Risk of natalizumab-associated progressive multifocal leukoencephalopathy
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INTRODUCTION

- Natalizumab (TYSABRI), indicated for treating multiple sclerosis (MS) and ulcerative colitis (UC), was withdrawn worldwide as March 2012, corresponding to approximately 210,000 patient-years of experience.
- Natalizumab has demonstrated efficacy in reducing MS and ulcerative colitis disease severity.
- Independent of baseline disease activity, natalizumab decreased sustained disability progression by 46%, 80%, and placebo-adjusted disability scores by 46%, 80%, and 95%.
- Thirty-seven percent of natalizumab patients compared with 64% placebo patients were free of disease activity (clinical relapse or gadolinium-enhancing lesion activity) during the last 2 years, respectively (P=.003).
- Although no increase in the risk of progressive multifocal leukoencephalopathy (PML), an opportunistic viral infection caused by the JC virus, was noted in a complex case series, a unique case report described late-onset PML in natalizumab-treated patients.
- Established risk factors for PML include the presence of anti-JCV antibodies, immunosuppressant use, and duration of natalizumab treatment.

OBJECTIVES

- To quantify PML risk in real-world natalizumab-treated MS patients using a combination of retrospective and prospective analyses of clinical trial and observational data.
- To compare the risk of PML in natalizumab-treated MS patients within the clinical trial data with real-world data from observational registries and a large population-based cohort.
- To determine the impact of the natalizumab withdrawal on the risk of PML in patients who have discontinued natalizumab treatment.

METHODS

- Patients, samples, and data collection: For the purpose of calculating PML incidence rates, data on natalizumab-treated MS patients were collected from various sources: clinical trials, registries, and population-based cohorts.
- Identification of natalizumab treatment duration and prior use as independent risk factors for PML: Natalizumab treatment duration and prior use were assessed using a combination of clinical trial data and observational registries.
- Identification of risk factors for PML: Risk factors for PML were identified using a combination of clinical trial data and observational registries.
- Identification of PML incidence: PML cases were identified using a combination of clinical trial data and observational registries.
- Identification of anti-JCV antibody status: Anti-JCV antibody status was assessed using a combination of clinical trial data and observational registries.

RESULTS

- Overall, the risk of PML in the postmarketing setting was 3.3 cases per 10,000 patients.
- The risk increase in patients in the United States was similar to that observed in the postmarketing period after the 2012 withdrawal of natalizumab for 31-odd patients treated.
- Identification of prior use as a risk factor for PML: Prior use of natalizumab was associated with a lower risk of PML compared to patients without prior use.
- Anti-JCV antibody status was assessed using a combination of clinical trial data and observational registries.
- Sensitivity analysis: Sensitivity analysis was performed to assess the impact of different assumptions on the estimated PML risk.

CONCLUSIONS

- Anti-JCV antibody status is an important factor in determining risk of PML to provide individual benefit risk assessment.
- Patients with anti-JCV antibody status were at lower risk of PML (0.64 cases per 10,000 patients) treated, but higher risk of PML (2.8 cases per 10,000 patients) treated.
- Clinical trials are ongoing to further investigate the risk of anti-JCV antibody positive and negative patients.

References

- Anti-human monoclonal antibody to CD20.

APPENDIX: PML risk table

- Table 1: PML risk associated with anti-JCV antibody status prior to the diagnosis of PML.
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