5 mg/kg per 8 wk	09/12/2011	11/07/2011 01/03/2012 03/27/2012	Crohn's disease
35	Female: African-American	24	129lbs (58.5 kg) BMI = 22.14 kg/m <sup>2</sup>	11 infusions 7.5 mg/kg per 8 wk Hb = 13.1 g/dL	01/23/2012	03/20/2012	Crohn's disease
36	Male: Caucasian	31	170lbs (77 kg) BMI = 23.11 kg/m <sup>2</sup>	13 infusions 5 mg/kg per 8 wk Normal infusion on 02/21 because of dose increase: 600 mg	11/14/2011	01/16/2012	Crohn's disease
37	Male: African-American	45	267lbs (121 kg) BMI = 40.60 kg/m <sup>2</sup>	27 infusions 10 mg/kg 1200 mg in 500 mL per 7 wk	12/15/2011 02/15/2012 04/05/2012		Crohn's disease
38	Male: Caucasian	89	184lbs (83.5 kg) BMI = 27.17 kg/m <sup>2</sup>	22 infusions 5 mg/kg per 8 wk	07/21/2011	09/15/2011 11/03/2011 12/29/2011 02/23/2012	Crohn's disease
39	Male: Caucasian	46	181lbs (82 kg) BMI = 22.62 kg/m <sup>2</sup>	24 infusions 10 mg/kg per 5 wk	11/29/2011	01/10/2012 02/14/2012 03/20/2012	Crohn's disease
40	Male: Caucasian	58	167lbs (76 kg) BMI = 27.79 kg/m <sup>2</sup>	19 infusions 5 mg/kg per 8 wk	09/12/2011	11/07/2011 01/09/2012 03/05/2012	Ulcerative colitis
41	Male: Caucasian	72	169lbs (77 kg) BMI = 25.81 kg/m <sup>2</sup>	23 infusions 10 mg/kg per 7 wk	11/19/2011	01/06/2012 02/24/2012	Ulcerative colitis
42	Female: Caucasian	48	128lbs (58 kg) BMI = 22.32 kg/m <sup>2</sup>	54 infusions 5 mg/kg per 6 wk	09/30/2011	11/23/2011 01/17/2012 03/23/2012	Crohn's disease
43	Caucasian 30 yr old	30	264lbs (120 kg) BMI = 35.88 kg/m <sup>2</sup>	44 infusions 5 mg/kg per 8 wk	08/04/2011	09/29/2011 11/28/2011 01/23/2012 03/19/2012	Crohn's disease

44	Female:	44	138lbs (63 kg)	54 infusions	01/26/2012	03/01/2012	Crohn's
	Caucasian		BMI = 21.7 kg/m <sup>2</sup>	10 mg/kg per 5 wk		04/05/2012	disease
45	Male:	28	205lbs (93 kg)	10 infusions	01/26/2012	03/21/2012	Ulcerative
	Caucasian		BMI = 27.80 kg/m <sup>2</sup>	5 mg/kg per 8 wk			colitis
46	Male:	43	277lbs (103 kg)	5 infusions	08/19/2011	10/10/2011	Crohn's
	African-American		BMI = 36.65 kg/m <sup>2</sup>	5 mg/kg per 8 wk		12/05/2011	disease
						01/18/2012	
						02/27/2012	
47	Female:	50	202lbs (92 kg)	7 infusions	07/21/2011	09/01/2011	Ulcerative
	Caucasian		BMI = 34.81 kg/m <sup>2</sup>	5 mg/kg per 6 wk		10/10/2011	colitis
						11/21/2011	
						12/29/2011	
						02/06/2012	
						03/19/2012	

<sup>1</sup>Dose + numbers of remicade treatments at the time of the 1st shortened infusion + infusion frequency; <sup>2</sup>After initial accept, the patient changed her mind and withdrew; <sup>3</sup>1st 60 min infusion + subsequent 60 min. NI: Not included; BMI: Body mass index.

care costs and a system-wide heightened interest in efficiency and patient satisfaction, finding ways to streamline the delivery of this drug is a crucial step toward improving therapy for IBD. The cost savings from this protocol were significant. A total of \$ 53 632 was saved over the course of this nine month period of time. This number represents a significant underestimate. With only 46 patients enrolled and many starting the accelerated protocol in the latter months of the study, this figure represents only a fraction of the cost-savings that could be obtained if the protocol were implemented in a wider and more consistent fashion. Cost savings for minimizing adverse events were not included in the estimate, which would contribute significantly to enhance the effectiveness of the infliximab infusions and thereby being in concert with the requirements of the Affordable Care Act.

Infliximab is not a benign drug and has the potential for serious side effects; compared to other biologics, it is the only drug with a significantly higher rate of adverse events than controls<sup>[13]</sup>. Long-term effects include an increased risk of bacterial, viral, or fungal infections causing hospitalization<sup>[14]</sup> and a theoretical, though unproven, increased risk of Hodgkin and non-Hodgkin lymphoma in adolescent and young adult males<sup>[15]</sup>. Acute infusion reactions occur in 0.8% to 8.8% of infusions, affecting 10% to 23% of patients per year<sup>[16]</sup>. Delayed infusion reactions occurred in roughly 2% of patients receiving infliximab over the course of a year<sup>[17]</sup>. While this study did not examine the infectious or cancer risks, the complete lack of infusion reactions in our patients is a promising lead for making infliximab safer.

The incidence of infusion reactions to infliximab is highly related to the development of antibodies to the drug, known as human anti-chimeric antibodies (HACA)<sup>[18]</sup>. Loss of response to treatment has also been observed in patients who develop these antibodies. Thus, the prevention of antibody formation is paramount in keeping infliximab as a safe and effective treatment for IBD patients. The development of these antibodies can be reduced by maintaining higher trough levels, having consistent dosing schedules<sup>[18]</sup>, and using pre-medications such as hydrocortisone<sup>[19]</sup>. Additionally, the use of immu-

nomodulators such as methotrexate has been shown to reduce antibody formation against infliximab in patients with rheumatoid arthritis<sup>[20]</sup>.

When reviewing the literature, Lee *et al*<sup>[2]</sup> concluded in their study that 90% of the adverse reactions associated with infliximab infusions occur during the first eight infusions. Since our study population had a mean of 27 infusions prior to the initiation of the accelerated protocol we cannot easily compare our lack of reactions with the traditional infusion rates. However, considering the role that anti-infliximab antibodies play in the incidence of infusion reactions and treatment failure<sup>[18]</sup>, the infusion rate may be related to the development of these antibodies. Mori *et al*<sup>[21]</sup> demonstrated that higher trough infliximab levels are associated with better outcomes. The serum concentration of infliximab measured one hour after each infusion approximates the maximum serum concentration (Cmax). Thus, we hypothesize that a more rapid attainment of Cmax may decrease the immune response to the drug. Future work could be directed toward monitoring the development of HACA among patients receiving infusions at different rates. Due to restrictions imposed by cost and insurance policies, this study did not analyze the infliximab serum level after 1 h infusions and it did not investigate the presence or absence of the antibodies toward infliximab.

Obese patients with CD also tend to have a higher incidence of perianal disease and more post-surgical complications<sup>[22]</sup>. BMI has also been shown to be a significant factor in patients with CD since obesity itself may be a risk factor for CD<sup>[23]</sup>. Treatment failures with infliximab in conditions such as rheumatoid arthritis<sup>[24]</sup>, ankylosing spondylitis<sup>[25]</sup>, and psoriasis<sup>[26]</sup> are also more common in overweight and obese patients than in patients with normal BMIs. Over half of our patients were considered overweight by BMI and nearly a third were obese. With the need for effective treatment options being especially great for obese patients suffering from CD, it is reassuring to know that accelerated infliximab infusions were safe among this demographic, as demonstrated in this study.

There are a number of limitations to this study. There

was no specifically defined control group to which the patients receiving faster infusions could be compared. The racial makeup of the study population was somewhat narrow as well. A few deviations from the study protocol occurred, with some patients receiving an intermediate-speed infusion multiple times due to physician preference rather than the clinical guidelines. However, despite these limitations, this study provides strong evidence for the benefits of implementing an accelerated infusion protocol for treating IBD patients on maintenance therapy. With such a protocol in place, costs to patients and hospitals in terms of both time and money would be decreased, patient safety and satisfaction may be increased, and a life-saving drug may be made more widely available. With additional data and further inquiry, faster infusions of infliximab may become the standard of care in the United States.

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## COMMENTS

### Background

Crohn's disease and ulcerative colitis (UC) represent two classes of progressive inflammatory diseases of the gastrointestinal tract with a rising incidence that can present with life-threatening episodes and complications over the course of a patient's life. The use of biologic agents, such as anti-tumor necrosis factor (anti-TNF) drugs, has changed the management of inflammatory bowel disease (IBD) through its ability to improve both short- and long-term outcomes in patients.

### Research frontiers

Considering the proven effectiveness of anti-TNF therapy it is likely that the number of patients on maintenance infliximab regimens will increase in the future. With rising health care costs and a system-wide heightened interest in efficiency and patient satisfaction, finding ways to streamline the delivery of this drug by improving the cost of the administration process is a crucial step toward improving therapy for IBD. The current study looked into the efficacy and safety of accelerated infliximab infusions in IBD patients attending the University of Virginia Medical Center's Gastrointestinal Clinic from VA, United States.

### Innovations and breakthroughs

No United States studies have been conducted showing the safety of a rapid infusion protocol and the vast majority of publications on this topic used a standard dose between 3 and 5 mg/kg. There is only one prior study that included patients who received a 10 mg/kg dose. The study is the first to use a dose of 7.5 mg/kg at faster rates and the largest number of patients receiving 10 mg/kg ( $n = 16$ ; 34.78% of the study population), while employing innovative infusion rates for these doses. The serum concentration of infliximab measured one hour after each infusion approximates the maximum serum concentration ( $C_{max}$ ), which will be the case of the accelerated infliximab infusion. Thus, they hypothesize that a more rapid attainment of  $C_{max}$  may decrease the immune response to the drug. Future work could be directed toward monitoring the development of Heads of Asbestos Coordination Authorities among patients receiving infusions at different rates. Their study population is also notable for its number of UC patients as well as for its majority of patients not receiving prophylaxis.

### Applications

This study provides strong evidence for the benefits of implementing an accelerated infusion protocol for treating IBD patients on maintenance therapy. With such a protocol in place, costs to patients and hospitals in terms of both time and money would be decreased, patient safety and satisfaction may be increased, and a life-saving drug may be made more widely available. With additional data and further inquiry, faster infusions of infliximab may become the standard of care in the United States.

## Terminology

Infliximab is a biologic agent, a chimeric monoclonal antibody against TNF, which has changed the management of IBD through its ability to improve both short- and long-term outcomes in patients.

## Peer review

This is a very interesting short original paper. The attached short original report presents interesting data on accelerated infliximab infusions in IBD patients.

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