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Cases of necrotising fasciitis associated with the use of bevacizumab (Avastin®)

Rare cases of necrotising fasciitis, including fatal cases, have been observed worldwide in patients treated with bevacizumab. The majority of the cases were secondary to wound healing complications, gastrointestinal perforation or fistula formation.

Necrotising fasciitis is a rare, but life-threatening soft tissue infection, characterised by rapidly spreading necrosis of the superficial fascia and subcutaneous tissue. Immunocompromised patients have an increased risk of developing necrotising fasciitis.

As a doctor you should be aware of the following:

- Bevacizumab should be discontinued immediately upon diagnosing necrotising fasciitis, and appropriate treatment should be initiated.

The summary of product characteristics for Avastin® will be updated, and a letter of information has been sent to relevant doctors. See the Danish Health and Medicines Authority's website: *Direct Healthcare Professional Communication (DHPC) sent to healthcare professionals.*

Indication for bevacizumab
Bevacizumab in combination with chemotherapy is indicated for the treatment of several types of cancer: Metastatic colorectal cancer, metastatic breast cancer, non-small cell lung cancer, advanced and/or metastatic renal cell carcinoma, epithelial ovarian cancer, fallopian tube cancer, and primary peritoneal cancer.

Tolvaptan (Samsca®) and potential risk of hepatic injury

Drug-induced hepatic injury has been observed in a clinical study involving tolvaptan[1]. The study assessed the effect on a potential indication (autosomal dominant polycystic kidney disease). Hepatic injuries were observed during long-term use of tolvaptan at higher doses than when used for the approved indication.

In other clinical studies involving tolvaptan, including studies supporting the approved indication, increased incidence of hepatic injury, compared with placebo, was not observed. However, these data are not adequate to exclude the possibility that patients receiving tolvaptan for its indicated use have a higher potential increased risk of liver injury.

As a doctor you should be aware of the following:

- Hepatic function tests should be performed immediately in patients receiving tolvaptan, if they experience symptoms that may indicate liver injury, including fatigue, anorexia, right upper abdominal discomfort, dark urine or jaundice.
- If hepatic injury is suspected, tolvaptan must be discontinued immediately, appropriate treatment must be initiated, and investigations must be performed to determine the possible cause. Tolvaptan should not be re-initiated in patients unless the cause of the observed hepatic injury is definitively established to be unrelated to the use of tolvaptan.

The summary of product characteristics for Samsca® has been updated with information on the potential risk of hepatic injury and information on the management of patients with symptoms and signs of hepatic injury.

In May, a letter of information was sent to doctors and other healthcare professionals. Additionally, the letter is available on the Danish Health and Medicines Authority's website: *Direct Healthcare Professional Communication (DHPC) sent to healthcare professionals.*

Indication for tolvaptan
Treatment of adult patients with hyponatraemia secondary to syndrome of inappropriate antidiuretic hormone secretion (SIADH).

Dosage:
Should be initiated at a dose of 15 mg once daily. The dose may be increased to a maximum of 60 mg once daily, depending on tolerance.

Report adverse reactions to the Danish Health and Medicines Authority on: *http://laegemiddelstyrelsen.dk/en/topics/side-effects-and-trials/side-effects/report-a-side-effect-or-incident/humans*

1) Torres VE, Chapman AB, Devuyst O, Gansevoort RT, Grantham JJ, Higashihara E, Perrone RD, Krasa HB, Ouyang J, Czerwiec FS; the TEMPO 3:4 Trial Investigators. Tolvaptan in Patients with Autosomal Dominant Polycystic Kidney Disease. N Engl J Med. 2012 Nov 3. [Epub ahead of print]

Liver fibrosis reported as a potential adverse reaction from the use of methotrexate

In March, the Danish Health and Medicines Authority (DHMA) received an adverse reaction report concerning a patient with psoriasis vulgaris and arthritis who was diagnosed with liver fibrosis following two months of treatment with methotrexate.

The patient had been treated with 15 mg methotrexate once weekly for two months. The medicine showed good clinical efficacy, so the dose was reduced to 10 mg once weekly. However, immediately after the dose reduction, P-III-NP levels were elevated in blood samples. A fibrosis scan revealed that the patient suffered from liver fibrosis.

The DHMA has received a total of nine adverse reaction reports of possible development of liver fibrosis/liver cirrhosis in association with the use of methotrexate.

As a doctor you should be aware of the following:
Hepatic toxicity such as cirrhosis and fibrosis may be present, even when there are no correlative changes in the hepatic function test. Sometimes, these changes can only be identified by biopsy.

- Methotrexate should not be initiated in case of presence of abnormalities in a hepatic function test or liver biopsy during therapy. Treatment with methotrexate should be discontinued in case of detection of abnormalities. The abnormalities may disappear again within two weeks, after which treatment may be re-initiated based on the doctor's assessment.

- Liver biopsy should be considered in patients with risk factors such as high alcohol consumption, continuous increase in hepatic enzymes or marker for fibrosis (P-III-NP), previous liver disease, family history of hereditary liver disease, diabetes mellitus, obesity and prior exposure to hepatotoxic drugs or substances.

Indication for methotrexate

Used:
– Anti-rheumatically: Active rheumatoid arthritis in adults that cannot be controlled with anti-inflammatory substances (NSAIDs).
– for psoriasis: Disseminated chronic psoriasis, when other treatments have failed.
– Cytostatically.

All cases referred to in the article originate from the Danish Health and Medicines Authority's adverse reaction database.
The cases have been forwarded to all relevant pharmaceutical companies and to the EudraVigilance database.
Therefore, pharmaceutical companies should not report these cases to the Danish Health and Medicines Authority.

The European Medicines Agency (EMA) has started a review of the efficacy and risks of combined use of renin-angiotensin system (RAS)-blocking agents

The review was started due to concerns that combining several RAS-acting agents may increase the risk of the adverse reactions hyperkalaemia, hypotension and renal insufficiency and that the efficacy may not be increased compared with using one RAS-acting agent alone.

The evaluation is based on a number of published studies, including a recent meta-analysis of 33 studies. Read the article *here.*

The EMA has previously evaluated the combination of aliskiren (direct renin inhibitor) with an angiotensin converting enzyme inhibitor (ACE inhibitor) or an angiotensin receptor blocker (ARB) and found that these combinations cannot be recommended. Read the article on aliskiren in *Danish Pharmacovigilance Update from March 2012*.

See the press release on the *EMA's website*.

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