Did risk stratification modify the incidence of PML in natalizumab-treated MS patients in France?

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Background Progressive multifocal leukoencephalopathy (PML) is the major limitation to the use of natalizumab in multiple sclerosis (MS). Since 2012, three factors allow to identify patients in whom the risk of PML might overweight treatment benefits: exposure to natalizumab for more than 24 months, previous use of immunosuppressants and a positive JC virus serology. So far, the impact of risk stratification on PML incidence has not been evaluated.

The objective of this study was to describe the temporal evolution of the incidence of natalizumab-associated PML in France between 2007 and 2016 and to evaluate the impact of risk minimization procedures on PML incidence before and after 2013.

Methods

Retrospective, observational, multicentric, epidemiological study on data collected in OFSEP (Observatoire Français de la Sclérose en Plaques).

Population of interest

Patients with both MS and PML related to a treatment with natalizumab, since April 15th 2007.

PML cases identified in the OFSEP database were sent to each center, to validate the case, the certainty of PML diagnosis, the date of PML onset and to inform whether each case was followed by the center before onset or referred because of the suspicion of PML. Any additional PML that was not reported in the OFSEP database was identified and data were completed. Suspicious PML cases were excluded, as well as those referred only because of PML, but not followed in the center before, as they did not contribute to the at-risk population.

At-risk population

All patients exposed at least to 1 infusion of natalizumab since April 15th 2007. The period of interest for each patient was defined from the date of the first natalizumab infusion to the occurrence of either the event of interest (PML), or natalizumab cessation plus 6 months (as PML cases are known to be diagnosed in the 6 months after stopping which still constitutes an at-risk-period), or the last clinical evaluation if the patient was still under treatment.

Risk-mitigation practice survey

A questionnaire was sent to all OFSEP participating centers, to describe their practice regarding PML risk stratification. Data included questions about risk factors, how and since when they modified their practice in terms of indication of natalizumab, duration and specific follow-up (JCV testing frequency, MRI follow-up).

Statistical analysis

Crude annual PML incidence rates in natalizumab-treated patients were estimated as the number of PML cases identified by calendar year reported to the number of person-years exposed to natalizumab each year, from 2007 to 2016. A univariate Poisson regression model was considered by integrating the year as a linear covariate and patient-years exposed to natalizumab were considered in the offset term. This model allowed to estimate the annual variation in incidence rate ratio (IRR) and the number of expected cases. A multivariate analysis was performed by adjusting for sex and age at treatment initiation and a stratified analysis by period before and after 2013 to evaluate the impact of risk stratification. Analyzes were performed with SAS 9.4 software and R 3.4.3. P <0.05 was considered statistically significant.

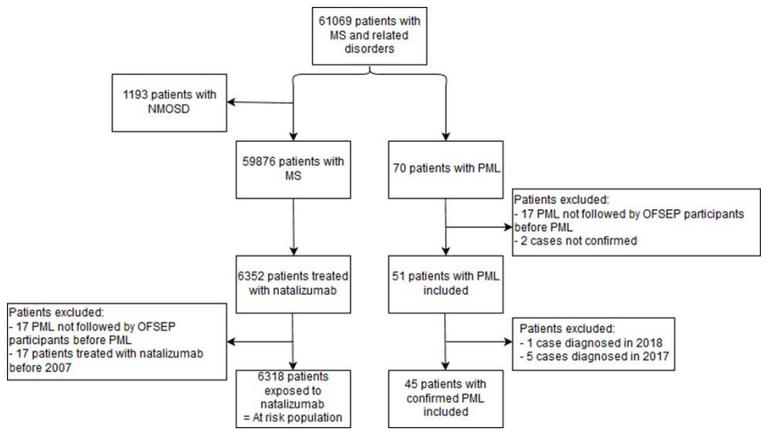
Results

Baseline characteristics of the study population (Flow-chart in Figure 1)

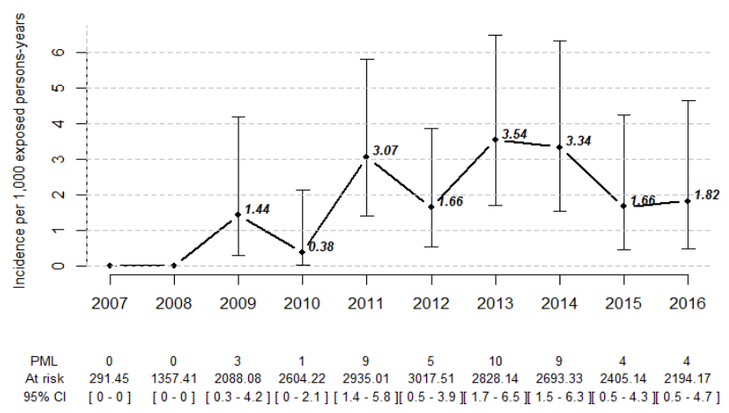
6318 patients were included in the at-risk population. Age at MS onset was 28.5 ± 9.1 years (range 1.1–72.4), with 74.1% females. Mean exposure to natalizumab was 39.6 +/- 30.2 months (range 0.03–164.8). 1372 (21.7%) were exposed to at least one immunosuppressive treatment before natalizumab.

61 PML were registered originally in the database and 9 additional cases were reported during the validation procedure. Twenty-five cases were excluded from the analysis: 2 cases were only suspected but not confirmed by CSF PCR for JC virus or brain biopsy, 6 cases occurred after 2016 (5 in 2017, 1 in 2018) and 17 cases were not followed by OFSEP participants before the diagnosis of PML. 45 definite PML were finally analyzed. Thirty-one (68.9%) were females, mean age was 28.7 ± 6.7 years (range 17.4-42.6) at MS onset and 43.5 ± 7.0 years (range 27.1-58.8) at PML onset. Eight cases (17.7%) started after natalizumab was stopped (mainly because of a positive JCV serology), 5 in the first 3 months, 3 between 3 and 6 months. Mean exposure to natalizumab was 52.0 ± 24.2 months (range 4.7-117.1). One case (2.2%) occurred in the first 12 months of treatment, 3 (6.7%) between 12 and 24 months, 5 (11.1%) between 24 and 36 months, 18 (40.0%) between 36 and 48 months and 18 (40.0%) after 48 months. Ten (22.2%) were exposed to at least one immunosuppressant before natalizumab, including 4 mitoxantrone, 4 cyclophosphamide, 4 azathioprine and 1 mycophenolate mofetil. Eleven patients (24.4%) died from the consequences of PML.

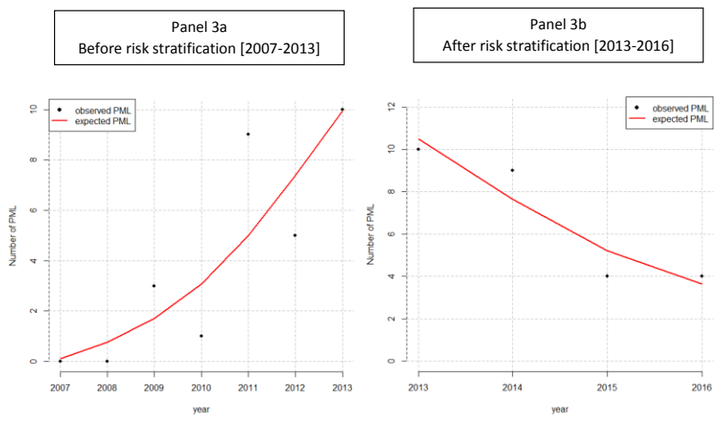
Flow-chart



Crude incidence rates between 2007 and 2016



Stratification by period (before and after 2013)



For the 2007-2013 period, the univariate Poisson regression showed a significant increase in the incidence of PML (IRR=1.439 [1.149-1.801], p=0.001), corresponding to a modeled increase of incidence by 43.9% every year. The multivariate analysis, introducing sex and age at treatment onset as covariates, confirmed the significant increase of the incidence (IRR=1.453 [1.154-1.828], p=0.001). Sex was not associated with the risk of PML, whereas younger patients (less than 30 years at treatment onset) were significantly less likely to develop PML (IRR=0.203 [0.062-0.672], p=0.009), with a reduction by more than 80% of their risk compared to oldest patients.

By contrast, in the 2013-2016 period, the univariate analysis found a significant decrease in the incidence of PML (IRR=0.764 [0.696-0.839], p<0.001), ie a reduction by 23.6% per year. This decrease remained significant in the multivariate analysis (IRR=0.699 [0.609-0.973], p=0.028), where we found a trend toward a more important risk in males (IRR=1.602 [0.976-2.629], p=0.06) and again a significantly lower risk in patients younger than 30 (IRR=0.435 [0.214-0.885], p=0.022).

Risk mitigation procedures in practice in France

The questionnaire was completed by 33 of the 34 participating centers (97.1%). All declared using JCV results in the management of their patients, 97% at natalizumab initiation and 3% after 18 months. Two centers do not consider previous use of immunosuppressants and 3 duration of treatment in the risk/benefit discussion.

Initiation of natalizumab is considered by up to 90.9% in JCV(+) patients, whereas 9.1% do not use natalizumab at all in this situation; 86.7% use JCV index, with variable high-risk thresholds: 0.7 in 2 centers, 0.9 in 22 and 1.5 in 4; 96.5% limit the duration of exposure to natalizumab to 12, 18 or 24 months (4, 9 and 13 centers respectively).

In JCV(-) patients, retesting is done every 6 months in 30/33 centers, more frequently in 2 and only annually in 1. MRI follow-up is done annually in 27 centers and every 6 months in 6.

In JCV(+) patients with a low index (according to the local threshold), restesting is done every 6 months in 24/32 centers, more frequently in 7 (3-4 months) and only annually in 1. MRI follow-up is done more frequently in 28 centers (quarterly in 11, bi-annually in 17) after 12, 18 or 24 months of exposure (respectively 8, 9 and 8 centers) and since onset in 3; it remains annual in 4.

In JCV(+) patients with a high-index, MRI follow-up is increased to every 3 months in 27 and every 6 months in 2 centers, after 12, 18 or 24 months (8, 12 and 4 centers respectively). After 24 months of exposure in high-index patients, 13 centers systematically stop natalizumab, 20 discuss the benefit/risk balance and alternative drugs in expert concertation meetings and with the patients and 6 also use CD62L dosage for the discussion.

Conclusion Our study described for the first time, at a country level, a significant decrease in the incidence of natalizumab-associated PML since 2013, in a temporal concomitance with the introduction of risk mitigation guidelines based on JCV serology and index, treatment duration and prior immunosuppressant use. If the overall risk recently decreased, PML did not disappear so far. It is likely that natalizumab was maintained despite the detection of risk factors in patients for whom the fear of a poorer control of MS activity exceeded the perception of the risk of PML. Although a causal relationship cannot be established, this encourages continuing and reinforcing all educational activities to prevent the risk of PML.

The Observatoire Français de la Sclérose en Plaques (OFSEP) is supported by a grant provided by the French State and handled by the "Agence Nationale de la Recherche," within the framework of the "Investments for the Future" program, under the reference ANR-10-COHO-002, by the Eugène Devic EDMUS Foundation against multiple sclerosis and by the ARSEP Foundation.

SV has received consulting and lecturing fees, travel grants and unconditional research support from Biogen, Geneuro, Genzyme, MedDay, Merck Serono, Novartis, Roche, Sanofi Aventis and Teva Pharma. RM has received consulting and lecturing fees, travel grants and research support from Biogen, Genzyme, Novartis, Merck Serono, Roche, Sanofi Aventis and Teva Pharma . AR has received consultancy fees, speaker fees, research grants (non personal), or honoraria approved by the institutions from Novartis, Biogen Idec, Genzyme, Medday, Roche, Teva and Merck, outside of the scope of the submitted study. HZ received fees for consulting or lectures, and invitations for national and international congresses from Biogen, Merck, Teva, Sanofi-Genzyme, Novartis and Bayer, as well as research support from Teva and Roche, and academic research grants from Académie de Médecine, LFSEP, FHU Imminent and ARSEP Foundation. EM received consulting and lecturing fees from Biogen, Novartis, Genzyme, Teva Pharmaceuticals, Merck Serono, Roche and Ad Scientiam and research support from Novartis and Roche. CLF received fees for consulting or lectures from Biogen, Merck, Medday, Roche and Novartis. ND has received funding for speakers honoraria from Merck-Serono, Biogen-Idec, Sanofi-Genzyme, Novartis and Roche. EB has received research supports from Biogen, honoraria and consulting fees from Novartis, Sanofi Aventis, Biogen, Genzyme, Roche and Teva Pharma. XM has received funding from Teva, Novartis, Sanofi-Genzyme, Merck-Serono, and Astellas, and non-financial support from Biogen, Sanofi-Pasteur-MSD, GSK, Astrazeneca, Pfizer, and Roche, not related to the submitted work BS has received consulting and lecturing fees, travel grants and unconditional research support from Biogen Idec, Merck-Serono, Novartis, Genzyme, Teva Pharma, and Roche; has a patent pending for the identification of a compound that stimulates demyelination; and received academic research support from ANR, PHRC, ARSEP Foundation and the Progressive MS Alliance. OH received consulting and lecturing fees from Bayer Schering, Merck, Teva, Genzyme, Novartis, Almirall and BiogenIdec, travel grants from Novartis, Teva, Genzyme, Merck Serono and Biogen Idec and research support from Roche, Merck and Novartis. BB served on scientific advisory board for Merck Serono and has received funding for travel and honoraria from Biogen, Merck Serono, Novartis, Sanofi-Genzyme, Roche and Teva. CB has received consulting and lecturing fees, travel grants from Biogen, Genzyme, Novartis, Merck Serono, Roche and Teva Pharma. AM has received funding for travel from Merck Serono, Teva, Novartis, Sanofi-Genzyme and Biogen. MV has received funding from Roche, Novartis, Biogen, Merck Serono, and Teva. AMG received fees for consulting or lectures from Biogen, Merck, Sanofi-Genzyme and Roche. .CL received consulting and lecturing fees from Biogen, Novartis and Genzyme. IP has received honoraria and consulting fees from Novartis, Genzyme and Roche, research supports from Biogen and Novartis and travel grants from Genzyme, Novartis and Roche. AT has received consulting and lecturing fees, travel grants and research support from Medday, Biogen, Sanofi-Genzyme, Novartis, Merck Serono, Teva Pharma, and Roche. PV has received honoraria and consulting fees from Biogen, Sanofi-Genzyme, Novartis, Teva, Merck, Roche, Servier, Celgene, Medday and Almirall, and research supports from Biogen, Novartis, Sanofi-Genzyme, Roche and Merck. DL has received consulting and lecturing fees, travel grants and unconditional research support from Biogen, Genzyme, Novartis, Merck Serono, Roche, Sanofi Aventis and Teva Pharma. FR, RC, JP, GM, GE, DB, JDS, PL, TM, AR, ET, AAK, PC, JPC, AW, NM, CN, KH, have nothing to disclose.