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Anti-CD20 Drugs and Natalizumab Confer Equal Protection Against Progression Independent of Relapse Activity (PIRA) in People With Multiple Sclerosis

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ABSTRACT

Background: Highly effective (HE) disease-modifying therapies (DMTs) reduce relapse-associated worsening (RAW) and progression independent of relapse activity (PIRA). Natalizumab (NTZ) and anti-CD20 agents show similar efficacy on relapse suppression, but long-term comparative data on PIRA are limited. We aimed to compare PIRA accrual in relapsing–remitting MS (RRMS) patients treated with NTZ and anti-CD20 drugs over a long follow-up.

Methods: We included RRMS patients followed at our centre and recorded in the Italian MS and Related Disorders Register with at least 5 years of continuous treatment with NTZ or anti-CD20 agents (Ocrelizumab, Rituximab, Ofatumumab), at least 3 Expanded Disability Status Scale (EDSS) assessments, and complete demographic and clinical data. Patients were matched for gender, age, EDSS, disease duration, MS phenotype at treatment initiation. Logistic regression and Cox proportional hazard models were applied.

Results: Of 267 eligible patients (178 NTZ, 89 anti-CD20), optimal matching yielded 89 balanced pairs. A first PIRA event was observed in 27.0% of NTZ-treated and 28.1% of anti-CD20-treated patients. The total number of PIRA events was comparable between NTZ-treated and anti-CD20-treated patients (36 vs. 30; $p = 0.451$). Adjusted analyses revealed no significant differences in cumulative risk (RR: 1.48; 95% CI: 0.66–3.40; $p = 0.333$) or time to first PIRA event (HR: 1.51; 95% CI 0.83–2.77; $p = 0.179$).

Conclusion: In this real-world cohort with long-term follow-up, NTZ and anti-CD20 therapies showed no significant differences in PIRA accrual or time to first PIRA, suggesting comparable long-term control of disability progression beyond relapse. Larger studies are warranted to confirm and refine these observations.

1 | Introduction

Recent observations have challenged the phenotypical dualism between relapsing and progressive multiple sclerosis (MS), highlighting that a mutual contribution of relapse-associated worsening (RAW) and progression independent of relapse activity (PIRA) exists in traditionally classified relapsing–remitting MS patients (RRMS) [1]. PIRA events, especially those that occurred early in the disease course, have been demonstrated to be predictors of unfavourable long-term disability prognosis [2].

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The advent of highly effective (HE) disease modifying therapies (DMTs) has radically changed the prognosis of MS patients, and these drugs have proved effective in reducing accumulation of PIRA events [1]. Among HE DMTs, Natalizumab (NTZ) and anti-CD20 drugs have demonstrated efficacy in reduction of disability accrual [3–9]. Previous comparative studies reported overall favourable and comparable effectiveness of NTZ and anti-CD20 therapies using no evidence of disease activity (NEDA-3) and its components as outcome measures [5–7]. More recently, two studies directly comparing PIRA outcomes between these treatments also reported comparable effects [8, 9]. However, there is a lack of data comparing the effectiveness of these two drugs on PIRA accrual over a long follow-up. This framed the scope of the present investigation, where we aimed at comparing the risk of PIRA accrual between patients treated with NTZ and those treated with anti-CD20 in a cohort of RRMS patients treated at our centre.

2 | Methods

2.1 | Study Population and Outcomes

We conducted a retrospective analysis on MS patients followed at the MS Center of San Raffaele Hospital (Milan), with longitudinal clinical records extracted from the Italian MS and Related Disorders Register (IMS&RD). All patients signed an informed consent for the recording and use of their clinical data for research purposes. The study was approved by the local ethical committee.

We included patients with a diagnosis of RRMS as per 2017 McDonald's criteria, treated with NTZ or anti-CD20 drugs (including Ocrelizumab, Rituximab and Ofatumumab) for at least 5 years, with at least 3 EDSS score evaluations, and available demographics and clinical information. For patients who switched between different anti-CD20 therapies, treatment periods were considered cumulatively, summing the duration of exposure across all anti-CD20 agents. Patients who received Rituximab started anti-CD20 therapy before Ocrelizumab and Ofatumumab approval. The baseline EDSS score evaluation was set at ≥ 3 months from DMT start. We kept in the analyses patients with temporary treatment interruption for less than 3 months, such as those who postponed intravenous anti-CD20 therapy for up to 3 months based on CD19 cell count, delayed Ofatumumab administration for a few weeks, or temporarily discontinued NTZ due to pregnancy. Patients with treatment interruptions ≥ 3 months were excluded.

PIRA was defined according to the proposed standardised definition by Muller et al. [10], i.e., a disability worsening compared with a baseline (reset after each PIRA event, relapse, and EDSS score improvement), occurring in the absence of relapses since the previous EDSS, confirmed with EDSS scores (not preceded by relapses within 30 days) that remained above the worsening threshold for at least 12 months. PIRA events were identified using recorded EDSS scores, independently of the availability of individual Functional System scores, by means of the msprog R package [11].

Disability worsening was defined as an increase of EDSS of at least 1.5 points from a baseline score of 0, 1 or more points from a baseline EDSS score of 1.0 to 5.5, and at least 0.5 points from a baseline EDSS score of 6 or more [10].

The study endpoint was the number of PIRA events occurring during exposure to each treatment.

2.2 | Statistical Analysis

To mitigate the impact of potential biases, patients were matched based on gender, age, EDSS, disease duration and MS phenotype at DMT start. Matching was performed using the MatchIt package in R [12]. Three pairwise 1:1 matching methods were applied, i.e., nearest neighbour, optimal, and Mahalanobis distance matching. The quality of the procedure in each pair of matched cohorts was assessed with absolute standardised mean difference (SMD), considering SMD less than 10% acceptable, as absolute value. Among the three approaches, the optimal matching was selected over the other two methods, based on maximisation of the final sample size while maintaining all matching variables below the predefined SMD threshold. This defined the analytical cohorts on which the efficacy comparisons for protection against PIRA events were subsequently performed.

We fitted negative binomial regression model to compare the cumulative PIRA event accrual between the two matched populations, including the logarithm of time on treatment as offset variable. Cox proportional hazard model was employed to assess the risk of reaching the first PIRA event. Analyses were adjusted for the number of EDSS assessments, baseline inflammatory disease activity, defined as the evidence of any clinical or neuroradiological (i.e., new lesions in T2/FLAIR sequences or contrast-enhancing lesions) disease activity in the 2 years preceding the DMT start, and prior DMT exposure at baseline. $p < 0.05$ were deemed statistically significant. All analyses were performed using the R Statistical Software version 4.4.1 (R Foundation for Statistical Computing, Vienna, Austria).

3 | Results

A total of 178 patients treated with NTZ and 89 treated with anti-CD20 drugs were selected after applying the inclusion criteria (Figure 1A). Application of the matching procedure subsequently resulted in 89 pairs of patients. Baseline characteristics of the study population before and after matching are reported in (Table 1). Median follow-up (IQR) after treatment start was 8.6 years (6.2–11.5) for the NTZ group and 5.8 years (5.5–6.5) for the anti-CD20 group. A first PIRA event was reached in 24 patients (27.0%) among the NTZ-treated group, and 25 patients (28.1%) from the anti-CD20-treated group. Median (IQR) time to first PIRA event was 6.3 years (4.5–9.2) among NTZ-treated patients and 5.0 years (3.9–5.5) among anti-CD20-treated patients. The total number of PIRA events was 36 in NTZ-treated patients and 30 in anti-CD20-treated patients ($p = 0.451$; Figure 1B, left panel). In adjusted negative binomial regression, using NTZ-treated patients as the reference group, anti-CD20-treated patients showed a comparable rate of PIRA event accrual [rate ratio (RR): 1.48; 95% confidence interval (CI): 0.66–3.40; $p = 0.333$]. Similarly, adjusted Cox

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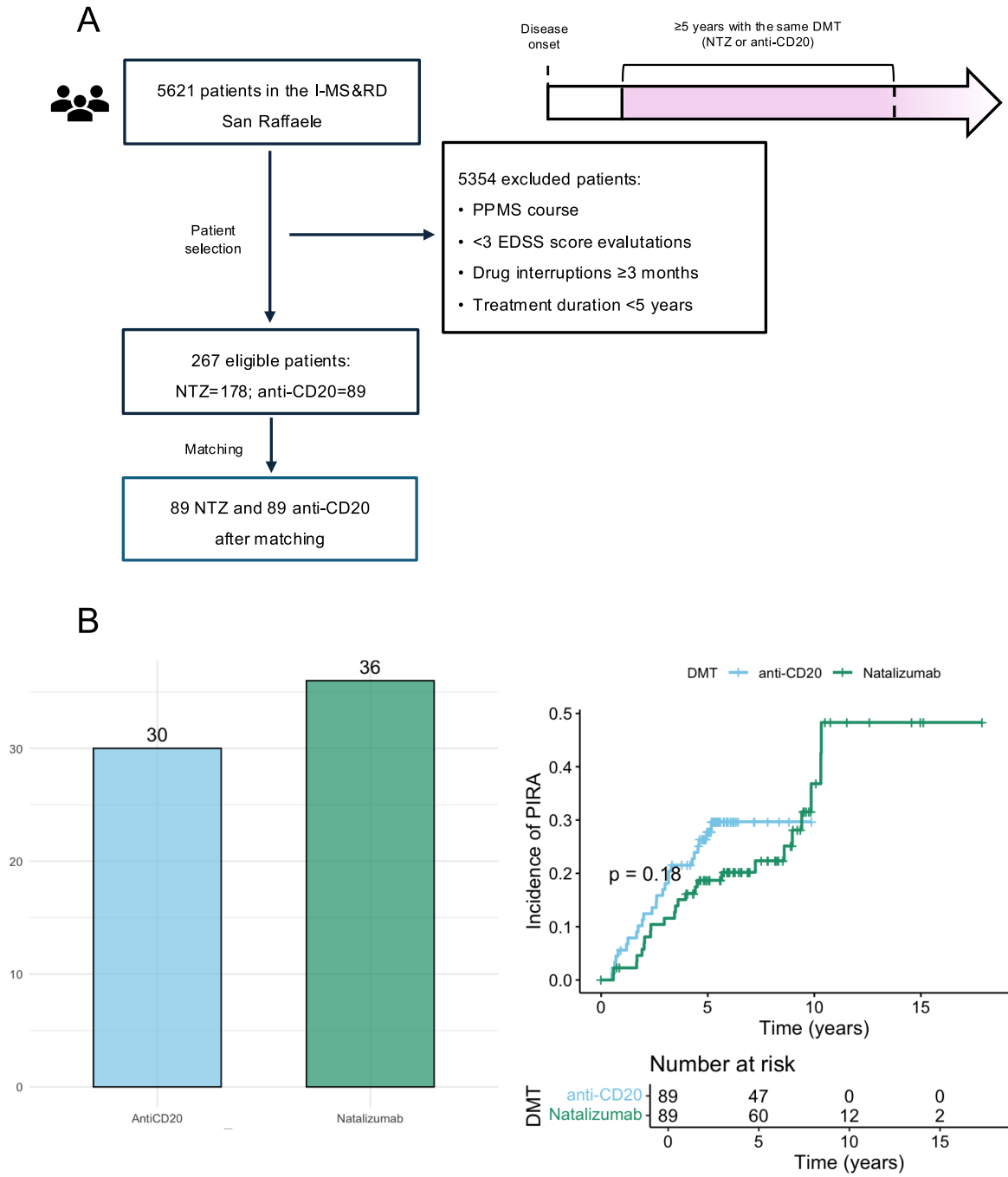


FIGURE 1 | (A) Flowchart of the study. (B) On the left bar plot displaying the total number of PIRA events in natalizumab-treated patients (green bar) compared with anti-CD20-treated patients (light blue bar). On the right Kaplan Meier curves and risk table of time to first PIRA in the two groups. The *p* value shows the result of the log rank test.DMT, Disease modifying therapy; EDSS, Expanded disability status scale; I-MS&RD, Italian MS and Related Disorders Register; NTZ, Natalizumab; PPMS, Primary progressive MS.

regression analysis revealed that hazard of reaching the first PIRA event did not significantly differ between NTZ-treated and anti-CD20-treated patients [hazard ratio (HR): 1.51; 95% CI: 0.83–2.77; $p = 0.179$; (Figure 1B), right panel].

4 | Discussion

In this study, we compared the effect of NTZ and anti-CD20 drugs on PIRA event accrual over at least 5years follow-up in a real-life cohort of RRMS patients. All the newly approved HE DMTs have demonstrated an excellent profile of effectiveness in reducing clinical and radiological disease activity over the years, with NTZ and anti-CD20 drugs reaching the highest ranking of effectiveness both in clinical trials and real-world settings with a well-established safety profile [13].

However, the assessment of DMT effect on PIRA accrual has not been properly investigated, and only a few comparative analyses between anti-CD20 and NTZ have been carried out so far [8, 9]. In a recent study conducted on data from the IMS&RD, NTZ and Ocrelizumab showed comparable protective effect on the

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TABLE 1 | Clinical and demographic characteristics of natalizumab and anti-CD20-treated patients, before and after the matching procedure.

	Non-matched			Matched		
Variable	**NTZ (*N* = 178)**	**Anti-CD20 (*N* = 89)**	***p***	**NTZ (*N* = 89)**	**Anti-CD20 (*N* = 89)**	***p***
Age at baseline; mean (SD)	33.2 (10.1)	35.7 (11.5)	**< 0.001**	36.0 (9.3)	35.7 (11.5)	0.835
Sex (female); *n* (%)	124 (69.3)	53 (59.6)	0.167	56 (62.9)	53 (59.6)	0.758
EDSS at baseline; median (IQR)	2.0 (1.5–3.5)	3.0 (1.5–4.5)	**0.003**	3.0 (2.0–4.0)	3.0 (1.5–4.5)	0.418
Disease duration at baseline (years); median (IQR)	7.1 (2.0–13.5)	11.4 (6.9–17.5)	**< 0.001**	12.3 (5.2–16.4)	11.4 (6.9–17.5)	0.736
Relapsing–remitting phenotype at baseline; *n* (%)	159 (89.3)	65 (73.0)	**< 0.001**	65 (73.0)	65 (73.0)	1.000
Inflammatory disease activity at DMT start*; *n* (%)	160 (89.4)	67 (75.3)	**0.003**	78 (87.6)	67 (75.3)	0.054
Prior DMT exposure at baseline; *n* (%)						
Naïve	138 (77.1)	57 (64.0)	**0.025**	60 (67.4)	57 (64.0)	0.752
Platform DMT[a]	40 (22.4)	23 (25.8)	**< 0.001**	1 (1.2)	23 (25.8)	**< 0.001**
HE DMT[b]	1 (0.5)	9 (10.2)	**0.039**	28 (31.4)	9 (10.2)	**0.001**
JCV serological status at baseline (+); *n* (%)	21 (15.0); *N* = 140	51 (92.7); *N* = 55	**< 0.001**	13 (18.6); *N* = 70	51 (92.7); *N* = 55	**< 0.001**
Follow-up on treatment (years); median (IQR)	8.4 (6.4–11.2)	5.8 (5.5–6.5)	**< 0.001**	8.6 (6.2–11.5)	5.8 (5.5–6.5)	**< 0.001**
Number of EDSS score evaluations; median (IQR)	34 (26–50)	12 (10–14)	**< 0.001**	36 (27–54)	12 (10–14)	**< 0.001**

Note: Data are reported as numbers (percentage) or means (SD), and medians (interquartile range) are indicated in case of non-normal distributions. In case of missing values, the total number of patients with available data is indicated. Statistically significant *p* values are highlighted in bold.
Abbreviations: (+), positivity; DMT, disease modifying therapy; EDSS, expanded disability status scale; HE, highly-effective DMT; IQR, interquartile range; JCV, John Cunningham virus; NTZ, natalizumab; SD, standard deviation.
*Inflammatory disease activity is defined as the evidence of any clinical or neuroradiological (i.e., new lesions in T2/FLAIR sequences or contrast-enhancing lesions) disease activity in the 2 years preceding the DMT start.
[a]Dimethyl fumarate, teriflunomide, interferon beta, or glatiramer acetate.
[b]Sphingosine 1-phosphate receptor modulators, cladribine, alemtuzumab.

risk of achieving the first 6 months confirmed PIRA and RAW events and severe EDSS disability milestones on naïve RRMS patients [8]. Similarly, another study using data from the Danish MS registry found no significant differences in the time to first PIRA event between NTZ- and Ocrelizumab-treated patients [9]. Consistently, we herein found similar efficacy against cumulative PIRA event accrual of NTZ and anti-CD20 drugs over a significantly longer treatment period compared to previous reports [8, 9].

Other recent studies have explored the effect of HE DMTs in preventing PIRA events and found only minimal effects, with no significant differences compared with moderate efficacy drugs, highlighting the need to better investigate PIRA's pathological substrates to further evaluate appropriate treatment strategies. A recent study [14] reported that early initiation of HE DMTs compared with moderate efficacy DMTs was associated with a significantly reduced risk of RAW but not of PIRA. In another study [4], ocrelizumab was not superior to teriflunomide in protecting against smouldering activity, measured as time to first PIRA, underscoring the need for additional therapies that are effective in preventing silent progression due to PIRA.

An important methodological issue in studies on PIRA is the variability in the reported incidence of events, which depends heavily on the operational definition applied [10, 15]. Recent

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works [10, 15] have highlighted that the number of detected PIRA events may vary substantially according to different definitions. The definition employed in our study has demonstrated balanced sensitivity and specificity in capturing incidence and persistence of PIRA events in a large cohort of MS patients [10].

As regards the limitations of this study, we should consider the retrospective design, which may have introduced information and selection biases. Secondly, although our matching procedure reduced confounding, the relatively limited number of included patients constrains the statistical power to detect subtle differences between treatment groups. We are also aware of the intrinsic limitation of the PIRA definition, which does not account for MRI activity as a potential substrate of disease accumulation; future studies integrating clinical and radiological data will be needed to better elucidate this aspect. Nevertheless, our study included a carefully selected and closely monitored cohort, with all patients undergoing at least three EDSS evaluations and being followed for a long period, allowing to assess long-term protection. Importantly, the population was stringently matched for factors known to impact PIRA risk (e.g., gender, age, baseline EDSS), and patients with treatment interruptions for at least 3 months were excluded, thus providing a clean real-world cohort for comparative analysis.

In conclusion, our results confirm that both anti-CD20 drugs and NTZ confer equal protection against PIRA event accrual. A larger cohort and harmonised definitions of PIRA will be essential to confirm and refine these observations.

Author Contributions

Leonardo Palazzo: conceptualization, investigation, methodology, writing – review and editing, visualization, writing – original draft, formal analysis. **Ferdinando Clarelli:** investigation, validation, methodology, formal analysis, data curation, supervision, writing – review and editing. **Michele Surano:** investigation, visualization, writing – review and editing. **Antonino Giordano:** investigation, supervision, validation, visualization, writing – review and editing, resources. **Lucia Moiola:** supervision, writing – review and editing, validation, resources. **Maria A. Rocca:** supervision, resources, data curation, writing – review and editing, validation, funding acquisition. **Massimo Filippi:** funding acquisition, writing – review and editing, validation, project administration, data curation, supervision. **Federica Esposito:** supervision, data curation, resources, project administration, writing – review and editing, validation, methodology, conceptualization, funding acquisition.

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Ethics Statement

All patients signed an informed consent for the recording of their clinical data on the Italian MS and Related Disorders Register (IMS&RD) and use for research purposes. The study was approved by the local ethical committee.

Conflicts of Interest

Lucia Moiola received compensations for speaking activities and/or for participating to advisory boards from Merck, Celgene, Biogen, Sanofi, Novartis, Roche, Alexion, and Amgen. Maria A. Rocca received speaker honoraria from Bayer, Biogen, Bristol Myers Squibb, Celgene, Genzyme, Merck Serono, Novartis, Roche, and Teva and research support from the Canadian Michele Surano Society and Fondazione Italiana Sclerosi Multipla. Massimo Filippi is Editor-in-Chief of the Journal of Neurology and Associate Editor of Human Brain Mapping, Neurological Sciences, and Radiology, received compensation for consulting services and/or speaking activities from Alexion, Almirall, Bayer, Biogen, Celgene, Eli Lilly, Genzyme, Merck Serono, Novartis, Roche, Sanofi, Takeda, and Teva Pharmaceutical Industries, and receives research support from Biogen Idec, Merck Serono, Novartis, Roche, Teva Pharmaceutical Industries, the Italian Ministry of Health, Fondazione Italiana Sclerosi Multipla, and ARiSLA (Fondazione Italiana di Ricerca per la SLA). Federica Esposito received speaking honoraria from Merck and Genzyme.

Data Availability Statement

Anonymized datasets used in this study are available from the corresponding author upon reasonable request.

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