Prevention of infusion reactions to infliximab in pediatric patients with oral acetylsalicylic acid

Sirs,

For those with refractory forms of inflammatory bowel disease (IBD), the use of infliximab, a monoclonal TNF-α antibody, is emerging also in paediatric patients (1). For juvenile idiopathic arthritis (JIA) infliximab is not licensed although proven efficient (2). Infusion reactions ranging from flushing or urticaria to anaphylaxis (3) remain a poorly preventable type of adverse event (4). Recently, we showed that prevention of acute infusion reactions with acetaminophen and cetirizine was not effective (5). In some cases, methylprednisolone has not worked, either (5-7).

In 2004, Becker et al. reported a successful prevention of infusion reactions in 3 patients with acetylsalicylic acid (ASA) hypothesis that ASA prevented a niacin-like reaction dependent on cycooxygenase (COX)-mediated synthesis of prostaglandin D₂ (PGD₂) (8). Thus, we set up a prospective observational study to determine the efficacy of ASA in preventing infliximab-related infusion reactions in paediatric patients.

A total of 88 paediatric patients (37 JIA (or related) and 51 IBD) were treated with infliximab during a 67-week period between March 2009 and June 2010 in the Children’s Hospital, Helsinki, Finland. ASA was administered orally 30 minutes prior to infusion according to established weight-adjusted guidelines. Trained personnel administered the infliximab infusions non-blinded on weeks 0, 2 and 6 at introduction and at a median interval of 7.1 weeks (range 4–8 weeks) during maintenance. The median dose was 5.2 mg/kg (range 3–13).

The total number of infusions during the study period was 547 (induction n=113, maintenance n=434): 482 with routine ASA premedication and, due to protocol violations, 54 without ASA. One patient was given 11 infusions with intravenous methylprednisolone (IVMP) combined to ASA. The median number of infusions was 7.0 per patient.

Three children (3.4%) presented with an infusion reaction, while the total number of reactions was 6: 1 with routine ASA premedication (482 infusions, 0.2%), 1 without any premedication (54 infusions, 1.9%) and 4 (infusions 2–5/11) in the patient with IVMP and ASA. In our previous study(5), 11 (383 infusions) 2.9%) infusion reactions were seen in a total of 8 patients with acetaminophen and cetirizine (Table). Thirty-four children carried over from our previous study (5). Four of them had previously presented with an infusion reaction but here, only one of them had a reaction. This particular patient was the one treated with combined IVMP and ASA. One of the previously non-reacting 30 patients had a reaction under no premedication in this study.

Infliximab is of considerable importance in treating refractory IBD and has been successfully used in JIA. So far, infusion reactions remain poorly preventable. Recently, acetaminophen and cetirizine have proven ineffective (5) while the efficacy of glucocorticoids is debatable (6). Concomitant immunosuppressive therapy does not seem to prevent acute reactions either (4, 6, 9). The present study suggests that ASA could be considered for clinical trials as a prophylactic agent against infliximab-related reactions, with a mechanism possibly through inhibition of COX-mediated PGD₂ synthesis (8).

Of the few infusion reactions one was observed in a ASA-premedicated child and one in a child with no ASA. Though younger children are more prone to infusion reactions (4), two of the three patients who now experienced a reaction were older than 10 years of age.

Optimising dosage and timing, now determined by established dosages, could improve the usefulness of ASA as premedication. In irregular use with common doses serious adverse effects with ASA are unlikely, although aspirin-induced asthma (10) was suspected in one patient here.

In conclusion, in our preliminary study we report few infusion reactions with ASA as premedication and less when compared to our earlier results on acetaminophen and cetirizine. Neither glucocorticoids nor concomitant immunosuppression could prevent all reactions. Given the small number of in-

<table>
<thead>
<tr>
<th>Type of premedication</th>
<th>No. of reactions</th>
<th>No. of infusions</th>
<th>% of reactions per infusion</th>
<th>Significance vs. ASA, p-value</th>
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</thead>
<tbody>
<tr>
<td>ASA</td>
<td>1</td>
<td>482</td>
<td>0.2%</td>
<td>-</td>
</tr>
<tr>
<td>None</td>
<td>1</td>
<td>54</td>
<td>1.9%</td>
<td>0.1942</td>
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<tr>
<td>Previous study (ref. 5)</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Acetaminophen and cetirizine</td>
<td>11</td>
<td>383</td>
<td>2.9%</td>
<td>0.0017</td>
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</tbody>
</table>

B.

<table>
<thead>
<tr>
<th>Patient number</th>
<th>Diagnosis</th>
<th>Sex, age</th>
<th>Maintenance therapy</th>
<th>Premed.</th>
<th>Wks since previous infusion</th>
<th>No. of infusions (period)</th>
<th>Infliximab dose</th>
<th>Adverse reaction</th>
<th>First aid</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Crohn’s, asthma</td>
<td>F, 18</td>
<td>Prednisolone 10mg x1</td>
<td>ASA</td>
<td>3</td>
<td>2 (2)</td>
<td>300 mg, 5.0 mg/kg</td>
<td>Nausea, vomiting, dyspnea</td>
<td>Discontinuation</td>
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<tr>
<td>2</td>
<td>JIA + CATCH22</td>
<td>F, 13</td>
<td>MTX 15 mg/wk</td>
<td>ASA+ IVMP</td>
<td>6</td>
<td>31 (1)</td>
<td>200 mg, 6 mg/kg</td>
<td>Flushing, rhinorrhea</td>
<td>Cetirizine</td>
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<tr>
<td></td>
<td>Reaction 1</td>
<td></td>
<td></td>
<td>ASA+ IVMP</td>
<td>8</td>
<td>32 (1)</td>
<td>200 mg, 6.2 mg/kg</td>
<td>Urticaria, flushing</td>
<td>Cetirizine</td>
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<td>Reaction 2</td>
<td></td>
<td></td>
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<td>8</td>
<td>33 (1)</td>
<td>200 mg, 5.7 mg/kg</td>
<td>Flushing</td>
<td>None</td>
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<td>Reaction 3</td>
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<td></td>
<td>ASA+ IVMP</td>
<td>6</td>
<td>34 (1)</td>
<td>200 mg, 5.6 mg/kg</td>
<td>Nausea, flushing</td>
<td>None</td>
</tr>
<tr>
<td>3</td>
<td>JIA + uveitis</td>
<td>M, 9</td>
<td>None</td>
<td>None</td>
<td>6</td>
<td>39 (1)</td>
<td>100 mg, 3.4 mg/kg</td>
<td>Urticaria, dyspnea, flushing</td>
<td>Oxygen, Ringer, IVMP, discontinuation</td>
</tr>
</tbody>
</table>

JIA: Juvenile idiopathic arthritis; MTX: methotrexate; ASA: acetylsalicylic acid; IVMP: intravenous methylprednisolone.
Letters to the Editors

fusion reactions, and the small number of patients with no premedication, a controlled clinical trial is warranted.

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References