Medicines & Healthcare products Regulatory Agency

DRUG SAFETY UPDATE (DSU)

Thiopurines and intrahepatic cholestasis of pregnancy

Specialisms: *GI, hepatology and pancreatic disorders, rheumatology, dermatology, haematology and oncology, immunosuppression and transplantation, obstetrics, gynaecology and fertility, pregnancy, cancer.*

Summary

Intrahepatic cholestasis of pregnancy (ICP) has been rarely reported in patients treated with azathioprine products and is believed to be a risk applicable to all drugs in the thiopurine class (azathioprine, mercaptopurine and tioguanine). Cholestasis of pregnancy associated with thiopurines tends to occur earlier in pregnancy than non drug-induced cholestasis of pregnancy, and elevated bile acid levels may not reduce with ursodeoxycholic acid.

Advice for Healthcare Professionals:

- cholestasis of pregnancy has rarely been reported in association with azathioprine therapy
- this risk is believed to also apply to the other thiopurine drugs, mercaptopurine and tioguanine
- it may occur earlier in pregnancy than non drug-induced cholestasis of pregnancy, and it may not respond to ursodeoxycholic acid
- withdrawal or dose reduction of the thiopurine drug may improve liver function tests
- remain vigilant to signs and symptoms of ICP in pregnant patients taking thiopurines and discuss any concerns with clinicians managing the patient's immunosuppressant therapy and a hepatologist, as necessary
- if cholestasis of pregnancy occurs, a case-by-case assessment is required to determine the appropriate course of action. Consider the risks and benefits of remaining on the product against the risks and benefits of stopping.
- in patients with ICP, measure serum bile acids to identify pregnancies at particular risk of spontaneous preterm birth (≥40uM) or stillbirth (non-fasting serum bile acids ≥100uM)

Advice for Healthcare Professionals to Provide to Patients:

- talk to your doctor or midwife immediately if you experience symptoms of cholestasis of pregnancy which include intense itching without a rash, nausea, and loss of appetite
- do not stop taking your medication unless advised to do so by your doctor or midwife

Background

The thiopurines include azathioprine, 6-Mercaptopurine and thioguanine (also known as tioguanine). Their uses are in anticancer indications, primarily leukaemia, and immunosuppression to treat inflammatory disorders such as inflammatory bowel diseases (IBD) and to increase graft survival following organ transplant.

Thiopurines should only be used in pregnancy where a careful benefit/risk assessment for the individual patient has been made.

A risk of developing intrahepatic cholestasis of pregnancy (ICP) has been identified from a small number of case reports in the scientific literature. ICP has been reported in some pregnant patients treated with azathioprine and mercaptopurine and, due to similar metabolic pathways utilised by thiopurines, this risk is believed to be applicable to all drugs in the thiopurine class (azathioprine, mercaptopurine and tioguanine).

For context, the occurrence of thiopurine-induced ICP is thought to occur much less frequently than non thiopurine-induced ICP, which occurs in roughly 1 in every 150 pregnancies.

Case reports occur mainly in patients being treated for IBD or in transplant recipients. In many cases, ICP associated with thiopurine treatment has developed earlier in pregnancy than typical non drug-induced ICP and in some cases bile acid levels did not reduce with ursodeoxycholic acid. However, in some cases, improvement in bile acid and liver function did occur on stopping thiopurine.

Reported cases were often serious with some resulting in fetal death. However, reporting bias may result in the more serious cases being reported.

Early diagnosis and discontinuation or dose reduction of the thiopurine may minimise adverse effects on the fetus. A thorough assessment of the important benefits of treatment of the underlying disease against the risk of thiopurines to the mother and the effects of ICP on the fetus should be performed if ICP is confirmed.

In patients with ICP, measure serum bile acids to identify pregnancies at particular risk of spontaneous preterm birth (≥40uM) or stillbirth (non-fasting serum bile acids ≥100uM).

Patients should be made aware of the signs and symptoms of ICP, which include intense itching without a rash, nausea, and loss of appetite, and advised to seek healthcare professional advice immediately if they experience these symptoms.

Reporting advice

Healthcare professionals, patients, and caregivers are asked to submit reports using the Yellow Card scheme electronically using:

- the Yellow Card website.
- the Yellow Card app; download from the Apple App Store or Google Play Store
- some clinical IT systems for healthcare professionals (EMIS, SystmOne, Vision, MiDatabank, and Ulysses)

When reporting suspected adverse drug reactions, please provide as much information as possible, including information about medical history, any concomitant medication, onset timing, and treatment dates.

Additional information

You can sign up to receive email notifications for Drug Safety Updates.

You can sign up to receive our monthly roundup of safety communications.

For any enquiries, please contact info@mhra.gov.uk

For further information

1. British Society of Gastroenterology consensus guidelines on the management of inflammatory bowel disease in adults
2. British Society for Rheumatology guideline on prescribing drugs in pregnancy and breastfeeding: immunomodulatory anti-rheumatic drugs and corticosteroids

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