Letters to the Editors

Prevention of infusion reactions to infliximab in paediatric 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) hypothesising that ASA prevented a niacin-like reaction dependent on cyclooxygenase (COX)-mediated synthesis of prostaglandin D_2 (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 A. Infliximab infusions and reactions to infliximab in relation to premedication in the current study (547 infusions in 88 paediatric patients) and previous study(5) with acetaminophen and cetirizine (383 infusions in 65 patients). **B.** Acute adverse events observed during the current study.

A.

Type of premedication	No. of reactions	No. of infusions	% of reactions per infusion	Significance *vs*. ASA, *p*-value
ASA	1	482	0.2%	–
None	1	54	1.9%	0.1942
Previous study (ref. 5)				
Acetaminophen and cetirizine	11	383	2.9%	0.0017

B.

Patient number	Diagnosis	Sex, age	Maintenance therapy	Premed.	Wks since previous infusion	No. of infusions (period)	Infliximab dose	Adverse reaction	First aid
1	Crohn's, asthma	F, 18	Prednisolone 10mg x1	ASA	3	2 (2)	300 mg, 5.0 mg/kg	Nausea, vomiting, dyspnea	Discontinuation
2	JIA + CATCH22	F, 13							
Reaction 1			MTX 15 mg/wk	ASA+ IVMP	6	31 (1)	200 mg, 6 mg/kg	Flushing, rhinorrhea	Cetirizine
Reaction 2			MTX 15 mg/wk	ASA+ IVMP	8	32 (1)	200 mg, 6.2 mg/kg	Urticaria, flushing	Cetirizine
Reaction 3			MTX 15 mg/wk	ASA+ IVMP	8	33 (1)	200 mg, 5.7 mg/kg	Flushing	None
Reaction 4			MTX 15 mg/wk	ASA+ IVMP	6	34 (1)	200 mg, 5.6 mg/kg	Nausea, flushing	None
3	JIA + uveitis	M, 9	None	None	6	39 (1)	100 mg, 3.4 mg/kg	Urticaria, dyspnea, flushing	Oxygen, Ringer, IVMP, discontinuation

JIA: Juvenile idiopathic arthritis; MTX: methotrexate; ASA: acetylsalicylic acid; IVMP: intravenous methylprednisolone.

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

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