TRANSITIONING FROM NATALIZUMAB TO CLADRIBINE IN RELAPSING MS: SAFETY AND EFFICACY CONSIDERATIONS IN A REAL-WORLD COHORT

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INTRODUCTION

Natalizumab (NTZ) is a highly effective therapy for relapsing-remitting MS (RRMS), but its long-term use is complicated by increasing PML risk in JC virus antibody-positive patients and rebound disease activity after withdrawal.
Several studies have investigated the use of disease-modifying therapies (DMTs) to mitigate the risk of rebound disease activity, but a standardized sequencing strategy has not been established.
Since NTZ sequesters leukocytes in the peripheral blood, switching to Cladribine (CLAD) - a synthetic purine analogue that selectively depletes peripheral Lymphocytes - may represent a rational and effective sequencing approach.

AIM

This study aims to evaluate **CLAD efficacy as an exit strategy from NTZ** and its **safety profile** in a cohort of persons with relapsing-remitting MS (RRMS)

METHODS

A retrospective monocentric observational study was conducted in RRMS patients followed up at the MS Center of Tor Vergata University Hospital, Rome, who started CLAD after NTZ discontinuation, with at least 6 months follow-up after CLAD initiation, as per clinical practice.
The study design is summarized in Fig. 1

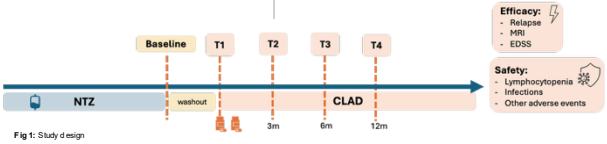

Fig 1: Study design

** Lymphocyte count monitoring is performed at 2 months after CLAD initiation as part of routine clinical monitoring*

RESULTS

23 patients were enrolled in the study whose baseline characteristics are summarized in Table 1.
The **mean** (±SD) **NTZ washout period was 34.6 ± 18.6 days**.

	N=23
Demographic	
Female, n (%)	18 (78,3%)
Age – yrs; mean ± SD	42 (±11.04)
MS Characteristics	
Disease duration – yrs; median (range)	11 (1-38)
EDSS – median (range)	1 (0-3.5)
NTZ history	
Previous infusions- nr; median (range)	50 (15-161)
Extended dose; n (%)	22 (95.7%)
JCV status (Stratify Index)	
Negative (<0.20)	3 (13%)
Positive	20 (87%)
Follow up – months; median (range)	31 (6-73)

Tab.1 : Baseline characteristics

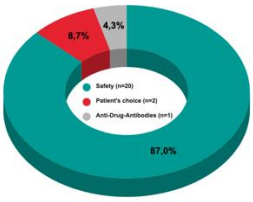

Fig.2 : Reason for switching

EFFICACY

No clinical relapses occurred during the washout period and at 6 (n=23) or 12 months (n=20); 1/23 patients relapsed within 3 months after CLAD start.
ARR in the 12 and 24 months post-CLAD (0.045 and 0.05) and in the 12 months pre-NTZ discontinuation (0.042, p=0.99) were comparable.

At 24-month follow-up, 80% of patients (12/14) **remained free of new/enlarging T2 lesions, and 100%** were **free of new T1 Gd-enhancing lesions**.
New T2 lesions were detected in 4/21 asymptomatic patients at the first MRI [mean 6 ± 4.4 months post-CLAD] and in 2/20 at the second MRI (mean 17± 10.1 months).
EDSS remained stable (median 1.5 [1.0-3.5]) at 24 and 36 months after NTZ withdrawal.

CLAD showed **a rapid and sustained reduction in lymphocyte counts**, detectable from month 2 of treatment (Fig. 3).

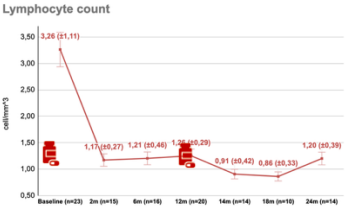

Fig.3 : Mean lymphocyte count (±SD) during FUP

SAFETY

Adverse events, including infections, recorded during the follow-up period are presented in Table 2.

Grade 3 lymphocytopenia occurred in 1/20 patients during year 1; **no grade 4 events were observed**.
Retreatment was delayed due to Grade 2 lymphopenia in 2/20 patients.
No serious adverse events or PML cases occurred.

ADVERSE EVENTS	n
Headache	4
Hair loss	2
Upper respiratory tract infections	2
Candidiasis	2
Herpes Zoster (VZV)	1

Tab.2 : Adverse events recorded during FUP

CONCLUSIONS

Our results show that a prompt switch to CLAD within about 4 weeks of NTZ discontinuation can prevent the MS rebound activity. Overall in our cohort, the rate of relapse within 6 months from the last NTZ infusion was very low (1/22 cases). Moreover, MS remission was maintained over time, and a very low incidence of adverse events was found.

These findings **support CLAD as a compelling and safe exit strategy after NTZ, both for minimizing PML risk and as a de-escalation strategy in older patients, for whom safety is a major concern.**

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