Dimethyl fumarate and progressive multifocal leucoencephalopathy (PML)

Introduction

Dimethyl fumarate Psorinovo® is not registered through the Medicines Evaluation Board (MEB). It is a compounded drug made by GMP compounding pharmacy Mierlo Hout in the Netherlands, and used for the indication *psoriasis* [1]. Psorinovo® has been compounded by pharmacy Mierlo Hout for 28 years. According to Dutch law Mierlo Hout pharmacy is regarded as a supplying-pharmacy.
Dimethyl fumarate, registered as Tecfidera®, was granted marketing authorization in the Netherlands on 30 January 2014 and is indicated *for the treatment of adult patients with relapsing remitting multiple sclerosis* [2].

Progressive multifocal leukoencephalopathy (PML) is a severe demyelinating disease of the central nervous system caused by reactivation of the polyomavirus JC (JC virus). Asymptomatic primary infection with the JC virus occurs in childhood, antibodies can be found in 86% of adults. PML occurs almost exclusively in immunosuppressed individuals. There were only isolated cases reported of PML in patients without apparent immunosuppression. However, there are reports of PML affecting patients who have conditions associated with minimal or occult immunosuppression, such as hepatic cirrhosis and renal failure [3]. PML has also been reported in patients treated with drugs such as belatacept, brentuximab, efalizumab, fludarabine, glucocorticoids, infliximab, mycophenolate, rituximab, ruxolitinib and natalizumab. In some cases, these drugs were used in combination with other immunosuppressive medications (eg, cyclophosphamide, leflunomide, methotrexate). Many of the patients had an underlying hematologic malignancy or collagen vascular disease [3]. There is no specific treatment for PML. The main approach is restoring the host adaptive immune response, a strategy that appears to prolong survival. PML is often fatal, the median survival of patients without HIV infection (excluding patients with natalizumab-associated PML) is only three months [4].

Reports

From 11 May 2013 until 21 November 2014 The Netherlands Pharmacovigilance Centre Lareb received two reports concerning progressive multifocal leukoencephalopathy (PML) associated with the use of dimethyl fumarate.

Case A (report number 154297) This serious (Hospitalisation, Disabling) spontaneous report from a specialist doctor concerns a female aged 41-50 years, with progressive multifocal leucoencephalopathy (PML) following administration of Psorinovo® (dimethylfumarate) for psoriasis with a latency of 5 years after start. The drug dimethylfumarate was withdrawn. The patient was treated with mirtazapine and mefloquine. Laboratory tests showed lymphopenia. After withdrawal of the medication, the patient developed Immune Reconstitution Inflammatory Syndrome (IRIS) and was treated with i.v. methylprednisolon. The patient has a right-sided hemiparesis. The patient was reported to be recovering at the time of notification. Concomitant medications were calciuwasm ascorbate and EPA-1000 fish oil capsules.
The reporter states that the reaction was probably caused by prolonged lymphopenia during years as a result of the medication. The patient has no known past drug therapy. This case has also been reported in literature [5].

Case B (report number 183011)
This serious (Death) spontaneous report from a specialist doctor concerns a female aged 61-70 years, with progressive multifocal leucoencephalopathy (PML) following administration of dimethyl fumarate (Psorinovo®) for psoriasis with a latency of 2 years after start. The drug dimethyl fumarate was withdrawn. The patient was treated with corticosteroids, mefloquine and mirtazapine. The patient died. The cause of death was PML and IRIS (Immune Reconsitution Inflammatory Syndrome). Concomitant medications were rizatriptan, betamethasone/calcipotriol.
The reporter mentioned that other causes for PML were excluded. The diagnosis of PML was proved after autopsy by PCR JC virus on brain tissue an liquor, although PCR in liquor

during life was negative. Besides dermal use of corticosteroids for psoriasis, the patient did not have immunomodulating therapies, also not in the past. Furthermore the patient had had no prolonged lymphopenia, and certainly not a deep lymphopenia, the lowest number of lymphocytes had been mildly decreased with a value of 0.8x10-9/L, and before that there had been no lymphopenia.
The patient has no known medical history. The patient has no known past drug therapy.

Other sources of information

SmPC

For dimethyl fumarate Psorinovo® there is no SmPC available through the Medicines Evaluation Board, because it is not registered but produced as a compounded drug.
The European SmPC of dimethyl fumarate Tecfidera® does not mention PML as an adverse reaction [2].
Progressive multifocal leucoencephalopathy (PML) is also not mentioned as an adverse reaction in the US FDA SmPC of dimethyl fumarate Tecfidera® [6].
Progressieve multifocal leucoencephalopathy (PML) is also not mentioned as an adverse reaction in the German SmPC of Fumaderm® containing dimethyl fumarate / ethylhydrogen fumarate, calciumsalt / ethylhydrogenfumarate, magensiumsalt / ethylhydrogenfumarate, sinc salt). Fumaderm® is registered in Germany for moderate to severe forms of psoriasis vulgaris, where a single external therapy is not sufficient [7].

Concerning infections, the SmPC of Tecfidera® mentions that in phase III placebo-controlled studies, the incidence of infections (60% vs 58%) and serious infections (2% vs 2%) was similar in patients treated with Tecfidera® or placebo, respectively. The SmPC also mentions that there was no increased incidence of serious infections observed in patients with lymphocyte counts <0.8x109 /L or <0.5x109/L. The SmPC reports that during treatment with Tecfidera® in the MS placebo controlled trials, mean lymphocyte counts decreased by approximately 30% from baseline at one year and then plateaued, and mean lymphocyte counts remained within normal limits. The SmPC mentions that if a patient develops a serious infection, suspending treatment with Tecfidera® should be considered and the benefits and risks should be reassessed prior to re-initiation of therapy; patients receiving Tecfidera® should be instructed to report symptoms of infections to a physician; and patients with serious infections should not start treatment with Tecfidera until the infection(s) is resolved [2].
Futhermore the SmPC mentiones that Tecfidera® has not been studied in combination with anti-neoplastic or immunosuppressive therapies and caution should, therefore, be used during concomitant administration. The SmPC adds that in multiple sclerosis clinical studies, the concomitant treatment of relapses with a short course of intravenous corticosteroids was not associated with a clinically relevant increase of infection [2].

Literature

In the literature four cases of PML associated with dimethyl fumarate were described. One of these cases concerned the patient of Case A described above [5].
Another case, described in the same volume of the same journal [8], concerned a 74-year-old man, who developed PML after receiving monotherapy with oral fumaric acid for psoriasis for 3 years, in doses of up to 120 mg of dimethyl fumarate and 95 mg of monoethyl fumarate, each taken twice daily. In the three years before starting fumaric acid, the patient had been treated with topical glucocorticoids, oral acitretin and methotrexate. Retrospectively, there had been lymphocytopenia grade 3 status within 1 year after the initiation of treatment with fumaric acid. Fumaric acid–associated lymphocytopenia was assessed as the probable cause of immunodeficiency. Other causes of immunodeficiency and cancer were ruled out. When PML was diagnosed, fumaric acid was discontinued and treatment with mefloquine and mirtazapine was started. Within 5 weeks, an immune reconstitution inflammatory syndrome (IRIS) developed. Methylprednisolone was administered for 5 days. The patient's condition improved.
Furthermore, two other cases were reported in the Manufacturer’s response on these two cases [9]. These concerned the development of PML in two patients with psoriasis who were treated with Fumaderm®. The report mentioned that there were significant confounding factors for PML. One patient had a history of sarcoidosis and was treated with methotrexate and steroids. PML was diagnosed 1 month after of exposure to Fumaderm®.

The other patient had been treated with efalizumab and was diagnosed with cancer. Efalizumab was withdrawn, and subsequently Fumaderm® was started for psoriasis. It was reported that the sarcoidosis, cancer, and efalizumab were known risk factors for PML.

Databases

Table 1. Reports of PML associated with dimethyl fumarate, in the Lareb [10], WHO [11] and Eudravigilance database [12]. For the Lareb and Eudravigilance database no reliable ROR can be calculated because of the small number of reports.

Database	Drug	MedDRA PT	Number of reports	ROR (95% CI)
Lareb	dimethyl fumarate	Progressive multifocal leucoencephalopathy	2	
WHO	dimethyl fumarate	Progressive multifocal leucoencephalopathy	9	83.1 (43.0-160.7)
Eudravigilance	dimethyl fumarate	Progressive multifocal leucoencephalopathy	1*	
	dimethyl fumarate / ethyl fumarate	Progressive multifocal leucoencephalopathy	9**	35.9 (18.5 – 69.4)

* The other Dutch case (report number 183011) has been sent by Lareb to Eudravigilance but has been filed as a "not recoded product" (report EU_EC_8612632).
** Reports all originating from Germany

Prescription data

The number of patient using dimethyl fumarate can't be determined yet through the GIP-database because dimethyl fumarate Tecfidera® has only been registered in 2014; and dimethyl fumarate Psorinovo® concerns a compounded preparation, and is not registered.

Mechanism

PML can occur in people on chronic immunosuppressive therapy, allowing for JC virus reactivation. For dimethyl fumarate pharmacodynamically preclinical and clinical studies demonstrated anti-inflammatory and immunomodulatory properties. In preclinical models, dimethyl fumarate and monomethyl fumarate, the primary metabolite of dimethyl fumarate, significantly reduced immune cell activation and subsequent release of pro-inflammatory cytokines in response to inflammatory stimuli. In clinical studies with patients suffering from psoriasis, dimethyl fumarate affected lymphocyte phenotypes through a down-regulation of proinflammatory cytokine profiles (TH1, TH17), and biased towards anti-inflammatory production (TH2) [2].

Discussion and conclusion

The Netherlands Pharmacovigilance Centre Lareb received two reports concerning PML associated with the use of dimethyl fumarate. It concerned the compounded preparation dimethyl fumarate Psorinovo®, used for psoriasis. Both patient were women, with ages of 42 respectively 64 years. Latencies were 5 and 2 years. Both patient also developed Immune Reconstitution Inflammatory Syndrome (IRIS). One patient recovered with sequelae (hemiparesis on the right side with permanent disability to work). The other patient died because of the PML and IRIS. The patient of case A had had lymphopenia for years as result of the drug and this might have resulted in the PML (also according to the reporter).
The patient concerning case B did not have prolonged lymphopenia, and certainly not a deep lymphopenia. The diagnosis was proved at obduction by PCR on the JC virus in braintissue and liquor. This patient did use betamethason / calcipotriol for dermal use as concomitant drug, and no other immunomodulating drugs. Bethamethason is a strong therapeutic class III steroïd, though. In the SmPC of betamethason / calcipotriol it is reported that systemic effects by local use of corticosteroïden are rare in adults, but they can be serious. The SmPC of betamethason / calcipotriol reports that especially after prolonged use infections can occur [13].
On the other hand the report concerning the patient of case B did mention the development of IRIS, where dimethyl fumarate was withdrawn, while concerning the betamethason /

calcipotriol no action was reported. The development of IRIS could also plea for a causal relationship between dimethyl fumarate and the development of PML.
In the WHO database there are 9 cases present of PML associated with dimethyl fumarate. In the WHO database the association is disproportionally present, with a ROR of 83.1 (95% CI 43.0-160.7).
In a communication from November 25, 2014 the U.S. Food and Drug Administration (FDA) is warning that a patient with multiple sclerosis (MS) who was being treated with Tecfidera®, developed PML, and later died. As a result progressive multifocal leukoencephalopathy, is being added to the Tecfidera® drug label [14].

Conclusion

Lareb received two cases of PML, although prolonged lymphopenia was a risk factor for PML in case A, and in case B a systemic effect of dermal corticosteroid can't be ruled out completely (although the occurrence of IRIS further pleas for a causal relationship with dimethyl fumarate). The association between dimethyl fumarate and the occurrence PML is further supported by a disproportional ROR in the WHO-database, and the relatively high number of 9 reports in the WHO database. In case B, the association was independent of the number of lymphocytes.
Although the two reports concerned the compounded version dimethyl fumarate Psorinovo®, is to be expected that this effect concerns dimethyl fumarate in general and the signal should be further investigated regardless of brandname or registration status of the products used. Therefore further investigation of the information of the marketing authorization holders and other national centres concerning dimethyl fumarate and other fumarate containing products, is warranted, and a discussion in an international setting to further evaluate the meaning of the other reports mentioned in the WHO database.

- Further investigation of the information of the marketing authorization holders and other national centres is needed to confirm the signal
- Discussion in an international setting is warranted

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This signal has been raised on March 2015. 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.cbg-meb.nl