Age at natalizumab start as risk cofactor for developing early onset progressive multifocal leukoencephalopathy

Sin
XLVII CONGRESSO
Venezia, 22-25 Ottobre 2016
Polo Congressuale - Lido di Venezia

Luca Prosperini[1], Cristina Scarpazza[2], Luisa Imberti[3], Nicola De Rossi[2], Cinzia Cordioli[2], Ruggero Capra[2]; on behalf of the Italian PML Study Group*.

[1] Dept. of Neurology and Psychiatry, Sapienza University, Rome, Italy
[2] Multiple Sclerosis Centre, Spedali Civili di Brescia, Montichiari, Brescia, Italy
[3] Centro Ricerca Emato-oncologia AIL, Diagnostics Dept., Spedali Civili of Brescia, Brescia, Italy

SAPIENZA UNIVERSITÀ DI ROMA
Regione Lombardia
ASST Spedali Civili

INTRODUCTION

- Six-hundred thirty-eight confirmed cases of natalizumab-related progressive multifocal leukoencephalopathy (PML) have been reported in patients with multiple sclerosis (MS) at March 2016, according to manufacturer data.
- Patients are considered at higher risk for developing PML if they have tested positive for John Cunningham virus (JCV), and have used an immunosuppressant, either have received more than 24 natalizumab infusions.
- Higher risk patients were recommended to have brain magnetic resonance imaging (MRI) scans every 3-4 months after 24 natalizumab doses; however, this risk management plan is still debated since about 15% of PML cases were diagnosed even before the 24th infusion.

OBJECTIVE

- To assess the potential predictors of early onset PML, defined as a PML diagnosed before 24 natalizumab infusions, by retrospectively analyzing natalizumab-related PML cases available in literature.

METHODS

- PubMed was searched for articles written in English language from January 2005 to June 2016 by inserting the search terms 'Natalizumab and Progressive Multifocal Leukoencephalopathy'. A total of 563 articles were identified. We extracted only those articles reporting individual description of natalizumab-related PML clinical cases, regardless the original study purpose.
- We took care of excluding cases and clinical series for whom an overlapping between articles was suspected.
- We collected information on each identified PML case, including country of origin, sex, age, disease duration and Expanded Disability Status Scale (EDSS) score at PML diagnosis, number of natalizumab infusions, prior immunosuppressant exposure, magnetic resonance imaging (MRI) pattern (unilobar versus multilobar or widespread PML), and viral load, estimated as number of JCV copies/mL detected by polymerase chain reaction on the first cerebrospinal fluid (CSF) collected at PML suspicion.
- Differences in demographic and clinical features were then investigated according to timing of PML diagnosis (before or after the 24th infusion) by means of non-parametric statistical tests.
- Analyses were also adjusted for demographic and clinical characteristics (sex, disease duration and EDSS score) and for several other covariates that could potentially either lead to delay in PML diagnosis (i.e. country of origin, MRI pattern, and viral load) or affect the PML risk (i.e. previous exposure to immunosuppressants).
- Two-sided p-values less than 0.05 were considered as significant.

Table 1. Characteristics of patients according to number of natalizumab infusions received before PML diagnosis.

	≤24 infusions n=54	>24 infusions n=167	p-value
Country, n (%) Europe US + ROW *unavailable data, n*	 43 (80) 11 (20) *0*	 129 (77) 38 (23) *0*	0.851 *
Sex, n (%) Men Women *unavailable data, n*	 15 (28) 39 (72) *0*	 54 (32) 113 (68) *0*	0.614 *
Age at natalizumab start, years mean (SD) median [range] *unavailable data, n*	 42.7 (9.7) 43 [22-69] *1*	 39.2 (9.5) 39 [18-65] *0*	**0.036** #
Age at PML diagnosis, years mean (SD) median [range] *unavailable data, n*	 44.1 (9.8) 45 [23-71] *1*	 42.5 (9.4) 42 [22-70] *0*	0.309 #
MS duration at PML diagnosis, year mean (SD) median [range] *unavailable data, n*	 13.0 (9.6) 12 [2-50] *20*	 12.2 (5.4) 11 [2-25] *80*	0.833 #
Prior immunosuppressant exposure, n (%) no yes *unavailable data, n*	 20 (40) 30 (60) *4*	 106 (68) 50 (32) *11*	0.309 *
MRI pattern, n (%) unilobar multilobar or widespread *unavailable data, n*	 25 (86) 4 (14) *25*	 106 (88) 14 (12) *47*	0.754 *
Viral load, copies/mL mean (SD) median [range] *unavailable data, n*	 40,729 (187,327) 183 [0-1,220,175] *1*	 78,628 (532,807) 342 [0-4,831,575] *25*	0.265 #
EDSS score at PML diagnosis [d] mean (SD) median [range] *unavailable data, n*	 4.25 (1.82) 3.75 [2.0-7.5] *36*	 3.94 (1.85) 4.0 [0-7.5] *100*	0.615 #

*** Fisher's exact test; # Mann-Whitney U test**

EDSS: Expanded Disability Status Scale; MRI: magnetic resonance imaging; MS: multiple sclerosis; PML: progressive multifocal leukoencephalopathy; ROW: rest of world; SD: standard deviation; US: United States.

RESULTS

- We identified 221 natalizumab-related PML cases described in 60 articles.
- Early onset PML was observed in 54 (24.4%) patients who were older at natalizumab start than those ones diagnosed after the 24th infusion (p=0.035); there were no other between-group differences **[Table 1]**.
- Only six PML cases (<3%) were diagnosed before the 12th infusions.
- A Spearman's rank-order correlation showed a weak negative correlation between age at natalizumab start and number of infusion received at PML diagnosis (rho=–0.192, 95% CIs from –0.056 to –0.321 with reiteration on 1000 bootstrap samples, p=0.004) **[Figure 1]**.
- This figure survived even after correction for multiple covariates, with correlation coefficients ranging from –0.283 to –0.174 (all p-values <0.05).
- The best possible age cut-off to discriminate early onset PML was 44 years (95% CIs from 32 to 48 with reiteration on 1000 bootstrap samples) according to receiver operator characteristic (ROC) analysis (area under the ROC curve: 0.603, 95% CIs from 0.535 to 0.668; p=0.022).
- The proportions of patients who developed early onset PML were 19% (30/154) in those ones aged equal or less than 44 years and 36% (24/66) in those ones aged above 44 years at natalizumab start **[Figure 2]**.
- A multivariable logistic regression was performed to ascertain the effect of age at natalizumab start on the risk of early onset PML, after adjusting for country, sex, and previous immunosuppressant exposure.
- Overall, there was a 4%-increased risk of early onset PML for each year of aging at natalizumab start (95% CIs from 1.1 to 8.1, p=0.025).
- Patients older than 44 years at natalizumab start were 2.4 times more likely to develop early onset PML (95% CIs from 1.2 to 4.9, p=0.015); this risk remains significant even after inserting other covariates (p<0.05).
- A sensitivity analysis was conducted to explore the impact of different definitions of early onset PML (±2 infusions respect to the established cut-off of 24 infusions).
- The outcome definition did not affect our estimates, being the odds ratio 3.2 (95% CIs from 1.5 to 6.9, p=0.003) for the 22-infusion cut-off and 2.1 (95% CIs 1.1 to 4.2, p=0.031) for the 26-infusion cut-off.

Figure 1

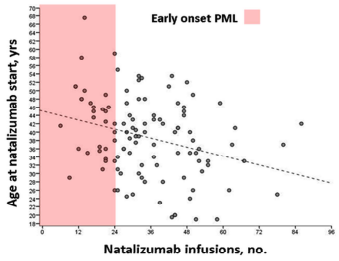
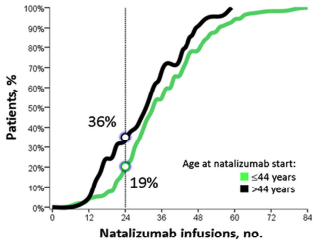


Figure 2



CONCLUSION

- Patients developing early onset PML were older at natalizumab start, with a 2.4-fold increased risk for ages above 44 years at treatment beginning.
- We hypothesize that age-associated impaired immune competence may at least partially explain our findings.
- Advanced age (i.e. about above 50 years) has been reported to be also a risk factor for PML under other MS therapies, such as fingolimod and dimethyl fumarate, suggesting that further efforts should be done to explore age as a risk stratifier for PML in patients on MS therapeutics.
- Our findings have a two-fold implication:

  (i) current recommendations to minimise PML risk in JCV-positive patients should be revised to encompass more frequent MRI scans as early as from the 12th infusion for older ages at natalizumab start;

  (ii) the phenomenon of immunesescence deserves further investigations in patients with MS treated with disease-modifying drugs that can further alter immune homeostasis.

DISCLOSURES

LP received consulting fees from Biogen and Novartis; speaker honoraria from Biogen, Genzyme, Novartis and Teva; travel grants from Biogen, Genzyme, Novartis and Teva; research grants from the Italian MS Society (Associazione Italiana Sclerosi Multipla) and Genzyme. CS has nothing to disclose. LI received consulting fees from Merck Serono and travel grants from Teva. NDR received speaker honoraria from Biogen and Teva and travel grants from Biogen, Teva and Merk Serono. CC received consulting fees from Novartis and Merk Serono. RC received consulting fees from Novartis, Biogen and lecture fees and/or travel grants from Novartis, Biogen, Genzyme and Sanofi-Aventis.

List of collaborators from the Italian PML study group (in alphabetic order): *Maria Pia Amato; Carlo Alberto Artusi; Fabio Bandini; Antonio Bertolotto; Vincenzo Bresciamorra; Guido Cavaletti; Paola Cavalla; Marco Capobianco; Marinella Clerico; Eleonora Cocco; Giangaetano D'Aleo; Marilena de Ria; Luciana Deotto; Luca Durelli; Maria Falcini; Eugenio Ferrari; Maria Luisa Fusco; Claudio Gasperini; Simonetta Gerevini; Angelo Ghezzi; Luigi Grimaldi; Mario Guidotti; Alessandra Lugaresi; Maria Giovanna Marrosu; Lucia Moiola; Paola Naldi; Patrizia Perrone; Matteo Pizzorno; Carlo Pozzilli; Monica Rezzonico; Marco Rovaris; Giuseppe Salemi; Marco Salvetti; Giuseppe Santuccio; Elio Scarpini; Edoardo Sessa; Claudio Solaro; Giulia Tabiadon; Carla Tortorella; Maria Trojano; Paola Valentino.*