Hypoglycaemia following JAK inhibitor treatment in patients with diabetes

Janus kinase inhibitors (JAKi) are effective drugs for the treatment of several immune-mediated inflammatory diseases and are increasingly prescribed.

The Netherlands Pharmacovigilance Centre Lareb received an adverse drug reaction (ADR) report of a potential glucose lowering effect in a 54-year-old male patient with diabetes mellitus type 1 (DM1) using baricitinib (4 mg daily) for rheumatoid arthritis (RA). Within 2 weeks after baricitinib initiation, this patient had to reduce the dosage of both insulin degludec (from 18 units to 14 units) and insulin aspart in order to prevent hypoglycaemia. Concomitant medication included methotrexate, tiotropium/olodaterol nebuliser and beclomethasone aerosol. When baricitinib was temporarily discontinued for 6 weeks due to a respiratory tract infection, the insulin dosages had to be increased, whereas insulin dosages needed to be reduced again after restarting baricitinib. The onset of glucose decrease shortly after initiation of JAKi treatment and recurrence after rechallenge with baricitinib suggests a causal relationship. Glucose lowering is not a labelled ADR and no warning for patients with diabetes is mentioned in the European or FDA product information of baricitinib, tofacitinib, upadacitinib and filgotinib. A comparable case has been published concerning a 71-year-old female patient with RA that was complicated by systemic sclerosis and DM1. This patient was resistant to multiple disease-modifying anti-rheumatic drugs but was successfully treated with baricitinib, with concomitant use of prednisolone for 3 weeks and methotrexate. In addition to improvements in RA and skin sclerosis, the required daily dose of insulin decreased from 17 to 11 units and did not increase for up to 1 year. The glycated haemoglobin (HbA1c) level decreased from 57 mmol/mol to 46 mmol/mol.

To further investigate the development of hypoglycaemia as potential ADR of JAKi, we collected and analysed ADR reports of tofacitinib, baricitinib, upadacitinib and filgotinib with Medical Dictionary for Regulatory Activities preferred terms ‘Hypoglycaemia’ or ‘Blood glucose decreased’ from EudraVigilance, the European Medicines Agency Pharmacovigilance database. From initiation until 17 September 2021, EudraVigilance included 39 671 ADR reports concerning JAKi. Out of these, 43 reports concerned baricitinib, tofacitinib or upadacitinib in patients with reported DM and/or with anti-diabetic drugs as concomitant medication (table 1). In 9 out of 43 reports (21%), one or more other drugs were suspected

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**Table 1** Suspected adverse drug reaction (ADR) reports indicating hypoglycaemia in patients with diabetes using a JAK inhibitor in the EudraVigilance database

<table>
<thead>
<tr>
<th>Concomitant Medication</th>
<th>Tofacitinib N (%)</th>
<th>Baricitinib N (%)</th>
<th>Upadacitinib N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insulin</td>
<td>15 (5)</td>
<td>24 (13)</td>
<td>3 (7)</td>
</tr>
<tr>
<td>Other antidiabetic</td>
<td>23 (10)</td>
<td>11 (5)</td>
<td>2 (4)</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>20 (9)</td>
<td>4 (2)</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Glucocorticoid</td>
<td>18 (8)</td>
<td>12 (6)</td>
<td>2 (4)</td>
</tr>
<tr>
<td>Other</td>
<td>11 (5)</td>
<td>3 (2)</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Not reported</td>
<td>4 (2)</td>
<td>3 (2)</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Reaction leading to hospitalisation</td>
<td>2 (2)</td>
<td>2 (2)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Time to onset after start of JAKi:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Within 1 month</td>
<td>8 (5)</td>
<td>16 (9)</td>
<td>2 (5)</td>
</tr>
<tr>
<td>2–6 months</td>
<td>4 (3)</td>
<td>12 (7)</td>
<td>2 (5)</td>
</tr>
<tr>
<td>More than 6 months</td>
<td>2 (1)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Not reported</td>
<td>4 (3)</td>
<td>10 (6)</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Drug withdrawal</td>
<td>5 (3)</td>
<td>1 (1)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Dose adjustments</td>
<td>1 (1)</td>
<td>1 (1)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Other</td>
<td>1 (1)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

No reports of filgotinib.

*Colitis ulcerative, Baricitinib: neuroendometritis, COVID-19.
†In one case of baricitinib, both hypoglycaemia and decreased blood glucose were reported.
‡Tofacitinib: metformin: 3; glimepiride, pioglitazone and vildagliptin: 1; sitagliptin: 1; gliclazide, saxagliptin and metformin: 1; glimepiride and sitagliptin: 1. Baricitinib: metformin: 1. Upadacitinib: pioglitazone, glipizide and metformin: 1; sitagliptin and gliclazide: 1.
*JAK, Janus kinase inhibitors; MedDRA, Medical Dictionary for Regulatory Activities.
Additionally, it has been demonstrated in preclinical models that DM1 and DM2 have been fully elucidated, physicians should be aware of the potential glucose lowering effect when starting a JAKi in patients with diabetes.

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Figure 1 The JAK/STAT pathway involved in pancreatic β cells, based on figure 4 of Gurzov et al’s work. IFN-γ, interferon-γ; IFNR, interferon receptor; JAK, Janus kinase; STAT, signal transducer and activator of transcription.

β-cell

Cytokines

Apoptosis

STAT1

P

IFN-γ

IFAK

JAK inhibitors

Figure 1

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While risk factors and comorbidities associated with gout are well established in adults, few studies have examined gout in children. There is no treatment guideline for juvenile gout and it is unclear how to manage this condition safely and effectively.

Clinical characteristics of juvenile gout and treatment response to febuxostat from 2016 to 2020. We also present data on the efficacy of febuxostat in patients with juvenile gout evaluated in our centre between 2016 and 2020. Here, we describe the clinical characteristics of 111 children. Here, we describe the clinical characteristics of 111 children. 

- Comparison of joint involvement in adults (n=533) and children (n=111) after 1 month and 3 months of febuxostat therapy.
- Box indicates median and IQR and whiskers denote 5th–95th percentile.
- *P<0.05, **p<0.01, ***p<0.001,

Current prednisolone (n=9), current non-steroidal anti-inflammatory drugs (n=24), current colchicine (n=9), and current cyclo-oxygenase-2 (COX-2) inhibitors (n=12) were comorbidities of gout in adults but not children.

In patients with juvenile gout (interval to tophi development: mean 1.5 years in children vs 7.5 years in adults; online supplemental data), tophi developed more rapidly in children vs adults (28% vs 24%), and tophi developed more rapidly in females vs males (28% vs 24%).


Clinical characteristics of gout in children and efficacy of febuxostat therapy. (A) Comparison of joint involvement in adults (n=533) and children (n=111) after 1 month and 3 months of febuxostat therapy. (B) Birefringent crystals in the synovial fluid and tophi associated with juvenile gout. (C) Tophi in third distal interphalangeal joint of a patient with juvenile gout. (D) Light microscopy image of synovial fluid birefringent crystals from patient with juvenile gout. (E) Serum uric acid levels in patients with juvenile gout at baseline (n=36), 1 month (n=37) and 3 months (n=24) after initiation of febuxostat therapy. 

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3. Collotta D, Fabbri L, Hayashida N, et al. PO5104: Clinical characteristics of gout in children and efficacy of febuxostat therapy. (A) Comparison of joint involvement in adults (n=533) and children (n=111) after 1 month and 3 months of febuxostat therapy. (B) Birefringent crystals in the synovial fluid and tophi associated with juvenile gout. (C) Tophi in third distal interphalangeal joint of a patient with juvenile gout. (D) Light microscopy image of synovial fluid birefringent crystals from patient with juvenile gout. (E) Serum uric acid levels in patients with juvenile gout at baseline (n=36), 1 month (n=37) and 3 months (n=24) after initiation of febuxostat therapy.