Ciclosporin and posterior reversible encephalopathy syndrome

Introduction

Ciclosporin (Neoral®) is indicated *after organ transplantation to prevent the rejection of a transplanted solid organ*, where ciclosporin can be used as monotherapy or in combination with low doses of corticosteroids or other immunosuppressive medication. Furthermore ciclosporin is indicated *after bone marrow transplantation for the prophylaxis of graft rejection, and for the prophylaxis or treatment of "graft-versus-host" (GVH) reaction.* In addition ciclosporin is indicated *for very severe psoriasis* when other therapies had not been effective, very severe therapy-resistant *atopical dermatitis* in adults, steroid-resistant *nephrotic syndrome as a result of glomerular pathology*, and *very severe rheumatoid arthritis* in adults when other therapies had not been effective [1].

Ciclosporin is a cyclic polypeptide consisting of 11 amino acids. It is a potent immunosuppressive agent. Preclinical studies showed that ciclosporin inhibits the development of cell responses, including the rejection of allogenic grafts, skin hypersensitivity of the delayed type, " graft versus host " reactions and T cell-dependent antibody formation. At cellular level, ciclosporin inhibits the production and release of lymphokine, including interleukin-2. It appears that ciclosporin blocks the resting lymphocytes in the G0 or G1 phase of the cell cycle and inhibits the antigen induced release of lymphokines from activated T-cells.
The available data suggest that ciclosporin has a specific and reversible effect on lymphocytes. In contrast to cytotoxic drugs, ciclosporin has no clinically relevant effect on hematopoiesis [1].
Ciclosporin was granted marketing authorization in the Netherlands in 1983 [2].

Posterior reversible encephalopathy syndrome (PRES), also referred to as reversible posterior leukoencephalopathy syndrome (RPLS), is a clinical radiographic syndrome of heterogeneous etiologies that are grouped together because of similar findings on neuroimaging studies. The clinical syndrome is characterized by headaches, altered consciousness, visual disturbances and seizures.
The syndrome is not always reversible, and it is often not confined to either the white matter or the posterior regions of the brain [3].
The incidence of PRES is unknown and all age groups appear susceptible. PRES has been described in a number of medical conditions, with hypertensive encephalopathy, eclampsia, and the use of cytotoxic and immunosuppressant drugs being the most common. Another risk factor is renal disease [3].

It is important to recognize and treat this condition promptly, in preventing the permanent damage that can occur in this otherwise typically reversible condition [3].

Reports

From 1 August 2013 1999 until 20 February 2014 the Netherlands Pharmacovigilance Centre Lareb received two reports of PRES as the reported reaction, associated with ciclosporin.
Of encephalopathy as the reported reaction, associated with ciclosporin, Lareb received six reports in the period from 29 April 1999 until 6 December 2012.

The two reports with PRES as the coded reaction, are described here:

Case A (158347)
This serious spontaneous report from a specialist doctor concerns a male aged 71 years and older, with progressive renal failure following administration of ciclosporin for nephrotic syndrome with a latency of 1 month after start. The dose for ciclosporin was reduced, followed by improved renal function. About 1 year and 3 months after start of ciclosporin the patient was hospitalized because of atrial fibrillation which spontaneously converted to sinusrithm after rate control. During this hospitalization the patient experienced progressive hypertension, despite elevation of the antihypertensive medication. Then the patient experienced unwellness and a convulsion wherefore admission to the intensive care unit, eventually designated or as occipital ischaemic CVA, or as PRES (differential diagnosis: caused by moxifloxacin/ciclosporin or hypertension). The drug ciclosporin was withdrawn. The patient recovered. Concomitant medications were prednisolone, moxifloxacin, rifampicin.
The medical history indicates renal failure due to focal segmental glomerulosclerosis. Furthermore the medical history indicates total hip replacement. For wound infection the patient used moxifloxacin and rifampicin. The past drug therapy indicates risedronic acid with aggravated hip pain and alendronic acid with back pain.

Case B (168399)
This serious (hospitalisation) spontaneous report from a pharmacist concerns a female aged 51-60 years, with reversible posterior leukoencephalopathy syndrome (RPLS/PRES) resulting in seizures, following oral administration of ciclosporin, in a dosage of twice a day 275 mg, for immunosuppression in graft versus host disease after donor lymphocyte infusion, with a latency of 12 days after start. The patient was hospitalized for graft versus host disease after donor lymphocyte infusion. The patient was hospitalized for 5 weeks. CT en MRI 11 days after start of ciclosporin indicated RPLS. The CT scan 19 days after start of ciclosporin showed subarachnoidal bleedings and diffuse white matter abnormalities, and the patient had seizures. The drug ciclosporin was withdrawn and replaced by sirolimus. The seizures were treated with levatiracetam. The patient was recovering at the time the report was submitted to Lareb. Concomitant medications were pantoprazole, alendronic acid, posaconazole, levofloxacin, valaciclovir, calcium / colecalciferol, prednisone, levothyroxine sodium.
The medical history indicates multiple myeloma stage IIIa, allogeneic stem cell transplantation, donor lymphocyte infusion in the month before start of the reaction. The patient used ciclosporin in the past without a similar reaction.

In Case A the diagnosis PRES was considered possible, since the differential diagnosis also comprised ischaemic CVA. In addition, the patient also experienced hypertension, which made have played a role in the possible PRES. The report did not contain information whether a cerebral imaging was performed. In Case B the symptomatology of the patient and the image of PRES on the scans, were described. In this case a change in blood pressure was not described. The latencies of the two cases were very different: about 1 year and 3 months, and 12 days respectively. One patient recovered and the other patient was recovering at the time the report was submitted to Lareb, after withdrawal of ciclosporin.

The six reports received by Lareb, with encephalopathy as the reported reaction are listed in Table 1.
In three of these cases other possible causes of encephopathy were described:

Case 34796 concerned progressive multifocal leukoencephalopathy. Case 64031 concerned hyperammonemia in a mycobacterium genavense infection, where the patient experienced septic shock, ARDS, hepatic failure and encephalopathy among other symptoms. Case 159238 concerned encephalopathy, hyponatremia, hyperammonemia, and fever, and lumbar puncture revealed infection.

Table 1. Reports of encephalopathy associated with the use of ciclosporin

Patient, Number, Sex, Age, Source	**Drug, daily dose Indication for use**	**Concomitant Medication**	**Suspected adverse drug reaction**	**Time to onset, Action with drug outcome**
A 46582 F, 21-30 years Pharmaceutical Company	tacrolimus 4mg per day lung transplant, ciclosporin 100mg 2dd lung transplant	mycophenolate mofetil, prednisone, levonorgestrel/ethinyle stradiol	headache, vision blurred, encephalopathy, somnolence, hemianopia, blood pressure increased, nausea	not reported discontinued recovered
B 24478 M, 61-70 years Specialist doctor	ciclosporin 2dd 175 mg kidney transplant	amitriptyline, acetylsalic acid, omeprazole, isradipine, prednisone, furosemide	encephalopathy	2 years discontinued recovering
C 34796 M, Pharmaceutical Company	ciclosporin dose unknown lung transplant		cataract, encephalopathy, death nos	not reported unknown fatal
D 64031 F, 61-70 years	ciclosporin dose unknown renal transplant	prednisolone, mycophenolate mofetil	disseminated intravascular coagulation, renal failure, body temperature increased, lymphopenia, glasgow coma scale abnormal, septic shock, diarrhea, encephalopathy, normocytic anemia, acute respiratory distress syndrome, hyperammonemia, neutrophilia, hemoglobin low, palpitations, tachycardia, mycobacterial infection, consciousness decreased, spleen enlarged, myocardial infarction, hepatic failure, abdominal tenderness, lymphadenopathy	214 days unknown fatal
E 159238 F,	non specified blood stem cell transplant chronic lymphocytic leukaemia, ciclosporin dose	mycophenolic acid	encephalopathy	38 days no change recovered

	unknown, fludarabine dose unknown chronic lymphocytic leukaemia, non specified drug prophylaxis, mycophenolate mofetil dose unknown chronic lymphocytic leukemia			
F 84712 M, 2-4 years Specialist doctor	ciclosporin 2 dd 90 mg graft versus host disease	co-trimoxazole	encephalopathy	18 months discontinued recovered with sequelae

Other sources of information

SmPC

There is a variation between SmPCs of ciclosporin within The Netherlands concerning the way this adverse drug reaction is mentioned.
The Dutch SmPC of generic ciclosporin mentions as an uncommon (between 1/100 and 1/1,000) occurring adverse drug reaction: "Signs of encephalopathy such as convulsions, confusion, disorientation, decreased reactivity, irritability, insomnia, visual disturbances, cortical blindness, coma, paresis, cerebellar ataxia". Furthermore the Dutch SmPC of ciclosporin mentiones that with JCvirus associated progressive multifocal leukoencephalopathy (PML), has been observed in patients treated with cyclosporine. PRES is not specifically mentioned in the The Dutch SmPC of generic ciclosporin [4].
The SmPC of ciclosporin Neoral® mentiones as an uncommon (between 1/100 and 1/1,000) occurring adverse drug reaction: “Encephalopathy including Posterior Reversible Encefalopathiesyndrome (PRES), signs and symptoms such as convulsions, confusion, disorientation, decreased responsiveness, agitation, insomnia, visual disturbances, cortical blindness, coma, paresis, cerebellar ataxia” [1].

The US SmPC of the FDA mentions that encephalopathy, including Posterior Reversible Encephalopathy Syndrome (PRES), has been described both in post-marketing reports and in the literature. It is mentioned that manifestations include impaired consciousness, convulsions, visual disturbances (including blindness), loss of motor function, movement disorders and psychiatric disturbances. Furthermore it is describes that in many cases, changes in the white matter have been detected using imaging techniques and pathologic specimens. The US SmPC also describes that predisposing factors such as hypertension, hypomagnesemia, hypocholesterolemia, high-dose corticosteroids, high ciclosporin blood concentrations, and graft-versushost disease have been noted in many but not all of the reported cases. The SmPC mentions that the changes in most cases have been reversible upon discontinuation of ciclosporin, and in some cases improvement was noted after reduction of dose. Furthermore the SmPC adds that it appears that patients receiving liver transplant are more susceptible to encephalopathy than those receiving kidney transplant [5].

Literature

In 1996 PRES was first described as an entity. It was described that PRES has diverse causes, immunosuppressive drugs being one of the common precipitants. In four of the cases the use of cyclosporine was described [6].
Afterwards many more cases have been published reporting PRES associated with the use of cyclosporine.
An article by Teive et al described eight patients who received ciclosporin A after allogeneic bone marrow transplantation or as treatment for severe aplastic anemia who developed PRES. In six of these patients neurological dysfunction occurred preceded by or concomitant with high blood pressure and some degree of acute renal failure. When lowering the dose or withdrawal of ciclosporin the symptoms and neuroimaging abnormalities improved [7].
Two patients after pulmonary transplantation for cystic fibrosis, developed arterial hypertension, headache, visual trouble and generalized seizures with diffuse cortical and subcortical lesions predominantly in posterior regions. Disappearance of the symptoms after withdrawal of ciclosporin confirmed the diagnosis of cyclosporine-related PRES [8].
A 27-year old patient with collapsing focal glomerulosclerosis developed abrupt elevation of blood pressure and neurological symptoms 3 weeks after start of ciclosporin. An MRI showed scan lesions suggestive of PRES. Two months after withdrawal of ciclosporin the MRI had normalized [9].
PRES related to ciclosporin has also been described in two cases after heart transplantation. A 68-year old woman developed arterial hypertension, headache, visual disturbances, and generalized seizures at day 14 after start of ciclosporin and mycophenolate mofetil and prednisone, and lesions on MRI were visible. A 19-year old man developed acute headache and generalized seizures on day 44 after start of ciclosporin and prednisone, with lesions on MRI. Ciclosporin concentrations were therapeutic. Both patients recovered. In the first case ciclosporin had to be withdrawn to reverse the symptoms [10].
A 35-year old woman with SLE was described who developed PRES during ciclosporin use. Althought this patient also had transient elevated blood pressure 3 days before development of the neurological symptoms, the authors estimated that ciclosporin had a causative role in the development of PRES, based on elevated serum ciclosporin level and dramatic neurologic recovery after withdrawal of ciclosporin [11].
In a study of 660 renal pediatric patients 11 patients (8 males, 3 females, age 3-15 years) experienced PRES, in which in one patient high trough level of ciclosporin was measured and ciclosporin toxicity was considered a contributory factor [12].

Databases

Table 2. Reports of posterior reversible encephalopathy syndrome associated with ciclosporine in the Lareb, WHO and Eudravigilance database

Database	MedDRA PT	Number of reports	ROR (95% CI)
Lareb	Posterior reversible encephalopathy syndrome	2	-
WHO	“	158	68.1 (57.5 - 80.7)
Eudravigilance	“	279	32.4 (28.4 – 36.8)

Prescription data

Table 3. Number of patients using ciclosporin in The Netherlands between 2009 and 2013 [13].

Drug	2009	2010	2011	2012	2013
Ciclosporin	7,629	7,407	7,055	6,826	6,737

Mechanism
The pathogenesis of PRES remains unclear, but it appears to be related to disordered cerebral autoregulation and endothelial dysfunction. Different mechanisms might be etiologically important in different clinical situations. Ciclosporin is associated with the neurologic deficits of PRES. After renal toxicity, neurotoxicity is the most serious side effect with ciclosporin, which affects 25 percent to 59 percent of transplant patients. Hypomagnesemia, hypocholesterolemia, the vasoactive agent endothelin and hypertension have been implicated in facilitating ciclosporin neurotoxicity. Ciclosporin may exacerbate hypertension by inhibiting nitric oxide production. The symptoms of ciclosporin neurotoxicity resemble mitochondrial encephalopathy indicating an underlying mechanism of mitochondrial dysfunction [3]. In a previous study [14] in sixteen patients with neurologic injury attributed to cyclosporine therapy, the clinical and radiologic findings in patients showing the neurotoxic effects of ciclosporin appeared to be identical to those with hypertensive encephalopathy. In this study the only major factor associated with the neurotoxic effects of ciclosporin in all patients was systemic hypertension, although microangiopathic hemolytic anemia, thrombocytopenia, and hypoalbuminemia were common.

Discussion and conclusion

The Netherlands Pharmacovigilance Centre Lareb received a report of possible PRES and one of PRES, associated with the use of ciclosporin. Lareb also received three reports of encephalopathy in which no other causes of encephalopathy were described, so which might have indicated PRES. In the WHO database there are 158 cases present of PRES associated with ciclosporine, with a ROR of 68.1 (95% CI 57.5 - 80.7). In the Eudravigilance database there is the large number of 279 cases of PRES associated with cyclosporine present, with a ROR of 32.4 (95% CI 28.4 - 36.8). The FDA SmPC of ciclosporine also mentiones PRES in ciclosporin and provides an extensive explanation. The FDA SmPC mentions that encephalopathy, including PRES, has been described both in post-marketing reports and in the literature and it describes it's manifestations. The FDA SmPC also describes that changes in most cases have been reversible upon discontinuation of ciclosporin, and in some cases improvement was noted after reduction of dose [5].
Also in the literature many cases of PRES in ciclosporin have been described.
In the Dutch SmPCs there is a variation on mentioning PRES between different ciclosporin products.
Because of the possible reversibility of the serious condition of PRES, it is important that PRES is specifically mentioned in the SmPCs of ciclosporin.

As reported on the website of the European Medicines Agency (EMA), the EMA completed a review of Sandimmun and Sandimmun Neoral on 27 June 2013, and the Agency's Committee for Medicinal Products for Human Use (CHMP) concluded that there was a need to harmonise the prescribing information for Sandimmun® and Sandimmun Neoral® in the European Union (EU) [15]. In the Sandimmun Article-30 referral-Annex III PRES is specifically mentioned [16].

- Posterior Reversible Encephalopathy Syndrome (PRES), should be mentioned in the SmPC of all ciclosporin products

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This signal has been raised on October 2014. It is possible that in the meantime other information became available. For the latest information, including the official SmPC's, please refer to website of the MEB www.cbgmeb.nl/cbg/en/default.htm