HHS Public Access

Author manuscript

*Inflamm Bowel Dis*. Author manuscript; available in PMC 2019 June 05.

Published in final edited form as:

*Inflamm Bowel Dis*. 2017 December ; 23(12): 2104–2108. doi:10.1097/MIB.0000000000001259.

# Rapid Infliximab Infusion in Children with Inflammatory Bowel Disease: A Multicenter North American Experience

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## Abstract

**Background:** Infliximab (IFX) infusion may lead to development of anti-IFX antibodies, and subsequent infusion reactions (IRs). The safety of rapid IFX infusion administered over 60 minutes has been under-investigated in children with inflammatory bowel disease. In a multicenter study, the frequency and nature of rapid infusion-associated IRs were examined.

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Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's Web site (www.ibdjournal.org).

The other authors have no conflict of interest to disclose.

**Methods:** The medical records of all consecutive children with inflammatory bowel disease receiving rapid IFX infusions between January 2014 and December 2016 were reviewed. Poisson regression analysis was used to identify possible associated factors with IRs.

**Results:** A total of 4120 rapid infusions for 453 children (median age 16 yrs [interquartile range 13.8–17.8], 289 males, 374 with Crohn's disease) were included. One hundred thirty-five participants (29.8%) received rapid IFX infusion for induction and maintenance while the rest received rapid IFX infusion after a median of 5 (interquartile range 4–9) standard infusions. The median dose of IFX using rapid protocol was 8 mg/kg/infusion (interquartile range 6–10). Two hundred sixty-seven (59%) patients received 1 or more premedications and 161 (35.5%) participants received concomitant immunosuppression. Twenty-one participants (4.6%) had IRs with rapid infusions and 2 participants discontinued IFX because of IRs (0.4%). Antihistamine premedications were associated with less frequent IR (adjusted relative risk = 0.30; 95% confidence interval, 0.14–0.64; $P = 0.002$).

**Conclusions:** In children with inflammatory bowel disease, rapid IFX infusion administered over 60 minutes is safe and well-tolerated. Antihistamine premedications may reduce frequency of IRs (see Video Abstract, Supplemental Digital Content 1, http://links.lww.com/IBD/B632).

## Keywords

colitis; Crohn; IBD; infliximab; infusion; reactions

**I**nfliximab (IFX) is a chimeric (part murine, part human) monoclonal antibody against tumor necrosis factor alpha used to treat several immune-mediated diseases including inflammatory bowel disease (IBD).[1] IFX is administered through intravenous infusion, traditionally over 2 to 3 hours. As IFX is a protein-derived medication, infusions can lead to formation of anti-IFX antibodies (ATI) which may lead to infusion reactions (IRs) on subsequent infusions. IRs are the most common adverse reaction to IFX and can be classified into acute and delayed reactions.[1,2] IRs are reported to occur in up to 5% of infusions and in up to 10% to 20% of patients. However, most of these reactions are mild. Symptoms of acute reactions include blood pressure changes, mucosal irritability, chest pain, dyspnea, and laryngospasm.[1–4] By contrast, delayed reactions, defined as any adverse reaction that occurs from 24 hours to 14 days after IFX infusion, may manifest with arthralgias, fevers, malaise, and myalgias. Management of acute reactions include use of medications such as antipyretics, antihistamines, corticosteroids, and/or epinephrine that are typically administered after the reaction has occurred. Delayed reaction could be managed by medications such as analgesics and antipyretics or increasing infusion intervals.[1–4]

Factors that may affect the incidence of IRs include frequency of IFX infusion and concomitant immunomodulatory medications.[1,2] However, it is not clear if prophylactic use of preinfusion medications such as antipyretics, antihistamines, and corticosteroids have any effect on the risk of IRs.

Typically, IFX is administered over 2 to 3 hours. Shorter duration of infusions, which may save significant time and health resources for both patients and health care providers, have been successfully used in several centers for adults with IBD.[1,3] Breynaert et al[1] compared

IRs associated with 4307 rapid infusions over 60 minutes to that of 4848 2-hours infusions. Mild acute reactions occurred in 0.6% of the rapid infusion group compared with 1.7% of the 2-hour infusion group ($P = 0.003$). Delayed reactions occurred in 0.2% of rapid infusion group and 0.5% of 2-hour infusion group ($P = 0.3$). However, the current experience with rapid IFX infusions in children with IBD is underreported. In a small pediatric single-center retrospective study, 16 children had 133 standard infusions over 2 to 3 hours followed by 50 rapid infusions over 60 minutes. The frequency of IRs was 2% in both groups.[5]

The primary aim of the study was to examine the frequency of IRs associated with rapid infusion of IFX. A secondary aim was to explore the impact of premedications and concomitant immunomodulatory therapy on the frequency of IRs.

## METHODS

The medical records of all consecutive children and young adults (≤23 yrs) diagnosed with IBD who were or had been on rapid IFX infusions were reviewed. Participants were recruited from 9 pediatric North American (6 in the United States and 3 in Canada) tertiary-care IBD centers. Rapid IFX infusion was defined as administration of IFX over 60 minutes. The timing of starting rapid IFX infusion whether at the start of IFX treatment or following any number of traditional IFX infusion over 2 to 3 hours was documented. The following variables were also collected:

1. Demographic characteristics including age, gender, IBD subtype, and duration of disease
2. Concurrent medications, including immunomodulators
3. Premedications before rapid IFX infusions
4. IFX dose (mg per kg) using rapid protocol
5. Total duration of IFX treatment
6. Any reported IRs, nature, degree of the reaction if documented, and whether:
    a. Immediate reactions: defined as any adverse event reported during or within the first 24 hours postinfusion.
    b. Delayed reactions: defined as any adverse event reported between 1 day–4 days postinfusion.
7. Management of IRs
8. Any discontinuation of IFX and reason for discontinuation

### Statistical Analysis

Data analysis was performed using SAS (9.4) SAS instate Inc., Cary, NC, USA. Univariate summaries (mean, median, range, standard deviation, and interquartile ranges [IQR]) were obtained for continuous variables, whereas frequency distributions were provided for categorical variables along with 95% confidence intervals (CIs) for means and proportions. Poisson regression analysis was used to calculate the incidence rate ratio of IFX infusions

per patient associated with IRs after adjusting the total number of rapid IFX infusions as an offset variable in the model (for each patient the total number of rapid infusions was different). Relative risk (RR) for IRs were calculated after adjusting for age, sex, disease subtype and duration, use of premedications, immunomodulatory, IFX dose, and duration of treatment. Statistical significance considered at alpha <0.05.

### Ethical Considerations

The protocol of the study was approved by the local health research ethics boards of all collaborating centers.

## RESULTS

The medical records of 478 participants who received rapid IFX infusions over the study period in all contributing centers were examined. Twenty-five patients were excluded for incomplete records. A total of 4120 rapid infusions in 453 participants (median age at the start of rapid infusion was 16 years [IQR 13.7–17.9], 289 males [63.4%], 374 with Crohn's disease) were included. Demographic and disease characteristics are summarized in Table 1. Forty-six (10%) patients were ≤10 years of age at the time of rapid IFX infusions and 84 (18.5%) ≥18 years of age. A total of 135 patients (29.8%) received IFX using rapid infusion protocol from induction, whereas the rest of patients received rapid IFX infusion after a minimum of 3 induction infusions (median of 5, IQR: 4–9 infusions) administered over the standard duration of 2 to 3 hours. The median number of rapid IFX infusions/patient was 8 infusions (IQR 5–15). The median dose of IFX using rapid protocol was 8 mg/kg/infusion (IQR 6–10) (see Appendix, Supplemental Digital Content 2, http://links.lww.com/IBD/B633).

### Infusion Reactions

Of 4130 rapid infusions, 22 IRs (0.5%) occurred among 21 participants; 9 (0.2%) immediate and 13 (0.3%) delayed reactions. Details and management of immediate and delayed reactions are summarized in Table 2. None of those reactions were fatal and only 1 acute reaction was perceived as severe by the treating physician. The remainder of the reactions was classified as mild or moderate. The most common acute and delayed reactions were nausea, headache, and myalgias. IFX was discontinued in 5 (1.1%) participants; 3 due to loss of response and 2 due to IRs (0.4%).

### Premedications

A total of 267 (59%) participants (2858 infusions) received 1 or more premedications that included corticosteroids (39 participants; 402 infusions), antihistamines (mainly diphenhydramine) (198 participants; 2293 infusions) and acetaminophen (260 participants; 2808 infusions). Although there was a trend toward less IRs with premedications, the overall use of premedications was not significantly associated with IRs occurrence compared with no-premedication use (adjusted RR = 0.61; 95% CI, 0.36–1.03; $P = 0.06$). However, antihistamine use was significantly associated with less frequent IR (adjusted RR = 0.29; 95% CI, 0.14–0.64; $P = 0.002$). In comparison, corticosteroid use was associated with more frequent IRs (adjusted RR = 8.42; 95% CI, 4.64–15.25; $P < 0.0001$). Table 3 summarizes the

number of patients who were given 1 of more premedications and adjusted RR for IRs associated with each premedication.

### Concomitant Immunomodulators

A total of 165 (36.4%) participants (1596 infusions) were on concomitant immunomodulators with rapid IFX; 101 (1145 infusions) on methotrexate, of whom 85 were on oral methotrexate, and 55 (451 infusions) on azathioprine. Overall, the use of immunosuppression compared with IFX monotherapy was not associated with IR occurrence (RR = 1.21; 95% CI, 0.64–2.28; $P = 0.55$). For specific immunomodulators compared with IFX monotherapy, methotrexate, and azathioprine were not associated with IRs occurrence (RR = 0.66; 95% CI, 0.32–1.38; $P = 0.27$ and RR = 1.21; 95% CI, 0.57–2.63; $P = 0.61$, respectively). The difference remained nonsignificant comparing immunomodulatory type between methotrexate to azathioprine.

### Other Factors

Other factors examined included dose of IFX, age, sex, disease subtype, and disease duration. Older patients were less likely to get IRs with an adjusted RR of 0.89 (95% CI, 0.83–0.97; $P = 0.004$) and those with longer disease duration were more likely to have IRs with an adjusted RR of 1.2 (95% CI, 1.12–1.28; $P < 0.0001$).

Sex and disease subtype (Crohn’s disease versus ulcerative colitis) did not have any significant effect on IRs with RR = 0.7 (95% CI, 0.40–1.17; $P = 0.2$) and 1.2 (95% CI, 0.63–2.41; $P = 0.5$), respectively.

### Subgroup Analysis

Excluding patients older than 18 years (84 patients) did not have any significant effect on the results except for the effect of concomitant immunomodulators on IRs. Patients were less likely to have IRs if they were on immunomodulators with an adjusted RR = 0.31 (95% CI, 0.14–0.67; $P = 0.003$), especially if they were on methotrexate (RR = 0.08; 95% CI, 0.02–0.27; $P < 0.0001$) compared with azathioprine (RR = 0.54; 95% CI, 0.21–1.34; $P = 0.18$).

## DISCUSSION

IRs are the most common adverse event associated with IFX. Our study showed that 21 patients (4.6%) had a total of 22 IRs (0.5%) among 4158 rapid IFX infusions. None of these reactions were fatal and only 2 patients (0.4%) discontinued IFX because of IRs. Our results are concordant with other studies. In a recent meta-analysis that included 10 mostly adult studies and compared over 13,000 standard (over 2–3 hours) infusions versus over 8000 (over 1 hour) rapid infusions in almost exclusively adult patients receiving IFX for several immune-mediated diseases, there was a decreased risk of IR (RR = 0.49, $P = 0.002$) in rapid infusion versus standard infusion in patients with IBD.[3] Similar to our study, the dose of IFX was not associated with IR occurrence; i.e., there was no significant difference in IRs between studies that used high dose (10 mg/kg) versus standard dose (5 mg/kg) IFX. Some of the included studies used shorter infusion periods such as 45 minutes/infusion, which also did not have any significant effect on the risk of IRs. There was insufficient data on

preinfusion medications and their effect on IRs as those details were provided in only 4 studies. The meta-analysis included only 1 pediatric single-center retrospective study with 16 children who had 133 standard infusions (2–3 hours) and then 50 rapid infusions (1 hour). The frequency of IRs was 2% in both groups.[5] Interestingly, 1 patient had similar IRs with both protocols. A more recent prospective multicenter study examined 63 adult patients with IBD who received 182 maintenance IFX infusions at a dose of 10 mg/kg/infusion with intravenous corticosteroids as a premedication given to all patients. Severe acute IRs occurred in 2 patients and delayed IR occurred in 1 patient. The authors concluded that rapid IFX infusions of 10 mg/kg/infusion were safe and well-tolerated.[6]

Preinfusion medications such as antipyretics, antihistamines, and corticosteroids have been used to prevent IRs.[2] Preinfusion injection with hydrocortisone was proven effective in reducing ATI formation in a small study by Farrell et al.[7] However, it did not have a significant effect on IRs. It is interesting that corticosteroid premedication in our study was paradoxically associated with higher IRs. One could argue, however, that this finding should be interpreted with caution because of possible selection bias; i.e., patients with a perceived higher risk of IRs or who already had IRs during the induction phase that were managed by corticosteroids might have typically received corticosteroids before IFX infusion. In a large pediatric multicenter retrospective analysis of 1652 infusions in 243 children with IBD, preinfusion medications did not seem to prevent IRs. Notably, this also applied to those who had previous IRs, as IRs recurred in 2 of 10 patients (20%) who were subsequently premedicated compared with 6 of 12 (50%) patients who did not receive subsequent premedication ($P = 0.15$).[8] It was not clear in that study what premedication was used. However, our study showed reduced risk of IRs with antihistamine premedication. Acetaminophen premedication did not have a significant effect on the risk of IRs. A recent North American survey to assess practice variability and clinician rationale for premedication use before IFX among gastroenterologists showed that acetaminophen (66%) and diphenhydramine (64%) were most often given before IFX infusions. Only 20% did not routinely use premedications and 18% identified the potential association of diphenhydramine use with increased reactions.[9] Previous data have suggested that administration of antihistamines, alone or in combination with corticosteroids and/or antipyretics, might be paradoxically associated with higher rates of immediate IRs.[10,11] This finding is obviously discordant from our findings; however, this difference again could be related to possible selection bias.[12] The role of antihistamines in prevention of IRs is yet to be defined and future studies are required to provide further clarity on the role of antihistamine premedication in prevention of IRs. Overall, prospective studies are required to better understand the role and safety of premedications with IFX infusions for prevention of IRs in IBD.

Although concomitant use of immunomodulators with IFX was not associated with reduced risk of IRs in the whole cohort, younger patients seemed to benefit more from being on concomitant immunomodulators especially methotrexate but not azathioprine. This is likely related to the fact that IRs were much less in older age group. The SONIC trial that showed reduction of IRs from 16% in adult patients on IFX monotherapy compared with 5% in those on IFX plus azathioprine.[13] Nonetheless, our study might be underpowered to show a similar result as only 55 patients were on IFX plus azathioprine. Other studies showed that

addition of immunosuppression to IFX reduce ATI, but they failed to show a similar reduction in IRs.[14] In our study, we did not have access to serum IFX or ATI levels, so we could not determine whether the use of immunosuppression resulted in higher IFX troughs and/or lower rate of ATI development. Of note is that while ATI development may lead to increased risk of IRs, only 20% may actually develop IRs. The exact mechanism of IRs is often unclear and many of those reactions could be related to nonimmunogenic mechanisms[12] in which case immunosuppressive medications may not have any effect on reducing the risk IRs.

The limitations of our study are the retrospective design including missing data, need for extrapolation, and truncated follow-up. However, all patients with incomplete data were excluded. Another limitation was the assumption that all IRs were secondary to IFX infusion. It is difficult to assume a cause-effect relationship for all reported reactions. However, our study is one of the few and certainly the largest study to date that examined the safety of rapid IFX infusion in children with IBD.

## CONCLUSIONS

Rapid IFX infusions administered over 60 minutes are safe and well-tolerated in children with IBD. Before IFX infusions, intake of premedications, mainly antihistamines, may reduce IRs while concomitant intake of immune-suppressive medications may have similar effect in those younger than 18 years. Prospective studies of rapid IFX infusions in children with IBD with investigating the effect of duration of infusion on formation of ATI are necessary to confirm our findings. Exploring the effect of this strategy on saving time and health care resources for both patients and health care providers is also important to address in future studies.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

## ACKNOWLEDGMENTS

The authors thank Dr. Rasheda Rabbani (PhD) for her help with statistical analysis and Ms. Vini Deora for her help in data collection.

W. El-Matary is supported with a grant from the University of Manitoba and the Children’s Hospital Research Institute of Manitoba.

Dr. El-Matary served as an advisory board member for both Janssen Canada and AbbVie Canada and received an unrestricted research grant from Janssen.

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**TABLE 1.**

Demographic and Disease Characteristics of 453 Participants at Start of Rapid IFX Infusions

| Characteristic | N = 453 Participants |
|---|---|
| Age (yrs), median (IQR) | 16.0 (13.7–17.9) |
| Disease duration (yrs), median (IQR) | 3.8 (1.9–8.7) |
| IFX duration (yrs), median (IQR) | 1.8 (0.8–3.3) |
| Rapid IFX dose (mg/kg), median (IQR) | 8.0 (6–10) |
| Male sex (%) | 289 (63.8) |
| IBD type (%) | |
| Crohn's disease | 374 (82.6) |
| Ulcerative colitis | 73 (16.1) |
| IBD-unclassified | 6(1.3) |
| IFX treatment phase using rapid infusion (%) | |
| Induction | 135 (29.8) |
| Maintenance | 318 (70.2) |

**TABLE 2.**

Infusion Reactions Associated with Rapid IFX (22 Reactions in 21 Patients)

| No. Reactions | Sequence of Offending Rapid Infusion | Nature of Reaction | Management |
|---|---|---|---|
| Acute reactions (total = 9 reactions) | | | |
| 3 | 1st, 4th and 21st | Malaise, headache, and nausea with or without vomiting | Monitoring—Use of acetaminophen with the offending infusions. One patient had corticosteroids for before future infusions. |
| 3 | 4th, 12th, 17th | Urticaria and pruritus | Monitoring—Use of an antihistaminic with offending infusion and future infusions. |
| 1 | 22nd | Rash, considered to be possibly Henoch Schonlein purpura or leukocytoclastic skin reaction | Stop IFX and switch to adalimumab. |
| 1 | 4th | Shortness of breath, chest tightness, hypotension, and desaturation | Stop IFX, IV steroids and antihistamines, then switch to adalimumab. |
| 1 | 18th | Nasal congestion | Reduced rate of IFX infusion |
| Delayed reactions (total = 13 reactions) | | | |
| 8 | 1st × 3, 2nd, 3rd, 4th, 11th, and 12th | Malaise, nausea, headache, and flu-like symptoms | Monitoring—Use of corticosteroids in future infusions—Use all 3 premedications in future infusions—One patient had interval increase of infusions |
| 2 | 1st and 12th | Rash including petechial eruption | Investigations (INR), dermatology referral, topical corticosteroid ointment |
| 2 | 1st and 5th | Elevated liver enzymes | Monitoring and investigations to exclude autoimmune hepatitis |
| 1 | 5th | Develops style after the infusion, lasted for 3 days and then self-resolved | Monitoring |

IV, intravenous.

**TABLE 3.**

Premedication Use and Risk of Association with Infusion Reactions Using Rapid IFX Infusion

| Premedications | No. of Patients[a] | No. of Infusions | RR | 95% CI | *P* |
|---|---|---|---|---|---|
| Any premedication | 267 | 2858 | 0.61 | 0.36–1.03 | 0.06 |
| Corticosteroids | 39 | 402 | 8.42 | 4.64–15.25 | <0.0001 |
| Antihistamines | 198 | 2293 | 0.29 | 0.14–0.64 | 0.002 |
| Acetaminophen | 260 | 2808 | 0.68 | 0.33–1.41 | 0.30 |

[a]Patients were using 1 or more premedications in the same time.

*Inflamm Bowel Dis*. Author manuscript; available in PMC 2019 June 05.