Premedications for infliximab infusions do not impact the risk of acute adverse drug reactions

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Abstract

Objective The purpose of this study was to identify the association of premedication with the adverse drug reaction (ADR) rate in infliximab infusions.

Design A retrospective chart review of 684 patients who received 4077 infusions in a network of community clinics over 16.5 months. Data collected included age, weight, sex, diagnosis, dose, premedications and ADR information, which was coded for time of onset, severity and outcome.

Setting Community infusion clinics located in Ontario, Canada.

Patients Patients aged 12–91 years who receive regular infliximab infusions to treat their autoimmune condition, mainly either Crohn's disease or rheumatoid arthritis.

Main outcome measures The number of infusions to the occurrence of an acute ADR by presence of premedication.

Results ADRs are not significantly different ($\chi^2(1, n=644, p=0.651)=0.204$) between those who always received premedications and those who never did. When controlling for age, sex, weight and diagnosis, patients receiving premedications were just as likely to experience an ADR as patients who never received any (OR 1.1, 95% CI 0.7 to 1.9, $p=0.5$). When assessing the number of infusions to the occurrence of an ADR using the Kaplan–Meier method, no significant difference was found between the two groups.

Conclusions The use of premedications is not associated with a decreased risk of ADR in patients receiving infliximab. This held true for patients who had never had an ADR prior to receiving premedications and while controlling for age, sex, weight and diagnosis.

Introduction

Acute adverse drug reactions (ADRs) have been well documented in relationship to infliximab infusions.^{1–4} It has become fairly routine for physicians to provide medications just prior to an

infliximab infusion (premedications) in an effort to prevent the recurrence of an ADR in patients who have already had such a reaction. Many physicians also initiate these premedications for patients at the onset of infliximab therapy, hoping to prevent ADRs from occurring, since some patients withdraw from infliximab infusion therapy due to the severity of the reactions. Premedications that are routinely used include paracetamol, antihistamines, steroids and antinauseants. Antihistamines and even epinephrine have been used to treat more severe ADRs that have not resolved with slowing or cessation of the infliximab infusion. However, infliximab-related ADRs do not appear to be allergic in nature. Cheifetz and Mayer⁵ felt that the ADRs did not appear to be related to the presence of antibodies. They stated that 'the reactions are largely not anaphylactic (IgE mediated), making it possible to re-treat patients using specific protocols.' Such information supports the concept that use of epinephrine, steroids or antihistamines to treat infliximab-related ADRs as if they were allergic in nature, or the use of steroids or antihistamines to prevent them, may be of little or no value.

Infliximab-related ADRs resemble the idiosyncratic reactions associated with the use of vancomycin.⁵ Often stopping an infusion, then restarting at a lower rate allows a treatment to continue without further symptoms. Furthermore, patients having had an ADR with one infliximab infusion may not have any reaction with the next infusion. If the ADRs seen with infliximab are idiosyncratic in nature, then it is possible that the use of adjunctive medications may offer no benefit, while exposing the patient to the recognised adverse effects of those medications. Furthermore, it is possible that drug–drug interactions may actually increase the risk

of a patient having an ADR rather than decreasing that risk. The purpose of this study was to identify the association of the use of premedication with the rate of ADRs seen with infliximab infusions. It is possible that an increased risk of an ADR could be explained by the fact that people having already had an ADR—and therefore now receiving premedication—would inherently be at greater risk for another ADR. To account for that possibility, as a second objective we wished to evaluate whether new patients who received premedications from the onset of infliximab therapy prior to having experienced a first ADR were at greater risk of an ADR than those new patients who received no premedication.

Methods

This is a retrospective chart review of all patients treated with infliximab in community infusion clinics during the period from 1 December 2006 to 15 April 2008. The infusion clinics are located across Ontario, Canada. All clinics follow the same standardised protocols for the infusion and monitoring of infliximab. Such an approach has been in place for over 6 years with an accumulated total of greater than 100 000 infusions. The methods used for this medical record review were as recommended by Gilbert *et al.*⁶ Ethics approval was obtained from the University of Western Ontario Research Ethics Board for Health Sciences Research. (See the paper by Ducharme *et al* for further details regarding the clinics and infusion protocols.)¹

The data required for this medical record review were partly available in an existing electronic database while the rest was available in the hard copies of the patients' records. Every new patient has an electronic record containing patient demographics and appointment data, which are mostly used to schedule appointments. The hard copy of a patient's record is a standardised datasheet that is filled out at each visit, and includes weight, presence and level of severity of new symptoms, history of infection(s) or hospitalisation(s) since the previous infusion, recent surgery or planned surgery, blood tests or other investigations (eg, colonoscopy) and any change in medications. Details of any previous or new ADR are included in the hard copy of the patient's record.

The required electronic data elements as explicitly defined prior to the study were extracted from the database and supplemented with data extracted from paper records. A 10% random sample of the study charts had data extracted by a second trained recorder to ensure interobserver reliability. The data elements obtained from the electronic database were: age, sex, diagnosis, weight, intervals of infusions, infliximab dosage, number of infusions received during the study period and medications to be taken prior to infliximab infusion. The data extracted from the paper records

Table 1 Infusion reaction stratification according to Cheifetz and Mayer⁵

Reaction	Severity classification
Diaphoresis	Mild
Dizziness	
Flushing	
Headache	
Nausea	
Palpitations	
Chest discomfort	
Hypo/hypertension (>20 points increase)	
Increased temperature	
Palpitations	
Shortness of breath	Moderate
Urticaria	
Chest discomfort	
Hypotension/hypertension (>40 points increase)	
Increased temperature with rigors	
Severe chest discomfort	
Severe flushing	
Shortness of breath with wheezing	
Stridor	
	Severe

were: steroid premedication dosage, presence and severity of adverse event according to Cheifetz and Mayer's⁵ stratification (see table 1), and time of onset of any adverse event (during infusion, within 24 h postinfusion or delayed).

Analysis

All descriptive statistics and statistical tests were obtained using IBM SPSS Statistics (V.19.0, SPSS). Only those patients who underwent and completed the standard loading dose regimen during the study period were included. This was to exclude those who started receiving infusions prior to the study period or outside of the network of clinics whose premedication and adverse event history are unknown.

The Kaplan–Meier survival analyses were done to evaluate the differences in the number of infusions until the occurrence of an ADR between patients who never received premedications and those who always did. The Breslow (generalised Wilcoxon) χ^2 test was used to test significance of differences in the Kaplan–Meier survival plots.

The logistic regression analyses were done to assess the association between premedications and ADRs while controlling for age, sex, weight and diagnosis; variables available with a potential association with the risk of ADR. Diagnoses were categorised as either arthritides or gastrointestinal conditions. Patients reported as having 'psoriasis' or 'other' were excluded due to their confounding effect on the regression models. The strength of the associations is reported as ORs.

For all tests assessing differences between presence and absence of premedications, patients who had changes in their premedication status prior to an ADR or without experiencing an ADR before the change were excluded since it meant that the presence (or absence) of premedications was not consistent.

Results

Altogether, 3161 patients received a total of 20 976 infusions during the study period. Of these, 684 patients who received 4077 infusions completed the standard loading dose regimen and were selected for this study. Forty (5.8%) patients had changes in their premedication status and were excluded from analyses where the associations with the presence of premedications were evaluated. Fifty-three (7.7%) patients were in the diagnostic categories 'psoriasis' or 'other' and were excluded from the logistic regression tests. The basic descriptive characteristics of the patient sample are outlined in table 2.

The most common diagnoses were Crohn's disease and rheumatoid arthritis (see table 3). More than half of the patients (56.6%, $n=387$) were always prescribed premedications. The most frequently used premedication type was steroids (78.7%, $n=347$, hydrocortisone in 98.8% of steroid usage). Further details on the types and combinations of premedications prescribed are outlined in table 4. The decision to prescribe premedications and which to prescribe was at the discretion of the patient's physician. Most patients with arthritides always received premedications ($n=144$, 63.4%) while most patients with gastrointestinal conditions never received them ($n=236$, 64%) and this difference is significant ($\chi^2(1, n=596, p<0.001)=42.394$).

There were 163 ADRs, of which 113 (2.8% of all infusions) occurred during the infliximab infusion, while 50 (1.2% of all infusions) occurred after the end of the infusion but within the first 24 h for an overall ADR rate of 4% occurring in 108 patients (15.8%). Most reactions were mild ($n=97$, 59.5%) and nine

were severe (5.5%). Of the nine severe reactions, one required the assistance of emergency medical services. Seven were noted as improved (includes the reaction where emergency medical services were called). No notes were included as to the improvement of the other two severe reactions.

Women were more likely to experience an ADR as 21.2% of women did versus 9.7% of men ($\chi^2(1, n=684, p<0.001)=16.839$); the predictive value of sex remained true when controlling for age, disease, weight and presence of premedication in the logistic regression analyses (OR 3, 95% CI 1.8 to 4.9, $p<0.001$). No other variable was predictive of ADR occurrence. The ADR rates of new patients who had premedications initiated from the onset of infliximab therapy versus those who never received premedications are not significantly different ($\chi^2(1, n=644, p=0.651)=0.204$). The severity of the first ADR was also not significantly different between patients who always received premedications versus those who never did ($\chi^2(2, n=107, p=0.35)=2.101$). The reaction rates between disease types were also non-significant overall, neither in those who never received premedications, nor in those who always received them ($p>0.571, \chi^2<0.306$ in each case). When controlling for age, sex, weight and diagnosis, patients receiving premedications were just as likely to experience an ADR as patients who never received premedications (OR 1.1, 95% CI 0.7 to 1.9, $p=0.5$). When assessing the number of infusions

Table 2 Patient sample characteristics

Variable	Mean	SD
Age (years)	45.1	± 15.1
Minimum	12	
Maximum	91	
Sex		
Male (n)	320	
Male (%)	47	
Weight (kg)	76.3	± 20.5
Dose (mg of infliximab per kg of bodyweight)	5.08	± 1.4
Number of infusions each patient received during the study	6	± 2.4
Number of weeks between infusions	6.6	± 2.3
Minimum	4	
Maximum	9	

Table 3 Patients by primary diagnosis

Primary diagnosis	N	Proportion (%)
Crohn's disease	238	34.8
Rheumatoid arthritis	111	16.2
Ulcerative colitis	111	16.2
Fistulising Crohn's	95	13.9
Ankylosing spondylitis	50	7.3
Psoriasis	27	3.9
Psoriatic arthritis	26	3.8
Other	26	3.8
Total	684	100.0

Table 4 Patients by premedications

Premedication(s)	N	Proportion (%)
None	243	35.5
Steroids	150	21.9
Antihistamines, paracetamol and steroids	110	16.1
Antihistamines and steroids	66	9.6
Antihistamines	40	5.8
Antihistamines and paracetamol	37	5.4
Paracetamol and steroids	21	3.1
Paracetamol	17	2.5
Total	684	100.0

to the occurrence of an ADR using the Kaplan–Meier method, there is also no significant difference between the length of survival of patients receiving premedications and the length of survival of those who do not receive premedications (χ^2 (Breslow) (1, $n=473$, $p=0.47$)=5.22) (see figure 1). Of note, however, when comparing patients who received antihistamines as part of their premedications with those who never received any premedications, those with antihistamines tended to have lower surviving proportions although the difference was not significant (χ^2 (Breslow) (1, $n=473$, $p=0.07$)=3.37) (see figure 2). Other regression and Kaplan–Meier analyses were conducted to assess the effects of the presence or absence of paracetamol or steroids; none of these analyses revealed any notable difference in reaction rates between patients who received these premedications and those who did not receive them.

Discussion

Any time a patient receives a medication, the patient is at risk of an adverse event. It is important therefore to avoid medications if there is no potential benefit, as the patient can only be at risk of harm. An obvious example of this would be if a physician were to prescribe an antibiotic to someone having a viral upper respiratory tract infection.

In the case of monoclonal antibody medications, acute adverse reactions are poorly understood. It has been known for years that infliximab, or any other monoclonal antibody medication for that matter, can generate an antibody response in patients. Many patients will no longer respond to infliximab once antibodies have developed.^{7–8} Farrell *et al*⁹ suggested that these antibodies could impair patient response to infliximab and they could also be the cause of many of the acute ADRs seen with infusions. In their study, they

Figure 1 Survival function by presence of premedications. Dark line, no premedications; grey line, with premedications.

identified that there was a decreased incidence in the development of antibodies to infliximab when a dose of 200 mg of hydrocortisone was given as a premedication. This held true only if the hydrocortisone was given within 8 weeks of the second infusion. However, the prevention of antibody development did not produce a decrease in adverse events. In a review, Mayer and Young also suggested that infusion reactions might be related to the presence of these antibodies.¹⁰ These studies were trying to imply that the acute adverse reactions might be allergic in nature. Acute allergic/anaphylactic reactions are IgE based, however, and the study by Cheifetz *et al*¹¹ demonstrated that infliximab reactions generate no IgE response. Steenholdt *et al*¹² demonstrated in 19 of 20 patients with acute adverse reactions that IgG antibodies were highly positive immediately after the reaction. Only 11 were re-tested prior to their next infusion; seven were negative for such antibodies. The absence of these IgG antibodies prior to reinfusion was not associated with the absence of another infusion reaction. As with the study by Cheifetz *et al*,¹¹ there were no IgE antibodies detected. Clinically, it is seen that the initial reaction can be stopped and additional reaction can be prevented during the same infusion by slower infusion rates or by temporarily stopping the infusion and flushing the intravenous line.¹¹ Both these points would seem to eliminate the possibility of an allergic origin for the acute adverse reactions. They are now considered to be idiosyncratic in nature.

It is possible that any medication used in conjunction with another may result in an adverse drug–drug interaction—there are numerous examples in clinical practice. It is reasonable therefore to suspect that use of medications in conjunction with infliximab

Figure 2 Survival function by presence of antihistamines versus no premedications. Dark line, no premedications; grey line, with antihistamines present.

may potentiate the severity of an adverse reaction or increase the rate of such events occurring. In our study, it was evident that the use of premedications was not associated with a reduced risk of an ADR in patients receiving infliximab. Overall, the rates of ADRs were the same in patients who received premedications. In a retrospective chart review like this, determining causality is not possible. One could argue that the at-risk patients were more likely to receive premedications so that their reaction profile remained similar to those not receiving premedications. However, since this study compared patients who received premedications before having had an ADR, the presence of premedications cannot be attributed to the premise that the patient was at a greater risk. Others might argue that the type of premedications play a role, maybe even a confounding one; it appears that those who receive antihistamines are more likely to experience an ADR at some point.

While a study of a retrospective nature cannot by definition impute causality, the absence of association with ADR rates suggests the necessity for further study into the need for premedications. The size of this study, however, prohibited a deeper examination of the role of premedications on ADR rates. Confirmation of associations, or lack thereof, of specific premedications in a large prospective randomised trial could confirm the lack of value of premedications. While this study shows no potential benefit, there is always an adverse event rate—potential harm—from every medication prescribed. Furthermore, our study suggests that trying to prevent ADRs with premedications may, in some instances, actually increase the risk of an ADR—we may be placing our patients at greater risk by attempting to be proactive.

Many physicians are concerned about the severity of reactions and the potential risk of morbidity or even death. Such concerns over patient safety may not be justified. While in ACCENT I, 3% of patients had their treatment suspended due to adverse events,² only 2/2211 infusions in a study by Colombel *et al*³ 'required' the use of epinephrine. In a study by Takeuchi *et al*⁴ the rate of serious adverse events was also low, occurring in 0.5%. What is reassuring is that, as we previously reported, most ADRs resolve with slowing down or temporarily stopping the infliximab infusion before restarting it at a lower rate.¹ Even in patients who had apparent severe reactions all symptoms improved or resolved prior to paramedics arriving in response to being called.

As the use of monoclonal antibody medications expands, we can expect to develop a greater understanding of their actions, both positive and negative. Until such time, we need to be cautious in applying therapy for adverse events that we understand, such as allergic reactions, to ADRs that we do not understand, hoping that somehow therapy will be beneficial. *Primo non nocere* is our mandate. Withholding premedications in an effort to decrease the risk of infliximab-induced ADRs appears to be a step in that direction.

What is already known on this subject?

- ▶ Acute adverse drug reactions (ADRs) are well documented in infliximab infusions.
- ▶ Physicians prescribe medications normally used for allergic reactions prior to infusion in an effort to decrease this risk despite evidence showing that reactions are idiosyncratic in nature.
- ▶ Briefly stopping or slowing the infusion almost always allows treatment to continue without further symptoms.

What this study adds?

Premedications may offer no benefit or even increase ADR risk.

How might it impact on clinical practice in the foreseeable future?

The lack of identified benefit from using premedications to prevent infusion-related ADRs raises the concern of overprescribing medications and elevating the potential for drug–drug interactions and non-infusion-related reactions. These results should encourage physicians to stop prescribing premedications for infliximab infusions.

Conclusions

The use of premedications was not associated with a decrease in acute ADRs in patients receiving infliximab. There was no identified benefit from premedications even in patients who received them from the onset of infliximab therapy. This retrospective study suggests that premedications need not be used. This finding should be validated in a randomised prospective study.

Competing interests None.

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Contributors All authors contributed significantly to the realisation of this study and the development of this manuscript. No other person provided any significant contribution to the study design, implementation and/or reporting.

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