

Cervical dysplasia associated with the use of natalizumab

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Dear editor,

Natalizumab is a monoclonal antibody against anti- α 4-integrin, which was registered in the Netherlands in June 2006. It is indicated for severe and highly active relapsing-remitting multiple sclerosis (MS) in adult patients. In the product information of natalizumab it is stated that opportunistic infections such as progressive multifocal encephalopathy due to reactivation of the John Cunningham (JC) virus, herpes infections and a fatal case of herpes encephalitis have occurred during therapy. Human papilloma virus (HPV) expression is not mentioned and until now no cases of HPV expression or cervical dysplasia in association with natalizumab have been reported.

HPV is the major cause of cervical intraepithelial neoplasia (CIN), the premalignant lesion of cervical carcinoma. Usually, acquired HPV infections are cleared by the immune system by 90% of women within two years. However, in immunocompromised patients persistent HPV infections, namely high-risk HPV types 16 and 18, may lead to progression of cervical squamous epithelial lesions. The risk of invasive carcinoma is increased in CIN-I (mild dysplasia), CIN-II (moderate dysplasia) and CIN-III (includes both severe dysplasia and carcinoma in situ).

A case series is presented where the use of natalizumab may have led to persistent HPV infections which resulted in cervical dysplasia in four patients with MS.

METHOD AND MATERIALS

The Netherlands Pharmacovigilance Centre Lareb maintains the voluntary adverse drug reaction (ADR) reporting system in the Netherlands. Lareb receives reports of ADRs spontaneously from healthcare professionals, pharmaceutical companies, and patients. Qualified

assessors review each ADR report case-by-case. Reports are sent to the European Medicines Agency (EMA) and are submitted to the worldwide database of the World Health Organisation (WHO).

RESULTS

Until 1 June 2013, Lareb received four reports of cervical dysplasia associated with the use of natalizumab. Cervical HPV testing for all four patients was positive but we have no information on HPV typing. Histological examination revealed CIN-II (cases 1-3) and CIN-III (case 4) lesions.

Case 1

The first report concerns a 30-year-old woman with cervical smear (PAP-IIIB), 45 months after starting natalizumab, 300 mg once a month for MS. Concomitant medications were modafinil, drospirenone/oestrogen, sumatriptan, and temazepam. Natalizumab therapy was interrupted for an unknown period, as the MS was stabilised at that time, one year before observation of the cervical dysplasia. Her past drug therapy was interferon beta-1a. The patient has a medical history of migraine and urinary tract infection. The patient has a family history of breast and colon carcinoma.

Case 2

The second report concerns a 33-year-old woman with dysmenorrhoea 20 months after starting natalizumab, dosage unknown. She had a cervical smear using thin layer cytology and was graded as PAP-IIIA. The patient also had a positive JC-virus test. Natalizumab was discontinued. Past drug therapy was glatiramer, which was administered for two years.

Case 3

A 30-year-old woman had a pap smear which was examined with thin layer cytology showing the presence of PAP-III B 35 months after starting natalizumab, dosage unknown. A control cytology was staged PAP-II. Natalizumab was continued. She had been using interferon beta-1a in the past.

Case 4

The final case concerns a 28-year-old woman who was treated with natalizumab with an unknown dosage for a period of nine months when a cervical pap smear was performed as part of the Dutch population screening programme. Thin layer cytology was graded PAP-III B. Natalizumab was discontinued. She had been using interferon beta-1a and glatiramer in the past.

DISCUSSION

These reports suggest a possible relation between natalizumab and cervical dysplasia. Three out of four reports were reported by one reporter (J.S.), who noted that over the last year three out of 16 patients treated with natalizumab were diagnosed with cervical dysplasia. Cervical dysplasia or HPV infections in association with natalizumab have not been described before in literature. Regarding other biologicals acting on the immune system, two cases of genital HPV infections have been published: one regarding infliximab and one regarding etanercept.¹ The mechanism by which natalizumab may cause cervical dysplasia is not fully elucidated. Natalizumab is known to cause opportunistic infections. From the literature it is shown that clearance of the HPV virus is far less likely to occur among immune-compromised patients, who are therefore at increased risk for developing HPV-related malignancies.² It is for these reasons conceivable that immune suppression caused by the use of natalizumab is responsible for the persistence of an HPV infection and subsequently cervical dysplasia. To what extent the past drug therapy contributed to the development of the cervical dysplasia is not clear. In the literature, no information was found on interferon beta-1a or glatiramer in association with cervical dysplasia or HPV infections. However, given the mechanism an effect of interferon cannot be excluded. In the literature, an increase in cancer risk, including cervical related cancers, was seen in immune suppressed patients.^{3,4} Adami *et al.*³ explored the cancer risk following organ transplantation in Sweden using a cohort design. The standardised incidence ratio (SIR) was used to estimate the relative risk of tumours for different categories. A small statistically non-significant difference was seen for cervical cancer *in situ* following organ transplantation (SIR 1.3 with 95% confidence interval

1.0-1.8) and for cervix cancer *uteri* (SIR 2.0 95% confidence interval 0.7-4.7). Exploring the cancer incidence before and after kidney transplantation, Vajdic *et al.*⁴ found a greater than threefold increase in risk for cervix cancer. For both studies the SIR for cervix cancer was not increased before transplantation; immune suppression may therefore be responsible for the increased risk.

For now, the number of reports of cervical dysplasia associated with natalizumab is low. More reports would make a causal relationship between the use of natalizumab and cervical dysplasia more likely. In order to make an estimation of the incidence of the possible ADR, controlled studies are needed.

CONCLUSION

The reports presented point towards a possible relation between the use of natalizumab and an increased risk for the development of cervical dysplasia. On the basis of these reports it cannot be concluded that frequent monitoring of these women is required. However, attention for this possible association is warranted.

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