Gangrene (2 cases), cyanosis (2 cases), cyanosis peripheral, peripheral vascular disease (2 cases) and peripheral ischaemia are other ADRs listed on these reports.

The PDR lists vasculitis as an event occurring in clinical trials with a frequency of 1-3%. There is no mention of vasculitis in the UK or Swedish SPCs for Arava. A search on PubMed found one reference to a published case report of a patient developing vasculitis with leflunomide[2]. The underlying disease in patients taking leflunomide may produce vasculitis and give effects similar to the symptoms of DIC . While there is a risk of confounding by indication in this instance the evidence of leflunomide being associated with vasculitis and disturbances of the coagulation processes seems important to investigate further.

the UMC has received a case report from the Netherlands Pharmacovigilance Foundation Lareb in which leflunomide was suspected of causing ischaemic necrosis of the fingertips. The necrosis in this case (see below) probably was not due to DIC as the patient is reported having normal thrombocyte count. However, platelet turnover can be increased in low grade DIC without evidence of thrombocytopenia and it may be relevant to consider it in context with the above.

It is clear that the possible clotting and vascular effects of leflunomide will need careful evaluation, given the range of disease which is likely to be treated.

Leflunomide - ischaemic necrosis of the fingertips. A case report from Lareb

A severe adverse reaction; ischaemic necrosis of the fingertips (not included in the SPC for leflunomide) was reported to the Netherlands Pharmacovigilance Foundation (Lareb). It concerned a 74-year-old woman, diagnosed for rheumatic factor-negative, APF-positive, erosive nodular rheumatoid arthritis in 1976. She has had various operations on different joints in the past. She was treated for rheumatic arthritis with hydroxychloroquine, D-penicillamine, methotrexate, sulfasalazine, prednisone and aurothioglucose.

As the patient became nauseous when using aurothioglucose, she was treated with leflonumide 20 mg daily instead. Upon starting leflunomide she experienced painful fingertips, two of which turned black after 2 weeks. No swelling occurred. She was hospitalized, also for pain and swelling in many joints caused by active rheumatoid arthritis. Both cardiologist and vascular surgeon were unable to find an explanation for the necrosis of the fingertips. Leflunomide was stopped immediately (no washout-period). Concomitant medication was continued: acetylacetic acid 100 mg daily, rofecoxib, 25 mg daily, prednisone 10 mg daily, omeprazole 20 mg daily, ferrosulfate 5 times a week and [metipranolol plus pilocarpine] (Normoglaucon) eyedrops.

Relevant findings from hospital examinations: blood pressure 140/85 mm Hg, BSE 70 mm/hour, leucocytes 11.3 x 10^9/L, thrombocytes 378 x 10^9/L, liver enzymes no abnormalities, lupusanticoagulans negative, cryoglobulines negative, cholesterol 3.8 mmol/L, HDL-cholesterol 1.06 mmol/L, triglycerid 0.95 mmol/L, LDL cholesterol 2.3

mmol/L. Initially the patient was treated with acetylacetic acid and nifedipine 30 mg daily, resulting in only minor improvement of the symptoms. After intravenous administration of epoprostenol further recovery set in, 11 days after hospitalization. Pain decreased and necrosis slowly demarcated.

Other cases

Lareb received 55 reports of suspected adverse reactions to leflunomide in 32 patients between September 1999 and May 2001. The starting dose for leflunomide is 100 mg daily during 3 days, followed by a maintenance dose of 10-20 mg daily. Six of the reports concerned the 100 mg dose, 44 reports referred to the 20 mg dose and the remaining 5 related to 10 mg leflunomide daily. Lareb received 2 reports of disturbed peripheral blood circulation among which the present case, described above.

Assessment

Several possible explanations can be given for the interference in the peripheral arterial blood circulation in the present case. A direct effect on the vascular wall by increased thrombocyte activity as is the case with SLE, diabetes mellitus, hypertension and hyperlipidemia, could not be diagnosed. About 7 weeks after starting leflunomide the patient was hospitalized upon reactivation of the rheumatoid arthritis. The therapeutic effect of leflunomide usually commences not until after 4 to 6 weeks and increases until over 4 to 6 months. Serious forms of rheumatoid arthritis can involve rheumatoid vasculitis, with digital gangrene as a possible complication. The reporting rheumatologist considered this explanation unlikely, since other clinical symptoms diagnostic of digital gangrene, associated with rheumatoid arthritis, were missing (e.g. nailfold lesions, infarcts). Other serious adverse reactions to leflunomide (serious pancytopenia and serious allergic skin reactions) appeared to occur especially when simultaneously treated with methotrexate, as was the case here. It is not possible to describe a causal connection between the use of leflunomide and ischaemic necrosis, on the basis of this case.

References

1. Online Prescribing information, Arava® homepage
2. Holm EA, Balslev E, Jemec GB. Vasculitis Occurring during Leflunomide Therapy. Dermatology 2001;203(3):258-9