Problem-based Learning

CASE ESSAY 6

61-year-old Man with Psoriasis and Sudden Muscle Pain

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A 61-year-old Caucasian man was referred for the treatment of psoriasis. He presented with a 15-year history of plaque psoriasis and mild arthritis symptoms, particularly in the small joints in the hands and in the spinal column. His medical history included moderate hypertension treated with ACE-blockers and hypercholesterolemia. During the past months he experienced a very rapid progression of his psoriasis. On physical exam we found psoriatic erythroderma with infiltrated psoriasis plaques in the scalp, palms and soles. There was onycholysis in all fingernails. The general condition was good, blood pressure 190/90 and the temperature 37.0°C.

We are presented with a patient with previously stable plaque psoriasis that during several months progressed into erythroderma. This patient presented also with typical psoriasis co-morbidities including hypertension, hypercholesterolemia and psoriatic arthritis. Psoriatic erythroderma should be treated promptly due to the risk of serious infectious complications. Methotrexate, cyclosporine or combination of both would be the treatment of choice.

Blood tests were normal apart from mild hyperosinophilia ($1.59x10^9$/l), lever and kidney function were within the normal range. The patient reported that he had previously been treated with 25 mg methotrexate weekly and with acitretin with no effect on psoriasis. Because of this fact the treatment with cyclosporine (Sandimmun Neoral®, 4 mg/kg, 150 mg bid) was initiated.

We should monitor this patient carefully for side effects of cyclosporine. It has been well documented that older patients with hypertension have a higher risk of nephrotoxicity and aggravation of hypertension. Moreover, it should be determined whether the patient has any erosive articular lesions. If so, treatment with anti-TNFα biologic agents will be indicated.

Neither X-rays of hands and spinal column nor bone scintigraphy revealed any pathological alterations. Psoriasis cleared rapidly on the treatment with cyclosporine. Because of constantly elevated blood pressure to 200/100 mmHg the diuretics and calcium-channel blocker (Verapamil) were added to intensify the antihypertensive treat-

Table: *Less well-known side effects of cyclosporine.*

Side-effect	Symptoms
Thrombotic thrombocytopenic purpura-hemolytic uremic syndrome	purpura, kidney failure
Posterior leukoencephalopathy syndrome	headache, altered mental functioning, seizures, cortical blindness and other visual disturbances, ocular flutter
Diffuse encephalopathy	neurologic cerebellar symptoms, extrapyramidal symptoms, pyramidal weakness
Brain macrohemorrhages	headache, focal neurologic deficit, visual disturbances
Hyperlipidemia	increased low density lipoprotein and total cholesterol
Calcineurin-inhibitor induced pain syndrome (CIPS)	severe pain in the feet
B-cell lymphoproliferative disorder	adenopathy and/or enlargement of tonsillae due to reactivation of Epstein-Barr virus
Cyclosporin A-associated myopathy	myalgia or muscle weakness and plasma creatine kinase elevation, probably due to inhibition of mitochondrial oxidation
Alopecia	Alopecia areata and alopecia totalis

ment. Because of mildly elevated low density lipoprotein-cholesterol (4.6 mM/l) simvastatin treatment (40 mg q.d.) was initiated.

There is a potential interaction with calcium channel blockers that can elevate blood concentrations of cyclosporine. In view of the rapid clinical response and blood pressure problems the dose of cyclosporine should probably be reduced.

The cyclosporine dose was reduced to 200 mg. Blood pressure was stable around 140/90. Shortly after tapering of cyclosporine the patient experienced very severe, generalized muscle pain which progressed over 5 days. He was referred acutely to the medical emergency unit where blood tests revealed markedly elevated creatine kinase (45924 U/l, normal 50–270), predominantly muscle fraction (59 U/l, normal <5) and lactate dehydrogenase (855 U/l). The diagnosis of DRUG-INDUCED RHABDOMYOLYSIS was made and treatment with forced diuresis was initiated. After a week of hospitalization the patient recovered completely and his muscle enzymes were back to normal.

Diagnosis

DRUG-INDUCED RHABDOMYOLYSIS (CYCLOSPORINE AND SIMVASTATIN)

Comment

The HMG-CoA inhibitors (statins) are the cornerstone in the treatment of hypercholesterolemia. Since many patients with psoriasis present with dyslipidaemias they are also likely to be treated with statins. Interactions between cyclosporine and statins are well described in the literature, but are often overseen in clinical practice. A recent survey revealed that harmful interactions with cyclosporine comprise 1.6% of all side-effects of statins (1). This risk is further increased in patients treated concomitantly with cytochrome P450 (CYP) 3A4 inhibitors or digoxin (1). Not all statins have the same potential of producing side effects. The proportion of patients with a potential drug-statin interaction was 12.1% for simvastatin, 10.0% for atorvastatin, 3.8% for fluvastatin and 0.3% for pravastatin (1). Interaction with cyclosporine is probably also specific for a given species of statins as exemplified by a recent report of a 59-year-old woman treated with cyclosporine and pravastatin, who after switching to simvastatin developed severe rhabdomyolysis (3). According to the FDA report, pravastatin, lovastatin, and fluvastatin have the lowest incidence of side-effects (2–10%) whereas simvastatin and cerivastatin are less well tolerated (approx. 30% incidence of side-effects) (3). Therefore, in my opinion, patients receiving cyclosporine should be in the first place treated with the low-risk statins such as lovastatin, fluvastatin and pravastatin.

Further reading

1. Ratz Bravo AE, Tchambaz L, Krahenbuhl-Melcher A, Hess L, Schlienger RG, Krahenbuhl S. Prevalence of potentially severe drug-drug interactions in ambulatory patients with dyslipidaemia receiving HMG-CoA reductase inhibitor therapy. Drug Saf 2005; 28: 263–275.
2. Sochman J, Podzimkova M. Not all statins are alike: induced rhabdomyolysis on changing from one statin to another one. Int J Cardiol 2005; 99: 145–146.
3. Omar MA, Wilson JP. FDA adverse event reports on statin-associated rhabdomyolysis. Ann Pharmacother 2002; 36: 288–295.