Review Article

What is the Safety of Existing Alternative Infliximab Infusion Protocols with Shorter Infusion Times?

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Infliximab is a chimeric monoclonal antibody indicated for the use in immune-related diseases, including inflammatory bowel diseases (i.e. Crohn's disease, ulcerative colitis). This antibody binds to tumor necrosis factor alpha (TNF-α) inhibiting the cytokine from binding to receptors on inflammatory cells. The suggested dosing schedule is a 2-3 hour intravenous (IV) infusion at 0, 2, and 6 weeks, then every 8 weeks thereafter.[1,2] Because infliximab is derived from mouse and human IgG1, patients may experience infusion site reactions such as fever, chills, pruritis, rash, and other adverse effects. Therefore, 1-2 hour monitoring is recommended post-infusion. The entire infusion process can take more than 4 hours, consuming large amounts of the patient and medical team's time. Given this limitation, the question posed is: **What is the safety of existing alternative infliximab infusion protocols with shorter infusion times?**

Evidence Summary

Boston Medical Center studied a shortened infusion time in 75 patients receiving >5 mg/kg dose of infliximab to treat inflammatory bowel diseases (IBD).[3] The multidisciplinary team consisting of a gastroenterologists, rheumatologists, and pharmacists developed an administration schedule and monitored adverse effects and efficacy. Each patient was initially infused according to the manufacturer's 2-hour IV infusion with 1-2 hours of post-infusion monitoring for 3 infusions. If the patient did not experience any infusion reactions, then the fourth infusion was administered over 1 hour. If the patient did not experience any infusion reactions during the fourth infusion, then the fifth infusion was administered over 30 minutes. If the patient did not experience any infusion reactions during the fifth infusion, then all future infusions were administered over 30 minutes. A total of 522 infusions were observed, 483 infusions were administered over 1 hour, and 39 infusions progressed to 30 minute infusions. No patients reverted back to the standard 2 hour infusion. Post-infusion monitoring was not required of the center per protocol. Instead, pharmacists called the patients 24 hours post-infusion to discuss any reactions or concerns. No acute or delayed reactions were observed, suggesting safety in an accelerated infusion.

Loss of clinical response is another common concern with maintenance infliximab treatment to achieve remission.[3] The Boston Medical Center study also measured instances of dose intensification (increase in dose or decrease in maintenance dose administration interval) to determine if an increase incidence of loss of clinical response was associated with faster infusion times. Ten subjects (13%) required either a dose escalation or decrease in maintenance interval with a median dose escalation time of 171 days. These results were compared to the landmark trial which established the efficacy of maintenance infliximab infusions, "A Crohn's Disease Clinical Trial Evaluating Infliximab in a New Long-Term Treatment" (ACCENT I).[2] ACCENT I was associated with 28.5% of subjects who required a dose escalation at 54 weeks. Although the study at Boston Medical Center was a small study compared to the ACCENT I trial, the incidence of dose escalation did not appear to differ.[2,3] Since the landmark trials did not use rapid infusion and the dose escalation rates were similar to those reported in rapid infusion protocols, it does not seem that rapid infusion affects efficacy.

Clare et al assessed an accelerated infliximab infusion protocol and identified risk factors that can precipitate an infusion reaction.[4] Patients being treated for various bowel diseases were initiated with four, 2-hour IV infusions followed by 2-hour post monitoring, then five, 1 hour IV infusions, and finally 30 minute IV infusions.[4] Overall, 144 patients were treated with 1,146 infliximab infusions. During the 344 standard infusions, 11 infusions were associated with mild infusion reactions (e.g. nausea, lightheadedness, wheeze, erythematous rash). Standard infusions were resumed after IV hydrocortisone and chlorpheniramine were administered. Four standard infusions were associated with delayed hypersensitivity reactions (e.g. myalgia, polyarthropathy, rash) and 3 standard infusions were associated with severe reactions causing a discontinuation of the infusion. During the 376 1 hour infusions, 13 mild infusion reactions, zero severe reactions, and 1 delayed hypersensitivity reaction occurred. Of the 426 30-minute IV infusions, 8 mild infusion reactions, 2 severe reactions, and zero delayed hypersensitivity reactions occurred. The only variable of note that investigators identified to possibly increase the risk of infusion reactions was episodic administration of infliximab. Otherwise, accelerated infliximab infusions were safe if given regularly.

Studies have also investigated accelerated infusion protocols in pediatrics to determine safety and tolerability in this special population. Rozette et al retrospectively assessed 540 infliximab infusions given over 2-3 hours and prospectively assessed 545 infliximab infusions given over 1 hour at

a freestanding children's hospital.[5] Most of these patients were prescribed infliximab to treat Crohn's disease or ulcerative colitis at doses 5 to 15 mg/kg. Similar to other accelerated infusion studies, patients required at least 2 infliximab standard infusions without experiencing infusion reactions before progressing to 1 hour infusions. There were no statistically significant differences in rates of infusion reactions between the groups. The standard infusion group saw 1 (0.19%) infusion with a reaction compared to 2 (0.36%) infusions in the rapid infusion group. This study also showed premedication was not a factor in decreasing infusion reaction incidence. All patients in the retrospective standard infusion duration group were premedicated with diphenhydramine and acetaminophen, whereas 60% of the prospective shortened infusion duration group who were premedicated only received acetaminophen. A notable limitation of this study was the variable indications. The majority of patients were treated for IBD while the remaining were treated for various autoimmune disorders (i.e. celiac disease, uveitis, juvenile idiopathic arthritis, and Takayasu's arteritis) at varying doses. Additionally, retrospective data were based on chart reviews without specified guidelines. The retrospective design caused fewer than expected patients to be available, thus limiting the statistical power achieved. Despite this limitation, there did not appear to be clinically significant differences between accelerated and standard infusions. This study center deemed accelerated infusions safe in pediatrics and adopted the protocol into current practice.

A large, multicenter, retrospective study assessed frequency and severity of infusion related reactions in pediatric patients treated for inflammatory bowel diseases.[6] Data was collected from infusion centers in Canada and the United states where 4120 60 minute infliximab infusions were given to 453 patients. Unlike other rapid infusion studies, standard 2-3 hour induction infusions were not required

TABLE 1. Infliximab Infusion Schedules for Doses >1000 mg with a Total Volume of 500 mL

Standard Infusion Schedule (> 2 hours)[3]	*Accelerated Infusion Schedule[3,7]*	
	Option A	*Option B*
10 mL/hr x 15 min 20 mL/hr x 15 min 40 mL/hr x 15 min 80mL/hr x 15 min 150 mL/hr x 30 min 250 mL/hr for remainder of infusion	50 mL/hr x 8 minutes 100 mL/hr x 8 minutes 350 mL/hr x 8 minutes 500 mL/hr x 8 minutes 750 mL/hr for remainder of infusion	100 mL/hr x 15 minutes 300 mL/hr for remainder of infusion

for these patients. Nevertheless, the results are similar to the incidence of infusion related reactions in the previously described studies. A total of 22 (0.5%) infusion related reactions occurred in 21 patients. The most common reactions were nausea, headache, and myalgias. Only 1 reaction was considered severe and the remainder were mild. All adverse effects were assumed to be infusion related. Premedication was not associated with infusion related reactions compared to no use of premedication (adjusted RR= 0.61; 95% CI, 0.36-1.03; P=0.06). Additionally, a standard dose, 5 mg/kg, compared to a high dose, 10 mg/kg, did not appear to differ in rate of infusion reaction. Interventions for the mild reactions included monitoring, treatment with acetaminophen, and use of premedication with future infusions. Shorter infusion times appear to be well-tolerated in the pediatric population regardless of premedication use or dose compared to standard infusion times.

Another large, retrospective, multicenter study involving rapid infliximab infusions in pediatric patients was conducted in Jerusalem.[8] Data was collected over 18-26 months across 3 centers treating inflammatory bowel diseases. Subjects were eligible for 1 hour rapid infusions if they received at least 4 standard duration infusions with no infusion reactions, no recent dose increase, and no more than 10 weeks had elapsed since the previous infusion. Premedication was used at the discretion of each center. A historical cohort of standard infusions occurring 5 years prior to the current study was used as a second comparison group. Among 102 children, 8 of 639 (1%) rapid infusions experienced a reaction, compared to 6 of 228 (2%) standard duration infusions, and 21 of 444 (5%) standard duration infusion in the historical cohort. Infusion reactions were described as "none-mild" and "moderate-severe", however, detailed descriptions of the reactions were lacking. Loss of response rates were also assessed. In the rapid infusion group 26 (41%) patients experiencing a loss of response to infliximab therapy compared to 15 (38%) patients receiving standard duration infusions and 21 (51%) patients in the historical cohort. Of note, patients in the historical cohort experienced higher rates of infusion and higher loss of response rates reactions despite greater use of premedication compared to rapid infusions. The investigators believed it may be due to less aggressive dosing in the past leading to antibody production which resulted in more infusion reactions and lower response rates. Prospective studies documenting dosing, premedication use, and descriptions of infusion reactions will be useful in accurately determining factors related to infusion reactions and loss of response rates in rapid infusions.

Evidence-Based Answer

It appears safe to administer infliximab over 1 hour in adults being treated for IBD. Table 1 describes standard and accelerated infusion schedules for an adult receiving a dose greater than 1000 mg with a total volume of 500 mL. Adverse effects seen with accelerated infusions are similar to rates with standard infusion times, however, efficacy should continue to be closely monitored. Current accelerated infusion data show loss of clinical response rates to infliximab requiring dose escalations at similar rates to standard infusion times, thus efficacy does not appear to be affected when accelerated infusions are used. Additional prospective studies identifying factors associated with loss of response are needed to establish the efficacy in adults being treated for IBD and other indications to further generalize the use of accelerated infusions. In terms of the pediatric population, limited data are available and more research is needed in this population as well. Many centers in Europe have employed accelerated infliximab infusion protocols, but only few centers in the United States have followed suit. Accelerated infliximab infusions have the potential to improve patient quality of life and efficiently use infusion center resources.

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