Natalizumab and cervical dysplasia

Introduction

Natalizumab (Tysabri®) is a monoclonal antibody against α4-integrin. It was registered for the European market on 18 June 2009 and is indicated as *single disease modifying therapy in highly active relapsing remitting multiple sclerosis (MS) in adult patients*. Natalizumab is administered by intravenous infusion once every 4 weeks [1].

In MS, lesions in the brains and spinal cord, are believed to occur when activated T-lymphocytes cross the blood-brain barrier (BBB). Natalizumab prevents mononuclear leukocytes transmigration across the endothelium into inflamed parenchymal tissue. It binds to the α4-subunits of integrin, which are highly expressed on the surface of leukocytes, with the exception from neutrophils. A further mechanism of action of natalizumab may be to suppress ongoing inflammatory reactions in diseased tissues and to inhibit further recruitment of immune cells into inflamed tissues [1].

Among the adverse drug reactions (ADRs) that are mentioned in the SmPC for natalizumab are opportunistic infections and progressive multifocal leukoencephalopathy (PML). The SmPC of natalizumab describes that no differences in incidence rates or the nature of malignancies between natalizumab- and placebo-treated patients were observed over 2 years of treatment. However, observation over longer treatment periods is required before any effect of natalizumab on malignancies can be excluded [1].

Cervical dysplasia or cervicale intra-epithelial neoplasia (CIN) is a premalignant lesion that can progress to cervical carcinoma. High-risk types of the human papilloma virus (HPV), HPV16 and HPV 18, are in nearly 100% of cases responsible for the cause of cervical dysplasia. Persistent HPV infections have a higher risk of progressing to cervical dysplasia. Cervical dysplasia is likely to progress to cervical carcinoma over a period of several years if left untreated [2]. In the Netherlands, 1 out of 170 women develops cervix carcinoma. Unlike many other cancers, cervix carcinoma mainly occurs in relatively young women; women 30 to 45 years old are among the population at the highest risk [3].

Reports

On 7 July 2012, the database of the Netherlands Pharmacovigilance Centre Lareb contained three reports (with one duplicate report by the marketing authorization holder) of cervical dysplasia associated with the use of natalizumab. The reports are listed in table 1. All three cases were reported by the same reporter, with one report also reported as a duplicate report by the Marketing Authorization Holder (MAH).

Table 1. Reports of cervical dysplasia associated with the use of natalizumab.

Patient, Sex, Age, Reporter	Drug Indication for use	Concomitant medication	Suspected adverse drug reaction	Time to onset, Action with drug Outcome
A 128850 F, 31 – 40 years Specialist doctor	natalizumab concentrate for solution for infusion		cervical dysplasia PAP IIIA (moderate	20 months discontinued recovered after

	20mg/ml flacon 15ml multiple sclerosis	dysplasia) [4]	chirurgical intervention
B 128870/ 139446* F, 21 – 30 years Specialist doctor/ MAH	natalizumab concentrate for solution for infusion 20mg/ml flacon 15ml multiple sclerosis	cervical dysplasia PAP IIIB (severe dysplasia) [4]	35 months dose not changed recovering after chirurgical intervention
C 128908 F, 21 – 30 years Specialist doctor	natalizumab concentrate for solution for infusion 20mg/ml flacon 15ml multiple sclerosis	cervical dysplasia	17 months not applicable (reaction after withdrawal of natalizumab) recovering after chirurgical intervention

* duplicate report by specialist doctor and marketing authorization holder (MAH)

All patients were treated with a surgical procedure.
Patient C used natalizumab for nine months. Because of pregnancy desire natalizumab was withdrawn. Eight months after withdrawal cervical dysplasia was diagnosed. The exact PAP classification is not known; this could be grade IIIA or IIIB.

Other sources of information

SmPC

The Dutch SmPC of natalizumab neither mentions HPV infection or cervical dysplasia [1].

Literature

In the literature no descriptions of cervical dysplasia were found for natalizumab. Aubin et al. reviewed genital HPV infections in patients with autoimmune inflammatory diseases. They found that an increased prevalence of HPV infections was only demonstrated in patients with systemic lupus erythematosus. Furthermore, no increased risk of genital HPV infection has been reported in patients taking biological agents [5]. Only three cases of genital HPV infections in patients on biologicals have been reported; two cases concerning infliximab and one concerning etanercept [5,6].
Shale et al. reviewed chronic viral infection in TNFα-inhibitors in inflammatory bowel disease (IBD). They found that IBD patients receiving immunomodulators have been reported to increased rates of PAP smear abnormalities. However, this finding has not been universally confirmed [7].

Database

The Lareb database was searched for natalizumab in association with the MedDRA Preferred Terms (PTs) cervical dysplasia and cervix carcinoma.
On July 24th, 2012, the database of the Netherlands Pharmacovigilance Centre Lareb contained three cases and one duplicate case of cervical dysplasia associated with the use of natalizumab. Cervix carcinoma in association with natalizumab has not been reported.
The reporting odds ratio (ROR) is determined with a 2x2 contingency table. Since the number of cases with the same drug, other ADR (n=104) and the number of cases with the same ADR, other drugs (n=5) are low for this association, the ROR is very high with a broad confidence interval (CI), namely 663.1 (95% CI 156.48 – 2809.9). The ROR was therefore considered as not reliable.

The database of the WHO was searched for natalizumab in association with the MedDRA PT cervix dysplasia and MedDRA High Level Term (HLT) cervix neoplasm malignant. This term covers the PTs: cervix cancer metastatic, cervix carcinoma, cervix carcinoma recurrent, and cervix carcinoma state 0 – IV.
The WHO database of the Uppsala monitoring centre contained 22 reports of cervical dysplasia associated with natalizumab and 16 reports of cervix neoplasm malignant.
When looking at the different PTs within cervix neoplasm malignant (n=16) there were 10 cases of cervix carcinoma, 4 cases of cervix carcinoma stage III, 1 case of cervix carcinoma stage 0, and 1 case of cervix cancer metastatic. Only the association natalizumab and cervical dysplasia is disproportionally present in the database.

Table 2. Reports of cervical dysplasia and cervix carcinoma associated with natalizumab in the database of the Netherlands Pharmacovigilance Centre Lareb and the WHO.

Drug	Number of reports	ROR (95% CI)
Natalizumab and cervical dysplasia	Lareb: 4 WHO: 22	- 3.79 (2.48 – 5.80)
Natalizumab and cervix carcinoma	Lareb: -	
Natalizumab and cervix neoplasm malignant	WHO: 16	0.84 (0.51 – 1.37)

The databases of Lareb was also searched for other biologicals with immunosuppressive properties (ATC-code L04, immunosuppressive) in association with above-described MedDRA terms, see table 3.

Table 3. Reports of cervical dysplasia and cervix carcinoma associated with other biologicals with immunosuppressive properties in the database of the Netherlands Pharmacovigilance Centre Lareb

Drug	Number of reports	ROR (95% CI)
Ustekinumab and cervical dysplasia	Lareb: 1	-
Interferonβ_{1A} and cervix carcinoma	Lareb: 3*	-
Etanercept and cervix carcinoma	Lareb: 2	-
Infliximab and cervix carcinoma	Lareb: 1	-

* The calculated ROR in this case was deemed unreliable due to the low number of cases for all drugs in the database

On August 8 2012, the Eudravigilance database contained 19 reports of cervical dysplasia or cervical cancer in association with natalizumab. The median age was 32.5 years (range 27 – 41 years). In three cases, the age was not reported. All reports were classified as serious. The criteria for seriousness were “hospitalization” and “other”. The reporting odds ratio (ROR) for Cervical dysplasia (n=13) was 7.7 (4.5 – 13.4) and the ROR for Cervical cancer (n=6) was 6.4 (2.8 – 14.2). The combined ROR (n=19) was 7.2 (4.6 – 11.4).

Prescription data

Because the application of natalizumab is restricted to hospitals, no prescription data are available through the Drug Information System of the Dutch Health Care Insurance Board [8].

Mechanism

Normally, genital HPV infections are cleared within a few months by the immune system. Clearance of the virus is far less likely to occur among immune suppressed patients [5,9]. Strickler et al. compared the rate of new HPV DNA detection in HIV-infected and HIV-uninfected women who reported 18 months of sexual abstinence with the rate of new HPV DNA detection in sexually active women. New HPV DNA was detected in both HIV-uninfected and HIV-infected women who were sexually inactive. The risk of new HPV DNA detection increased in the HIV-infected women with increasing immune suppression to a high of 22% in the most severely immune suppressed [10]. In a similar analysis it was found that recurrence and reactivation rates for HPV16 were nearly three times higher among HIV-infected woman compared to HIV-uninfected women [11]. The clinical observation of HPV-associated lesions following organ transplantation further support a role of immunologic control of lifetime persistent HPV infections. The increased risk of HPV-associated cancers in transplant women is similar to that in HIV-infected women [12].
Due to their pharmacologic mechanism, immunosuppressant are associated with opportunistic infections [1]. However, no evidence of natalizumab exacerbate HPV infections or induce cervical dysplasia is found in literature.

Class effect

Within the group of monoclonal antibodies, natalizumab is the only monoclonal antibody working against α4-integrin. Monoclonal antibodies belong to the group of biologicals. Within this group, there are several other drugs that have immunosuppressive properties, for example TNFα-inhibitors. Concerning all biologicals, on 7 July 2012, the database of the Netherlands Pharmacovigilance Centre Lareb contained one report of cervical dysplasia associated with the use of ustekinumab, see table 2. Further, the Lareb database contained three reports of cervix carcinoma associated with interferonβ_{1A}, two reports associated with etanercept and one report associated with infliximab.
Also, the database of the WHO contains several reports of cervical dysplasia and cervix carcinoma associated with biologicals with immunosuppressive properties. For this reason, a class effect cannot be excluded.

Discussion

Lareb received three reports and one duplicate report of cervical dysplasia associated with the use of natalizumab. This association is found to be disproportional in the WHO- and Eudravigilance database. Remarkably, all cases in the Lareb database were reported by the same specialist doctor. The reporter mentioned that over the last year, three out of sixteen patients he treated with natalizumab were diagnosed with cervical dysplasia.

Natalizumab is an immunosuppressive agent and is associated with opportunistic infections. In the literature no evidence of natalizumab exacerbate HPV infections or induce cervical dysplasia was found. However, several studies describe that immune suppressed women have a higher risk for developing persistent HPV-infections, which are likely to progress to cervical carcinoma over a period of several years if left untreated [2,10-12].

Conclusion

This observation describes a signal of HPV infections which can results in cervical dysplasia associated with natalizumab. Further investigation of the information of the marketing authorization holder is advisable

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References

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This signal has been raised on November 2012. It is possible that in the meantime other information became available. For the latest information please refer to the website of the MEB www.cbgmeb.nl/cbg/en/default.htm or the responsible marketing authorization holder(s).