A study investigating the association of dermatological and infusion reactions to infliximab and infliximab trough levels

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Les nadirs d’infliximab sont corrélés avec les événements indésirables liés à ce médicament chez les patients ambulatoires atteints d’une maladie inflammatoire de l’intestin sous traitement d’entretien à l’infliximab

HISTORIQUE : L’infliximab est un traitement efficace des maladies inflammatoires de l’intestin (MII), mais il s’associe à des événements dermatologiques et à des réactions aux perfusions. On ne sait pas s’il y a un lien entre ces événements indésirables (ÉI) et les nadirs d’infliximab.

OBJECTIFS : Rendre compte de la prévalence d’ÉI liés à l’infliximab chez les patients atteints d’une MII qui reçoivent un traitement d’entretien stable à l’infliximab et les corrêler avec les réactions aux perfusions d’infliximab.

MÉTHODOLOGIE : Les chercheurs ont recruté des adultes atteints d’une MII sous traitement d’entretien stable de l’infliximab à la clinique de perfusion de l’université de l’Alberta, à Edmonton. Ils ont mesuré les nadirs dans des échantillons de sang prélevés avant les perfusions et examiné le dossier des patients pour déterminer s’ils avaient eu des réactions dermatologiques à l’infliximab ou aux perfusions de ce médicament, soit neuf événements dermatologiques (12,7 %) et neuf réactions aux perfusions (12,7 %). Le nadir médian était similaire chez les patients ayant subi ou non ces ÉI (7,2 µg/mL [plage interquartile (PIQ) 2,0 µg/mL à 13,3 µg/mL] par rapport à 6,6 µg/mL [PIQ 3,2 µg/mL à 12,7 µg/mL]; P=0,648). Le nadir médian des patients qui avaient des réactions aux perfusions (2,0 µg/mL [PIQ 0,1 µg/mL à 5,7 µg/mL]) était plus bas que celui des patients qui n’avaient pas subi de perfusion (6,6 µg/mL [PIQ 3,2 µg/mL à 12,7 µg/mL]; P=0,008) et que celui des patients qui avaient subi des ÉI de nature dermatologique (13,3 µg/mL [PIQ 8,8 µg/mL à 17,4 µg/mL]; P<0,001).

CONCLUSION : Le quant des patients ambulatoires atteints d’une MII sous traitement d’entretien stable à l’infliximab a subi des réactions dermatologiques et aux perfusions. Des nadirs bas étaient liés aux réactions aux perfusions, et des nadirs normaux ou élevés, aux réactions dermatologiques

Pathophysiologiques mechanisms that have been postulated to contribute to infliximab-induced adverse events differ depending on the adverse event; however, these reactions are believed to be mediated through the immune system. Pathogenesis may include the development of antibodies to infliximab (ATI), either immunoglobulin (Ig) E resulting in a hypersensitivity type reaction (15,16) or IgG resulting in the formation of antibody/antigen complexes (1,8,17-20), or induction of autoantibodies such as antinuclear, antidual-stranded DNA and antihistone (1,10,13). Disregulation of the immune system and cytokine responses may also be involved (2,4,6,14,21-24). Given the importance of the pharmacodynamics of infliximab, the level of infliximab in the blood may be central to the generation of infliximab-induced side effects. However, to date, there have been no published
studies investigating the correlation between infliximab trough levels (ITLs) and infliximab-associated adverse events among IBD patients receiving stable maintenance infliximab therapy. The aims of the present study were to report the prevalence of infliximab-associated dermatological and infusion reaction events among IBD outpatients receiving stable maintenance infliximab therapy, and to correlate ITLs with infliximab-associated adverse events.

Methods

Study design and setting

The present cross-sectional study was conducted at the University of Alberta IBD Infliximab Infusion Clinic (Edmonton, Alberta) in 2013.

Participants

Consecutive IBD outpatients receiving infliximab maintenance therapy were systematically and prospectively identified at the infliximab infusion clinic and invited to participate in the present study. Patients were included in the study if they met the following criteria: a known endoscopic and histological and/or radiological diagnosis of Crohn disease (CD) or ulcerative colitis (UC); primary responders to the initial induction regimen of infliximab 5 mg/kg at weeks 0, 2 and 6 (defined as a decrease in their Harvey-Bradshaw index after induction therapy by 3 points, or a decrease in their partial Mayo score to 0 or 1); receiving stable maintenance infliximab infusions (defined as infusions subsequent to the third induction dose or subsequent to the first infusion after any dose or interval change); and having complete records of infliximab infusions since initial induction. There were no specific exclusion criteria. All consented patients had blood for the determination of ITLs drawn immediately before their infliximab infusion, and underwent a detailed history and chart review to confirm infliximab-associated adverse events.

Outcomes

The primary outcome of the present study was the prevalence of infliximab-associated dermatological and infusion reaction adverse events among IBD outpatients receiving stable maintenance infliximab therapy. The secondary outcome was the correlation between ITLs and infliximab-associated adverse events.

Data sources and definitions

ITL: ITLs were determined on serum samples collected within 30 min before the beginning of the infusion. Serum was separated and frozen within 4 h of collection. An ELISA method (Immunodiagnostik, Germany) was used to quantify levels of free infliximab. Results are reported down to 0.4 µg/mL, with an interassay precision of 8% at 1.8 µg/mL, 9% at 8.6 µg/mL and 20% at 12.9 µg/mL.

Demographics and infliximab-associated adverse events: At the authors’ centre, each infliximab infusion is characterized with the following: clinical disease activity scores (Harvey-Bradshaw index for CD, partial Mayo for UC); health care provider documentation of infliximab-associated adverse events; and patient completion of a questionnaire of infliximab-associated adverse events.

Data were extracted from several sources by two of the authors (VH and ND) using a standardized case report form: electronic medical records; infusion questionnaires completed by the patient at the time of each infusion; nurse-generated infusion reports produced at the time of each infusion; and physician-generated clinic letters at the time of each infusion or subsequent clinic visits.

Infliximab-associated adverse events were classified as dermatological or infusion reactions. Dermatological adverse events were documented by a gastroenterologist and, when possible, confirmed by a dermatologist. Infusion reactions were documented by the infusion nurse and confirmed by a gastroenterologist. Acute infusion reactions were defined as any adverse reaction occurring during or within 24 h of an infusion, while delayed infusion reactions were defined as any adverse reaction occurring between 24 h and 14 days after an infusion. The data were reviewed by four of the authors (VH, ND, KK and RF).

Infliximab treatment characteristics were obtained from the above listed sources and included: infliximab dose in mg/kg; infliximab dosing interval in weeks; cumulative infliximab dose in mg; and number of infliximab infusions.

Time to infliximab-associated adverse event was calculated by determining the number of weeks from the first stable maintenance infliximab infusion until the first report of the infliximab-associated adverse event. Censoring occurred if the patient reported no infliximab-associated adverse events; time to censoring was calculated by determining the number of weeks from the first stable maintenance infliximab infusion until the ITL measurement.

Study size

A total of 100 consecutive IBD patients receiving stable maintenance infliximab therapy were recruited and consented to participate. However, the final evaluable sample size (n=71) was determined by subsequent chart review, which excluded 29 patients due to incomplete infusion records.

Statistical methods

Continuous variables were presented as median (interquartile range [IQR]) due to the small sample size and nonparametric distributions. Nonparametric Mann-Whitney and Kruskall-Wallis tests were used to determine significant differences between median values. For categorical variables, proportions were calculated and comparison between subgroups was performed using Fisher’s exact test; P<0.05 was considered to be statistically significant.

Ethics

The present study was approved by the Health Research Ethics Board of the University of Alberta. Patients consented to provide a blood sample and allow review of their medical records.

Results

Patient characteristics

Table 1 summarizes the demographic and infliximab treatment characteristics of the 71 evaluable patients. The number of men (39 of 71 [45.1%]) and women (32 of 71 [34.9%]) were similar, and there were more patients with CD (46 of 71 [64.8%]) than patients with UC (25 of 71 [35.2%]). The median duration of time on stable maintenance infliximab therapy was 71.9 weeks (IQR 30.0 to 126.7 weeks), with a median time since last infusion of 7.2 weeks (IQR 4.1 to 8.2 weeks).

Infliximab-associated adverse events

More than one-quarter (18 of 71 [25.4%]) of study participants experienced either a confirmed infliximab-associated dermatological event (nine of 71 [12.7%]) or an infusion reaction (nine of 71 [12.7%]) while receiving maintenance infliximab therapy (Figure 1). Of the nine patients who experienced dermatological events, two (22.2%) had psoriasis and seven (77.8%) had persistent nonpsoriatic skin eruptions that had developed while on infliximab and were attributed to infliximab. Of the nine patients with infusion reactions, five (55.6%) experienced acute infusion reactions and four (44.4%) experienced delayed infusion reactions.

Comparing patients who experienced adverse events with those who did not, the median age was similar (Table 2). There were more women (12 of 18 [66.7%]) than men (six of 18 [33.3%]) in the group with adverse events (P=0.046). The proportions of CD and UC were similar between groups, with 62.3% (33 of 53) of patients without adverse events and 72.2% (13 of 18) of patients with adverse events having a diagnosis of CD, and 37.7% (20 of 53) of patients without adverse events and 27.8% (five of 18) of patients with adverse events having a diagnosis of UC (P=0.445).

There were slightly more patients on concomitant therapy among those without adverse events (40 of 53 [75.5%]) than among those...
TABLE 1
Demographics of inflammatory bowel disease outpatients receiving stable maintenance infliximab therapy at the Infliximab Infusion Clinic, University of Alberta, Edmonton, Alberta (n=71)

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<td>Age, years, median (IQR)</td>
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<td>37.0 (29.0–42.0)</td>
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<td>13</td>
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<tr>
<td>No</td>
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<td>12</td>
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<tr>
<td>Dose per infusion, mg/kg, median (IQR)</td>
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<td>5.1 (4.9–5.5)</td>
<td>0.195</td>
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</table>

Data presented as n (%) unless otherwise indicated. IQR Interquartile range

TABLE 2
Demographics of inflammatory bowel disease outpatients receiving stable maintenance infliximab therapy according to development of dermatological or infusion reaction to infliximab at the Infliximab Infusion Clinic, University of Alberta, Edmonton, Alberta (n=71)

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<td>0.540</td>
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<tr>
<td>No</td>
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<td>12</td>
<td></td>
</tr>
</tbody>
</table>

Data presented as n (%) unless otherwise indicated. *Dermatological or infusion reaction to infliximab. IQR Interquartile range

with adverse events (10 of 18 [55.6%]) (P=0.110). There were slightly more patients receiving premedication among those who experienced adverse events (12 of 18 [66.7%]) than among those without adverse events (31 of 53 [58.5%]) (P=0.540).

ITLs and infliximab-associated adverse events
The median infliximab dose at the time of trough collection was 5.3 µg/mL (IQR 4.8 to 5.7 µg/mL), with a median time since last infusion of 7.0 weeks (IQR 4.1 to 8.0 weeks). The median time to infliximab-associated adverse event was 38.2 weeks (IQR 18.0 to 94.7 weeks) and the median time to censorship was 73.1 weeks (IQR 34.0 to 143.1 weeks). As shown in Table 2, the proportion of patients who experienced dermatological or infusion reactions was similar among those receiving infliximab <6 weeks interval (21.4%) (P=0.360).

As shown in Figure 2A, patients who experienced any infliximab-associated adverse event during stable maintenance infliximab therapy had a median ITL of 7.2 µg/mL (IQR 2.0 to 13.3 µg/mL), which was similar to the median ITL of patients who experienced no adverse events of 6.6 µg/mL (IQR 3.2 to 12.7 µg/mL) (P=0.648).

Dermatological adverse events: As shown in Figure 2B, patients who experienced infliximab-associated dermatological adverse events had a median ITL of 13.3 µg/mL (IQR 8.8 to 17.4 µg/mL) while the patients who experienced no adverse events had a median ITL of 6.6 µg/mL (IQR 3.2 to 12.7 µg/mL) (P=0.058). The ITL of the two infliximab-induced psoriasis cases was 9.9 µg/mL and 13.3 µg/mL.

Infusion reaction adverse events: In contrast, Figure 2C shows that patients who experienced infliximab-associated infusion reactions had a significantly lower median ITL of 2.0 µg/mL (IQR 0.1 to 5.7 µg/mL) compared with the patients who experienced no adverse reactions (6.6 µg/mL [IQR 3.2 to 12.7 µg/mL]) (P=0.0167). The median ITL in those who had delayed infusion reactions (3.5 µg/mL [IQR 1.0 to 6.9 µg/mL]) was slightly lower than the median ITL of those who had no adverse reactions (6.6 µg/mL [IQR 3.2 to 12.7 µg/mL]) but the difference did not reach statistical significance (P=0.131).

Finally, as shown in Figure 2D, patients who experienced any infusion reactions had a significantly lower ITL, with a median of 0.60 µg/mL (IQR 0.1 to 5.7 µg/mL), compared with patients who experienced dermatological events, with a median of 13.3 µg/mL (IQR 8.8 to 17.4 µg/mL) (P<0.001).
Infliximab is one of the cornerstone therapies for refractory CD and UC. In the present study, we demonstrated that more than one-quarter of IBD outpatients receiving stable maintenance infliximab therapy experience infliximab-associated dermatological or infusion reaction adverse events. In addition, we have shown a correlation between ITLs and the type of infliximab-associated adverse event: patients with dermatological adverse events had significantly higher ITLs, while patients with infusion reactions had significantly lower ITLs compared with patients who did not experience adverse events.

Dermatological adverse events

Paradoxical skin eruptions of eczema and psoriasis are common in patients receiving anti-TNF therapy, with up to 39% of reported cases of anti-TNF-induced psoriasis occurring in IBD patients (5,25-27). Among studies specifically investigating IBD patients treated with anti-TNF therapies, the main focus has been on the induction or exacerbation of psoriasiform lesions, with reported incidence rates between 5% and 22% (1,4). The literature varies due to different inclusion criteria and definition of the skin lesions of interest.

In our study, we included both inflammatory skin lesions and any de novo skin eruptions that occurred during stable maintenance infliximab therapy, and estimated a prevalence of 12.7% for dermatological adverse events and 2.8% for anti-TNF-induced psoriasis. In a retrospective study conducted by Groupe d’Etude Thérapeutique des Affections Inflammatoires du tube Digestif (GETAID) centres in France, Rahier et al (12) estimated an incidence of 5% for inflammatory skin lesions, with 2% for psoriasiform lesions and 3% for eczematiform lesions, with reported incidence rates between 5% and 22% (1,4). The literature varies due to different inclusion criteria and definition of the skin lesions of interest.

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A limitation of the present study was the small number of dermatological and infusion reactions to infliximab. However, the prevalence of these adverse events is similar to that reported in previous studies, as mentioned above.

Another limitation was that at the time of the present study, we only had access to ELISA-based ITLs, but not to ATI levels. However, given the finding that the patients who experienced infusion reactions had lower ITLs, it would be important to determine whether they have ATIs. Both the ITL and the ATI level would be important to know in patients who develop adverse events such as infusion reactions to infliximab. Therefore, for future research studies, and also for clinical practice, it would be important to measure ATIs in patients who experience infusion reactions or who have low ITLs.

A strength of the present study was that it prospectively analyzed ITLs in all patients receiving stable maintenance infliximab therapy who consented to participate during the study period, regardless of whether they experienced dermatological or infusion reactions. This is in comparison with study designs that analyze ITLs in patients who have levels drawn for specific reasons (eg, loss of response or adverse events) because the latter study design would introduce selection bias into the analysis.

Based on the results of the present study, we propose a strategy to manage infusion reactions by measuring ITLs in patients who develop infusion reactions; if the ITL is low, ATIs should be measured with consideration to switch drugs if the patient has a high level of ATI.

CONCLUSION

Our study has shown that ITLs are correlated with infliximab-associated adverse events. Measurement of the ITL in patients who develop dermatological and infusion reactions to infliximab, with subsequent adjustment of infliximab dose may be a strategy to manage these infliximab-associated adverse events.

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REFERENCES
