Long-term management of natalizumab discontinuation in a large monocentric cohort of multiple sclerosis patients

Francesca Sangalli, Lucia Moiola, Laura Ferrè, Marta Radaelli, Valeria Barcella, Mariaemma Rodegher, Bruno Colombo, Filippo Martinelli Boneschi[1], Vittorio Martinelli and Giancarlo Comi

[1] Laboratory of genetics of neurological complex disorders and Department of Neurology, Institute of Experimental Neurology (INSPE), San Raffaele Scientific Institute, Milano, Italy;

Corresponding author:

Francesca Sangalli

Department of Neurology San Raffaele Scientific Institute

Via Olgettina, 48 20132 Milan Italy

e-mail address: sangalli.francesca@hsr.it

telephone: +39 02 2643 2990

ABSTRACT

Background: Several pPivotal and post-marketing studies showed demonstrated the efficacy and the good tolerability profile of natalizumab (NTZ) in Multiple Sclerosis (MS) patients. On the other hand, long-term safety of natalizumab NTZ therapy is burdened by the risk of progressive multifocal leukoencephalopathy, especially in anti-JCV seropositive patients treated for more than two 2 years, who sometimes are required. Therefore the need to stop natalizumab the treatment drug aroused, thus disclosing the issue ofat the risk of disease reactivation. **Objectives:** To evaluate the effects of natalizumab discontinuation in a monocentric cohort of MS patients followed for a mean time of 22.4 months and to compare the efficacy of different therapeutic strategies in this period of time. **Methods:** One hundred and ten MS patients who stopped NTZ after >12 infusions have been followed with periodic clinical and magnetic resonance imaging (MRI) evaluations.One hundred and ten patients stopped therapy after at least 12 infusions.. After drug interruption, oOne hundred patients of them started either immunomodulant therapy (nN=90) or fingolimod (nN=10), while 10 patients didn't start any treatmentremained without any drugs. We followed them with periodic clinical and magnetic resonance imaging (MRI) evaluations. **Results:** "Disease-activity free" patients were 25% at one year after discontinuation, and annualized relapse rate significantly increased from 0.06 to 0.84 compared to 0.06 on treatment (p<0.0001). We found that the risk of reactivation peaked despite alternative concomitant treatments bBetween the second and the eighth month after suspension, a so-called "high risk period", during which , risk of reactivation peaked despite alternative treatments; the majority of patients (xx?) showed a return to pre-natalizumab disease activity while and 10% of patients them presented "rebound activity". A higher pre-natalizumab disease activity is was correlated with an increased risk of reactivation (p=?).

Formattato: Tipo di carattere: Non Corsivo

Conclusions: Our data suggest that disease reactivation peaked during a "high risk period" between the second and the eighth month since stopping the drug. During this period, no alternative concomitant treatments seemed to provide an adequate protection from disease reactivation. Though transient, this phase could be potentially dangerous, therefore we need to develop more effective ~~better~~ strategies to deal with this challenge.

INTRODUCTION

Natalizumab is a monoclonal antibody directed against α4 subunit of integrin expressed on the surface of activated T-cells, preventing their transmigration through the blood-brain barrier (Chaudhuri et al, 2003). Post-marketing studies have confirmed both short and long term persistence of natalizumab efficacy in Multiple Sclerosis (MS) patients (Oturai et al., 2009; Putzki et al., 2010). However its profile is burdened with the risk of progressive multifocal leukoencephalopathy (PML), especially beyond 24 infusions (Clifford et.al, 2010). Nowadays the combination of anamnestic information and the result of anti-JC virus antibodies test allows a better assessment of PML risk, towards a more individualized treatment approach. (Sorensen et al., 2012; Bloomgren et al., 2012). For this reason, International Drug Agencies including FDA and EMEA recommended to re-evaluate natalizumab the bBenefit-Risk profile after two years of treatment in light of the increased risk of PML (puoi dare un link come referenza del documento emesso da queste agenize nel quale si precisa questo aspetto). On the other hand, the need to stop natalizumab treatment enlightened the risk of disease reactivation. A natalizumab phase II clinical trial already showed that the interruption of natalizumab treatment was associated to evidence of radiological and clinical activity (Miller et al., 2003). Afterward, some post-marketing studies suggested that stopping natalizumab therapy was associated with a rebound of clinical and MRI activity beyond the expected disease reactivation level in a significant proportion of patients starting three months after the drug interruption (Killestein et al., 2010; Kerbrat er al., 2011; Vellinga et al., 2008; Havla et al., 2011). Instead, some other studies showed a substantial return to pre-natalizumab disease activity (O'Connor et al., 2011; Stüve et al, 2009; Kaufman et al., 2011). Nevertheless, the reliability of these observations has been questioned because the majority of these studies consisted of small case series and/or short term observations.

Formattato: Evidenziato

Formattato: Evidenziato

The objective of this monocentric prospective study is to evaluate the effects of natalizumab discontinuation in a large cohort of patients with a follow-up of two years. The proportion of

patients who presented clinical relapses and/or new or enlarging T2-weighted lesions and/or Gadolinium (Gd)-enhancing lesions was assessed. The effect of different alternative therapeutic options on the prevention of disease reactivation was also evaluated.

MATERIAL AND METHODS

We collected clinical and MRI data of 110 consecutive MS patients, followed as out-patients at the San Raffaele MS Centre in Milan, who stopped natalizumab after at least one year of therapy. This study was planned within a post-marketing program ~~of evaluating~~aimed to evalutate the b~~B~~enefit-r~~R~~isk profile of ~~natalizumab~~ NTZ treatment. Included patients underwent a mean of 24 ± 10.7 natalizumab courses (range: 12-57). Demographic and clinical data of patients are shown in Table 1.

The mean follow-up after natalizumab discontinuation was 22.4 months (range: 6.3-37.8).

Reasons for drug discontinuation were: a) a shared decision with the treating neurologist due to anti-JC virus seropositivity combined with other risk factors (long treatment duration and/or previous use of immunosuppressive treatment) (n=94); b) self decision based on fear of PML (n=10) before the availability of anti-JC virus testing; c) pregnancy planning (n=6). ~~Ten patients decided on their own to discontinue natalizumab before the availability of anti-JC virus testing for fear of PML. Ninety four patients interrupted natalizumab after a shared doctor patient choice because of anti JC virus seropositivity combined with other risk factors (long treatment duration and/or previous use of immunosuppressive treatment). Additional 6 patients withdrawn therapy due to desire of pregnancy.~~

After ~~stopping natalizumab~~NTZ stop, we proposed to all patients ~~the~~ to ~~beginning~~ shift to ~~of~~ an alternative therapy ~~to all patients.~~ For patients who received natalizumab because of a breakthrough disease, the choice was based on a shared doctor-patient decision. Ninety patients (81.8%) started immunomodulant therapy, either glatiramer acetate (72 patients) or different formulations of ~~beta~~ interferon-beta (18 patients) within approximately one month after last natalizumab infusion. The choice between these two first-line treatments was based on which treatment the patients did not respond to in the pre-natalizumab period. Ten (9.1%) additional

patients who discontinued natalizumab started oral therapy with fingolimod after a mean of 4.6 months (range 3-6), such ~~. This~~ option ~~was~~ being available ~~only since~~since April 2012. The remaining 10 patients (9.1%) did not start any disease modifying treatment (6 for ~~desire of~~ pregnancy planning and 4 for refusal of injective therapy before ~~the availability of~~ fingolimod availability). ~~In order to prevent disease reactivation~~Moreover, 25 patients (22.7%) underwent monthly courses of intravenous (iv) methylprednisolone (1 g for 2 days ~~of 1 gram of~~) ~~intravenous (i.v.) methylprednisolone~~ starting 2 months after natalizumab discontinuation in addition to disease modifying therapies.

Neurological examinations were performed every three months, or in case of exacerbation. Most p~~P~~atients underwent brain MRI scans approximately at the 3rd (± 1), 6th (± 1) and 12th month (+3) after natalizumab interruption. Additional MRI scans ~~were sometime~~ have been performed in case of ~~if a~~ relapse occurrenc~~ed~~. One hundred patients (91.1%) underwent the 3rd month brain MRI and 80 (72.7%) the 6th month scan; all patients had at least one MRI in the first six months after ~~natalizumab~~ NTZ discontinuation. Moreover, 74 patients (67.2%) had a brain MRI ~~at~~ one year after ~~discontinuation~~drug stop. We ~~considered~~ defined new or enlarging T2-weighted lesions and/or Gadolinium (Gd)-enhancing lesions as active scans ~~those with new or enlarging T2-weighted lesions and/or Gadolinium (Gd) enhancing lesions~~. ~~Patients were classified as "disease activity free" if the absence of relapses was combined with the absence of active scans and disease progression.~~ Disease progression was defined as an increase ~~of Expanded Disability Status Scale (EDSS)~~ of 1.0 point on the Expanded Disability Status Scale (EDSS) for patients with baseline EDSS ≤ ~~or =~~ 5.5 and of 0.5 point for baseline EDSS ≥ ~~or =~~ 6.0. Patients were classified as "disease activity free" if the absence of relapses was combined with the absence of active scans and disease progression.

Based on the ~~pre-natalizumab~~ radiological and clinical features of ~~the~~ disease activity before NTZ start, we divided our cohort of patients in two subgroups, named "highly active" and "lowly active".

Formattato: Sottolineato

Formattato: Sottolineato

We classified our patients as “highly active” if they presented an annualized relapse rate (ARR) ≥ 3 in the year prior to natalizumab and/or ≥ 4 gadolinium-enhancing lesions at baseline brain MRI. The remaining patients were defined as “lowly active”.

We also tried to identify patients who presented the conventionally called “rebound activity”, during ~~in~~ which the severity of relapses and/or the number of new T2 or Gd-enhancing lesions was much higher than the ~~-~~pre-natalizumab activity. Literature lacks of a clear and univocal definition of “rebound activity”, therefore we ~~opted~~ decided to perform a ~~for a case by case~~ review case by case of disease activity by MS-expert neurologists (metti le iniziali fra parentesi). We arbitrarily decided to classify patients as rebound activity having ~~Selected patients presented~~ at least one of the following features: a) a clinically significant increase of relapse rate in comparison to pre-natalizumab disease course (cosa intendi?); b) one or more severe relapses with sustained disability progression; c) 5 or more new ~~large~~ T2 lesions and/or at least 10 more Gd-enhancing lesions than pre-natalizumab baseline scan.

Formattato: Evidenziato

T-test was used to compare parametric variables and Mann-Whitney test for non-parametric ~~values~~ones. Kaplan-Meier curves were built to evaluate the proportion of patients free from relapses, MRI activity or combined disease activity at different time-points. We compared survival curves by performing the log-rank (Mantel-Cox) test.

Local Ethical Committee approval was obtained before data collection.

RESULTS

The proportion of patients who was relapse free during the follow up was 83% at 3rd month, 60% at 6th month and 44% at one year (figure 1–a). Half of the patients presented a relapse within 10 months after last natalizumab infusion (median survival time of 9.77 months). The ARR in the first year after natalizumab NTZ discontinuation significantly increased to 0.84 compared to 0.06 observed on during the NTZ treatment (p<0.0001).

The risk of rRelapse frequencys in the entire population had a peaked at in the 4th month, remained high until the 98th month and then returned to a level similar to the one observed during natalizumab treatment declined at the end of the first year after discontinuation to a value close to that observed during natalizumab treatment (figure 2).

Similarly, aAt one– year follow-up the mean median Expanded Disability Status Scale (EDSS) significantly increased from xx to 3.0 (p<0.001). Specifically , and 16 patients (14.5% of the total), who had a baseline EDSS ≥3.0 at the time of NTZ discontinuation,.experienced aas a result of relapses a sustained progression was observed in 16 patients (14.5% of the whole cohort), especially in the subgroup of patients with a baseline EDSS equal or greater than 3.0. of disability after NTZ stop.

The proportion of patients "free from MRI activity" was 85% at 3rd month 3, 54% at 6th month 6 and 35% at one year (figure 1-b). The mean number of Gd-enhancing lesions increased from 1.46 at the 3rd month 3 to 3.07 at the 6th month 6 and then declined to 1.700 at one year, compared to xx during NTZ treatment.

The proportion of "disease-activity free" patients was 75% at 3rd month 3, 42% at 6th month 6 and 25% at one year (figure 1-c). The risk of disease reactivation was higher between the second and the eighth month after natalizumab suspension. Toglierei la frase in rosso: è già stata detta piu' volte Beyond this time-point the slop reducedAfter 1-year of follow-up, the proportion of disease activity

Formattato: Sottolineato

Formattato: Evidenziato

free patients did not substantially change (~~even prolonging the time of observation up to 25 months for patients who remained in immunomodulatory treatment~~ (survival proportion of 18.4% at 25-month follow-up).

Patients who received an alternative disease modifying therapy after natalizumab discontinuation had a significantly higher probability to remain "disease-activity free" compared to untreated patients (30% versus 0% at 1-~~one~~ year f-up after NTZ discontinuation). On the contrary, the type of ~~treatment~~drug ~~–~~, whether immunomodulants like IFN or GA (IM) or fingolimod (FTY), had no ~~effects~~ impact on the ~~condition~~ proportion of disease activity free patients (p=) (figure 3). In particular, a disease reactivation was observed in 6 ~~out of the~~ /10 patients who started fingolimod treatment and in xx/xx who began immunomodulant ones (p=). Moreover, we did not find any evidence of disease activity reduction in t~~T~~he 25 patients who received preventive steroid courses ~~monthly i.v. methylprednisolone cycles~~ after NTZ treatment compared to those who did not receive them (p=)~~did not show a significant lower level of MS activity if compared to patients who did not receive preventive steroid courses~~.

Twenty-five (34%) of 73 patients showing disease reactivation ~~during immunomodulante treatments~~under IM therapy in the first year after NTZ stop shifted to second-line therapies within 3 months after relapse and/or active MRI occurrence. Specifically 16 returned to natalizumab and 9 started ~~other~~ alternative second-line therapies (~~i.e.~~ fingolimod, n~~N~~=7~~;~~, ~~or i.v. immunosuppression with~~ pulsed cyclophosphamide immunosuppression,~~;~~ ~~N~~n=2). We compared these two groups of patients with 48 patients who did not change ~~disease modifying~~ therapy. At a mean follow ~~–~~up of 17 months we found a significant ~~lower risk of persistent~~reduction of frequency of disease activity in ~~the~~ those who returned to ~~natalizumab group~~NTZ (p< 0,05), while there was no apparent advantage in shifting to other second-line therapies (p=ns), even if data were inflated by a small sample size.~~;~~ ~~these data are probably affected by the small number of patients included in this analysis~~. Overall the risk of disease reactivation after NTZ stop was ~~statistically correlated~~increased in patients ~~both~~

with a higher ARR in the ~~last~~ year before ~~starting natalizumab~~NTZ start (2.08 in reactivated patients versus 1.54 in stable ~~patients~~ones~~;~~, p<0.005) and in those with a higher ~~mean~~ number of enhancing lesions in ~~the~~ pre-treatment brain MRI (2.60 versus 1.08~~;~~, p<0.~~037~~04). Moreover, patients defined as "highly active" in the year prior to natalizumab (ARR ≥ 3 and~~/~~ or ≥ 4 gadolinium-enhancing lesions at baseline brain MRI) had a higher risk of disease reactivation (xx vs xxx; p=0.004)~~;~~ (figure 4).

Formattato: Tipo di carattere: Non Corsivo

Finally we compared clinical and radiological disease activity in the period after NTZ stop with the one in the ~~reactivation after discontinuation to disease activity in the~~ year before starting natalizumab. Post-~~natalizumab~~ NTZ ARR was significantly lower than pre-~~natalizumab ARR~~NTZ one (1.98 v~~ersu~~s 0.84~~;~~, p<0.05). However it is interesting to note that the mean number of Gd-enhancing lesions at the 6th month after discontinuation was significantly higher than the number observed at the beginning of natalizumab treatment (3.07 v~~ersu~~s 2.24~~;~~, p<0.001).

Moreover we identified 11 patients (10%) who presented the conventionally called *rebound activity* in which the severity of relapses and/or the number of new T2 or Gd-enhancing lesions was ~~much~~ higher than pre-natalizumab activity. Specifically, 4 patients had ~~both~~ either clinical and neuro-radiological severe reactivation, ~~whereas~~ 5 patients ~~showed~~ only a remarkable MRI rebound activity, and remaining ~~. The last~~ two patients ~~experienced~~ had a ~~very~~ disabling relapse with only ~~a~~ few enhancing lesions probably because MRI scan was performed after i.v. steroid therapy.

DISCUSSION

Since natalizumab safety profile ~~forces~~ demands ~~to cautiously~~a cautious evaluation of its~~e~~ long-term ~~treatment~~use, concerns on disease reactivation after natalizumab suspension were addressed in many reports. Altogether available data confirm that disease stability, reached during natalizumab therapy, does not continue after treatment discontinuation, since the drug does not cause long-term immunological changes.

Our study is the result of ~~everyday clinical practice and was~~a real world study conducted in one of the largest monocentric cohort ~~–~~of MS patients stopping natalizumab with a 1-year follow-up~~.~~ ~~Moreover patients were followed for more than a year~~ thus providing long term data on disease course after ~~withdrawal from~~ natalizumab withdrawal. ~~These strengths could at least partially compensate the expected bias of every nonrandomised study conducted in the clinical setting.~~ Till now, a~~-~~part from ~~many~~ several observational studies with smaller cohorts than ours (references?), there is only one ongoing clinical trial (RESTORE) ~~which~~ that compares patients continuing natalizumab with ~~patients~~ those ~~receiving~~ using placebo or an alternative treatment (~~glatiramer acetate~~GA, ~~beta interferon~~IFN-beta or ~~IV~~ iv steroids according to neurologists' choice). Preliminary data of this trial showed a proportion of disease reactivation of about 50% seven months after withdrawal from natalizumab, with no significant differences between ~~either in the~~ placebo ~~or in~~and the alternative treatment ~~group~~ arm (Kaufman et al., 2012).

~~Our data show~~In this papr we show that only a quarter ~~25%~~ of our patients remained ~~"~~disease-activity free~~"~~ one year after discontinuation. ~~As~~ It is known ~~in~~ from the literature that the concentration of~~,~~ ~~natalizumab concentration~~NTZ progressively decrease within 3 months, whereas changes induced on the immune system could be detected until 6 months after discontinuation (Stüve et al, 2006). Accordingly we found a peak of ~~the risk of~~ relapse risk in the ~~at the~~ 4th ~~th~~ month after discontinuation, ~~and this~~the risk ~~is still~~being high until~~at~~ ~~the 8th~~ month 8 and decreasing at 1-year follow-up~~while after one year it returns to a lower value~~. Similarly ~~we have the~~

~~maximum number of~~also g~~G~~d-enhancing lesions at MRI scans ~~performed~~ were more frequent at the 6th month period after NTZ ~~suspension~~stop, being~~.~~ ~~The mean number of enhancing lesions~~ at this time point ~~is significantly~~ higher ~~even if compared to brain scans performed~~than in the period before ~~the beginning of natalizumab therapy~~NTZ start. Our study confirmed literature data since the majority of our patients showed a substantial return to their pre-natalizumab disease activity (references?). However according to clinical and radiological data only 10% of our cohort presented the so-~~-~~called rebound activity. Interestingly disease reactivation was observed mostly during a ~~"~~high risk period~~"~~ between the second and the eighth month after drug discontinuation. Then, after this period, we observed a reduction in the slop of the survival curve of disease activity, as well as a decline of relapse risk and ~~of the mean~~ number of Gd-enhancing lesions (figure 1 and 3).

Higher ARR and ~~mean~~ higher enhancing lesions in the year before natalizumab were identified as predictive factors associated to an increased risk of disease recurrence. Likewise O'Connor found that patients enrolled in~~of~~ ~~registrative~~ registered trials with a higher level of prior-to-natalizumab disease activity tended to have a higher ARR after discontinuation (O'Connor et al., 2011).

Our study was also aimed to evaluate the effects of starting an alternative treatment soon after natalizumab interruption. According to our analysis, first-line immunomodulants can reduce the degree of reactivation after natalizumab discontinuation only in a subgroup of patients~~however they fail to prevent it in most of the patients~~. These findings are consistent with data published by O'Connor (O'Connor et al., 2011) and Cohen (Cohen M et al., 2013) who observed a return of MS activity regardless the beginning of preventive therapy after natalizumab ~~suspension~~stop. Moreover we did not observe a statistically significant effect of ~~doses of i.v. methylprednisolone~~intravenous steroid cycles in preventing MS reactivation as reported in another survey (Borriello et al., 2012).

Considering that seventy-five percent of our cohort showed signs of disease reactivation after NTZ discontinuation, patients should be closely monitored -to detect clinical and/or radiological disease activity ~~as soon as possible~~ in order to readily change preventive therapy or~~,~~ even ~~going back~~to

return to natalizumab therapy despite PML risk. A strict clinical observation is even more important for patients with residual disability after relapse occurrence~~considering that relapses might result in a sustained progression~~.

Moreover, given that a higher pre-natalizumab disease activity seems to be a factor predicting reactivation, a careful evaluation of single-patient b~~B~~enefit-r~~R~~isk ratio is mandatory when stopping natalizumab. Patients at risk of developing PML ~~have also to~~should be stratified according to ~~MS~~ their own disease history, i.e. clinical characteristics before ~~starting natalizumab~~NTZ start, as well as ~~and~~ to residual therapeutic options and ~~, as well as~~ possible contraindications to other therapies.

Due to delays in ~~the authorization of~~ fingolimod approval in Italy, only a ~~very~~ small proportion of our patients started ~~the~~ an oral drug after natalizumab discontinuation, therefore we cannot give indication on its efficacy in preventing reactivation. The lack of difference of efficacy between fingolimod and ~~apparent similarity of behavior with~~ immunomodulants as shift therapy ~~that we~~ observed in our study could be ~~just~~ a statistical ~~bias due to~~artifact determined by the small sample size. Therefore, m~~M~~ore data are needed to determine if fingolimod could be a feasible therapeutic option ~~just~~ after natalizumab, even if it is worthwhile to mention that ~~first reports in literature show~~ disease reactivation was detected in half of the patients shifting to oral therapy by an Italian group (Rinaldi et al., 2012). More r~~R~~ecently, in a cohort of MS patients recruited for a safety study, those who started fingolimod after natalizumab discontinuation showed a low risk of relapses (aggiungi I numeri). Nevertheless this risk ~~is~~ was 3-fold higher in patients starting fingolimod 3-6 months after natalizumab compared ~~with~~ to naive patients who never received natalizumab (Comi et al., 2013).

CONCLUSIONS

In ~~our cohort~~this cross-sectional study, 3 out of 4 patients presented disease reactivation despite the ~~starting~~ beginning of an alternative treatment after natalizumab discontinuation. This observation suggests that at least between the second and the eighth month after the last dose, the so called ~~"~~high risk period~~"~~, n~~either~~~~or~~ immunomodulants nor fingolimod provide an adequate protection from disease reactivation. This phase, though transient, could be potentially dangerous, since 14.5% of our patients showed sustained progression as a result of relapses; therefore, we need to develop ~~better~~ more effective strategies to deal with ~~such a~~this challenge. ~~Frequent~~ Serial MRI evaluations in the first 6-8 months after discontinuation m~~ay~~ight help to detect patients with strong disease reactivation. In these patients, a more aggressive approach, such as an immunosuppressive treatment with ~~i.v.~~ pulsed cyclophosphamide, could be attempted. Finally in patients with lower risk of PML the opportunity to restart natalizumab should also be considered in combination with close clinical and MRI monitoring.

REFERENCES

Bloomgren G, Richman S, Hotermans C, Subramanyam M, Goelz S, Natarajan A, et al. Risk of natalizumab associated progressive multifocal leukoencephalopathy. N Engl J Med. 2012;366(20):1870-80.

Borriello G, Prosperini L, Mancinelli C, Gianni C, Fubelli F, Pozzilli C. Pulse monthly steroids during an elective interruption of natalizumab: a post-marketing study. Eur J Neurol. 2012;19(5):783-7.

Chaudhuri A, Behan PO. Natalizumab for relapsing multiple sclerosis. N Engl J Med. 2003;348(16):1598-9.

Clifford DB, De Luca A, Simpson DM, Arendt G, Giovannoni G, Nath A. Natalizumab-associated progressive multifocal leukoencephalopathy in patients with multiple sclerosis: lessons from 28 cases. Lancet Neurol. 2010;9(4):438-46.

Cohen M, Maillart E, Papeix C, Vukusic S, Brassat D. ENIGM: A French Observational Study about Switching from Natalizumab to Fingolimod in Multiple Sclerosis AAN 2013;S41.002

Comi G, Gold R, Dahlke F, Sinha A, von Rosenstiel P, et al. Relapse outcomes in fingolimod-treated patients previously exposed to natalizumab: post-hoc Aanalysis from the 4-month, open-label FIRST Study. AAN 2013;P07.103

Havla J, Gerdes LA, Meinl I, Krumbholz M, Faber H, Weber F, et al. De-escalation from natalizumab in multiple sclerosis: recurrence of disease activity despite switching to glatiramer acetate. J Neurol. 2011;258(9):1665-9.

Kaufman MD, Lee R, Norton HJ. Course of relapsing-remitting multiple sclerosis before, during and after natalizumab. Mult Scler. 2011;17(4):490-4.

Kaufman M, Cree B, De Seze J, et al. Effects of a 24-week natalizumab treatment interruption on clinical and radiologic parameters of multiple sclerosis disease activity: the RESTORE study. ENS 2012;O262

Kerbrat A, Le Page E, Leray E, Anani T, Coustans M, Desormeaux C, et al. Natalizumab and drug holiday in clinical practice: an observational study in very active relapsing remitting multiple sclerosis patients. J Neurol Sci. 2011;308(1-2):98-102.

Killestein J, Vennegoor A, Strijbis EM, Seewann A, van Oosten BW, Uitdehaag BM, et al. Natalizumab drug holiday in multiple sclerosis: poorly tolerated. Ann Neurol. 2010;68(3):392-5.

Melin A, Outteryck O, Collongues N, Zephir H, Fleury MC, Blanc F, et al. Effect of natalizumab on clinical and radiological disease activity in a French cohort of patients with relapsing–remitting multiple sclerosis. J Neurol 2012;259(6):1215-21.

Miller DH, Khan OA, Sheremata WA, Blumhardt LD, Rice GP, Libonati MA, et al. A controlled trial of natalizumab for relapsing multiple sclerosis. N Engl J Med. 2003;348(1):15-23.

O'Connor PW, Goodman A, Kappos L, Lublin FD, Miller DH, Polman C, et al. Disease activity return during natalizumab treatment interruption in patients with multiple sclerosis. Neurology. 2011;76(22):1858-65.

Oturai AB, Koch-Henriksen N, Petersen T, Jensen PE, Sellebjerg F, Sorensen PS. Efficacy of natalizumab in multiple sclerosis patients with high disease activity: a Danish nationwide study. Eur J Neurol 2009;16:420-3.

Putzki N,Yaldizli O, Maurer M, et al. Efficacy of natalizumab in second line therapy of relapsing-remitting multiple sclerosis: results from a multi-center study in German speaking countries. Eur J Neurol 2010;17:31–37.

Rinaldi F, Seppi D, Calabrese M, Perini P, Gallo P. Switching therapy from natalizumab to fingolimod in relapsing-remitting multiple sclerosis: clinical and magnetic resonance imaging findings. Mult Scler. 2012;18(11):1640-3.

Sorensen PS, Bertolotto A, Edan G, Giovannoni G, Gold R, Havrdova E, et al. Risk stratification for progressive multifocal leukoencephalopathy in patients treated with natalizumab. Mult Scler. 2012;18(2):143-52.

Stüve O, Cravens PD, Frohman EM, Phillips JT, Remington GM, von Geldern G, et al. Immunologic, clinical, and radiologic status 14 months after cessation of natalizumab therapy. Neurology. 2009;72(5):396-401.

Stüve O, Marra CM, Jerome KR, Cook L, et al. Immune surveillance in Multiple Sclerosis patients treated with natalizumab. Ann Neurol. 2006;59:743–747.

Vellinga MM, Castelijns JA, Barkhof F, Uitdehaag BM, Polman CH. Postwithdrawal rebound increase in T2 lesional activity in natalizumab-treated MS patients. Neurology. 2008;70(13 Pt 2):1150-1.

FIGURE

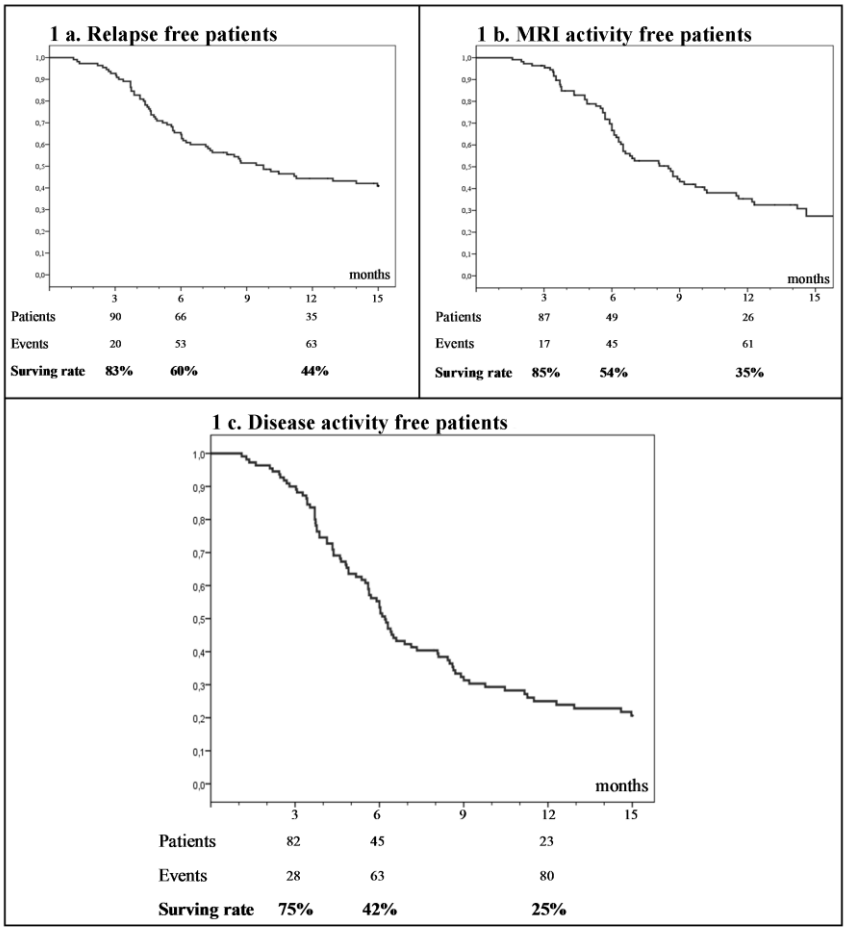

Figure 1. Panel a. Survival curve of relapse~~-s~~ free patients. Number of patients available for analysis (patients), number of observed events (events) and proportion of "relapse free" patients (surviving rate) are written under major time-points. Panel b. Survival curve of MRI activity~~--~~free patients. Number of patients available for analysis (patients), number of observed events (events) and proportion of ~~"~~MRI activity~~--~~free~~"~~ patients (surviving rate) ~~patients~~ are written under major time-points. Panel c. Survival curve of disease activity~~--~~free patients. Number of patients available for analysis (patients), number of observed events (events) and proportion of MRI activity-free patients (surviving rate) are written under major time-points. ~~Number of patients available for analysis,~~

~~number of observed events and proportion of "disease activity free" patients are written under major time points.~~ In all panels, the x~~X~~ a~~A~~xis ~~shows~~ refers to the months after ~~natalizumab~~ NTZ discontinuation.

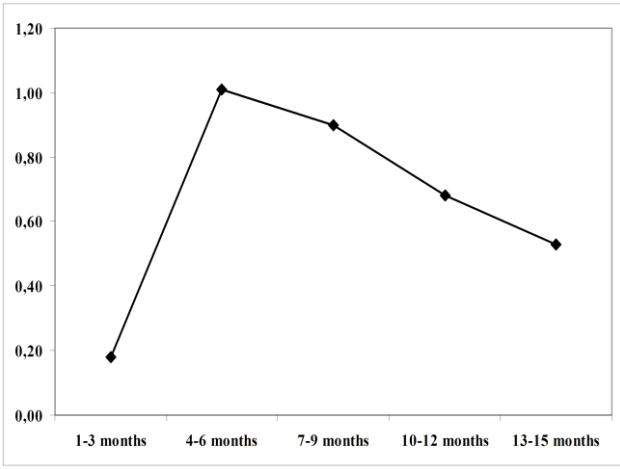

Figure 2. Annualized relapse rate (ARR) taken ~~at~~ during different time ~~points~~ intervals after natalizumab discontinuation. ARR peaks at 4-6 months, then it progressively decrease. The x axis refers to the months after NTZ discontinuation.

Io aggiungerei anche il livello di ricadute durante il trattamento con NTZ (puoi mettere solo un punto: NTZ treatment).

Formattato: Evidenziato

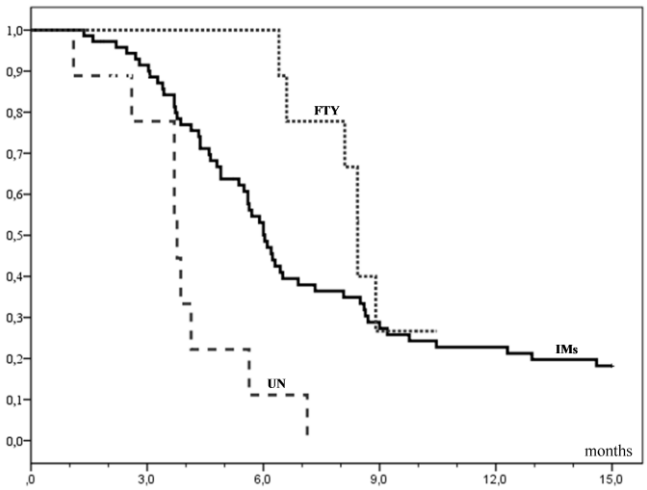

Figure 3. Survival ~~curves~~analysis of disease activity~~-~~free patients after ~~natalizumab~~ NTZ discontinuation comparing untreated patients (UN; dashed line), ~~and patients~~those who ~~receiving~~ received ~~either~~ immunomodulant therapy (IMs; dotted line) and those~~or~~ who were treated with fingolimod (FTY; continuous line). The x~~X~~ a~~A~~xis shows the months after natalizumab discontinuation. P values refer to the log-rank test (aggiungi I p-values).

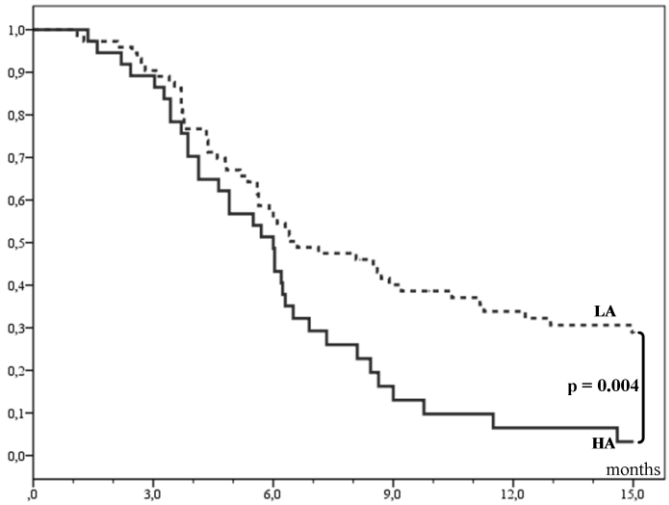

Figure 4. Survival ~~curves~~ analysis of disease activity-free patients ~~free from disease activity~~ after ~~natalizumab~~ NTZ discontinuation comparing ~~a group of~~ pre-natalizumab "highly active" patients (HA; continuous line) and ~~a group of~~ pre-natalizumab "lowly active" patients (LA; dashed line).

The x axis shows the months after natalizumab discontinuation.

The p value refers to the log-rank test.

~~Difference observed is statistically significant (p=0.004). X Axis shows months after natalizumab discontinuation.~~