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Frequency of Severe Infusion Reactions Associated with Outpatient Infusion of Infliximab without Pre-medications

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Abstract

In this report, we describe incremental changes, over a two year period at a single center with the administration of maintenance infliximab infusions. Given practice-driven changes consisting of one-hour infusions and omission of pre-medications, we aimed to investigate if these changes contributed to severe infusion reactions. We reviewed approximately 900 infliximab infusions in a pediatric ambulatory infusion center from January 1, 2014–December 31, 2015 for severe adverse reactions requiring either rescue epinephrine or a code blue or ‘rapid response’ activation. In 2015, these practice changes resulted in a 51% decrease in total infusion hours (1281 to 630 infusion hours), despite a 9% increase in total number of infusions. No increase in severe adverse events associated with either rapid 1-hour infusion or omission of pre-medications. Our findings highlight a quality-improvement opportunity to standardize infliximab infusions to streamline care in an ambulatory setting.

Keywords

pediatric; infliximab; rapid infusion; pre-medications; adverse reaction

Introduction

Infliximab is a chimeric monoclonal antibody targeting tumor necrosis factor alpha (TNF- α). It is a mainstay of therapy for children with inflammatory conditions such as Crohn's disease, ulcerative colitis, and rheumatoid arthritis¹⁻⁸. As with all biologic therapies, infliximab is associated with the potential, although rare, to cause severe infusion related hypersensitivity reactions including anaphylaxis⁴. Medications, such as antipyretics,

antihistamines, and corticosteroids, are often administered prior to infusion to prevent such reactions¹⁻³. It is known that pre-medications have some benefit in reducing infusion reactions once an instigating event has occurred, however, it is unclear if pre-medicating in the absence of an infusion reaction serves any additional benefit¹⁻³. Recent studies in adults reveal an increased risk of infusion reaction in the setting of pre-medications, especially antihistamines like diphenhydramine². Additionally, there is poor strength of evidence describing which patients are at-risk for severe infusion reactions, and there is high variability in current standard-of-care regarding pre-medications⁹. We observed practice variation regarding the use of pre-medications and the infusion rate of infliximab at our institution and investigated the consequences.

In this study, we aimed to determine (1) the variability in the standard of care that may be associated with increased risk of an adverse reaction during an infliximab infusion; and (2) the number of patients receiving rescue epinephrine and/or rapid response / code blue events as the result of a reaction to infliximab infusion.

Methods

We performed a review of ambulatory maintenance infliximab infusions between January 1, 2014 and December 31, 2015. Hospital-wide longitudinal data were available from a total of 427 infusions in 2014 and 466 infusions in 2015, representing a total of 123 unique patients (Cerner, Kansas City, MO; Epic, Madison, WI). This study was approved by the Stanford University Human Subjects Research Committee. The patient demographics are summarized in Table 1 and represent two distinct pediatric divisions, rheumatology (Rheum) and gastroenterology, hepatology, and nutrition (GI). This information was cross-referenced with electronic pharmacy records of epinephrine removal and return from the automated dispensing cabinets (Pyxis, Franklin Lakes, NJ; Omnicell, Mountain View, CA). Of note there were three epinephrine removals over the two year review, none of these removals are documented as administered to the patient, and the automated dispensing cabinet data confirm the return of the medication. Data collected by the hospital code committee regarding rapid response and code blue calls were analyzed for significant events involving patients receiving infliximab infusions. At our institution, any reaction to infliximab requiring evaluation by an attending physician at the ambulatory setting would require escalation to a rapid response or code blue call. The data regarding unplanned diphenhydramine and/or hydrocortisone administration are unavailable.

Results

During the two year review period, two significant practice changes occurred regarding ambulatory infliximab infusions. In 2015, in light of emerging evidence, the gastroenterology service converted to a 1 hour infliximab infusion from 3 hour infusions¹⁰⁻¹³, while the rheumatology maintained their infusions at 3 hours. Also in 2015, one gastroenterology provider omitted pre-medications from all infliximab infusions. Over a 1 year time span, these changes resulted in a 51% decrease in total infusion hours (1281 to 630 infusion hours), despite a 9% increase in total number of infusions. One hundred-eleven infusions were administered without pre-medications, representing 22 patients. There were

no epinephrine administrations associated with infliximab maintenance infusions in 2014 or 2015. Additionally, there were no code blue/rapid response calls associated with infliximab maintenance infusions (Table 2).

Discussion

In our experience, the frequency of severe infliximab infusion reactions requiring epinephrine is very low, and corresponds with recently published literature¹⁻¹³. The reported severe reaction frequency is estimated between 0.04 and 1 %^{1, 2, 11}, and we would have expected approximately between 1 and 9 severe reactions. Infusing infliximab over 1 hour rather than 3 and omitting standard pre-medications does not appear to increase the risk for severe infusion reactions. The adult data available support one hour infusions for both GI and rheumatologic indications. A meta-analysis by Neef and colleagues reports infusion reactions occurred in 2.2 % of standard infliximab infusions, and in 0.9 % of one hour infusions, without stratifying the reaction type¹¹. Our results and the growing body of literature support the omission of pre-medications without an instigating event. Omission of pre-medications translates to improved patient experience, shorter length of monitoring, and avoidance of potential adverse drug events. In addition, shortening infusion times presents an excellent opportunity to reduce cost associated with infusions, as non-drug cost constitutes more than 75 % of the total health care cost, the highest percentage of that attributing to personnel costs¹⁴. These findings highlight a quality-improvement opportunity to standardize infliximab infusions to streamline care in a pediatric ambulatory setting.

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What is known about this Subject?

- Rare, severe adverse reactions have happened with infliximab administration in children with inflammatory bowel disease (IBD).
- There is poor strength of evidence for the use of pre-medications, especially antihistamines, in preventing infliximab-related reactions.
- It is unknown whether rapid infliximab administration (1 hour) is associated with higher risk of severe reactions.

What are the New Findings and the Impact on Clinical Practice?

- During a two year review period, practice-driven changes included 1-hour infliximab administration and omission of pre-medications in children with IBD.
- In a one year review, these two changes resulted in a 51% decrease in total infusion hours (1281 to 630 infusion hours), despite a 9% increase in total number of infusions.
- There were no epinephrine administrations or code blue/rapid response calls associated with severe reactions to infliximab in 2014 or 2015.

Table 1
Patient Demographics

Characteristics	2014	2015	P-value
Age, median (years)	17 (2 – 28)	15 (2 - 24)	< 0.0001
Female (%)	49 %	51 %	0.64
Total Maintenance Infusions	427	466	
Total Infusion Hours	1281	630	
Total Patients	90	95	
GI Patients	78	81	
Rheum Patients	12	14	

Table 2

	2014	2015
Total Infusions	427	466
Total Infusion Hours	1281	630
GI Infusion Hours	1095	384
Pre-medicated Hours	1095	273
Not pre-medicated Hours	0	111
Rheum Infusion Hours	186	246
Epinephrine Administered Infliximab Maintenance Infusions	0	0
Code Blue/Rapid Response Infliximab Maintenance Infusions	0	0