Ublituximab use in a Real-World Setting: Rapid CD19+ B-Cell Depletion and Comprehensive Clinical Evaluation Beyond EDSS

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INTRODUCTION

Among disease modifying therapies (DMTs) for Multiple Sclerosis (MS), Ublituximab is a recently approved chimeric glycoengineered monoclonal antibody (mAb) that targets a unique epitope on the CD20 antigen and has a great antibody-dependent cellular cytotoxicity (ADCC).

With its enhanced ADCC and rapid onset of action, Ublituximab offers the **potential for swift disease control**, which is particularly valuable in patients with highly active or rapidly evolving MS.

AIM

This study aimed to:

Delineate the **longitudinal kinetics of circulating lymphocyte subsets** over the first six months following ublituximab initiation.

Investigate whether **relevant baseline demographic and clinical characteristics** predicted the **residual counts at day 30 after infusion of CD3⁺CD8⁺ T cells and CD19⁺ B naive cells**, the two subsets that exhibited the most distinctive early kinetics.

Provide a **comprehensive evaluation of efficacy** outcomes **beyond Expanded Disability Status Scale (EDSS)**, integrating cognitive assessment, patient-reported outcomes, and upper limb function evaluation.

METHODS

A real-world prospective study performed at the MS center of Foggia, Italy. Inclusion criteria were patients with a diagnosis of relapsing MS who started ublituximab between December 1st, 2024 and May 31st, 2025.

Demographic and clinical data were collected, together with patients reported outcomes (PROs), the Brief International Cognitive Assessment for Multiple Sclerosis (BICAMS), the 9-Hole Peg Test (9HPT) and Timed 25-Foot Walk (T25FW).

Immunophenotyping was performed on peripheral blood samples collected at the following ten time points: three days before ublituximab first infusion (day -3), immediately after the first split dose infusion of ublituximab (day 0), one week after the initial infusion (day 7), before the second split dose infusion of the first cycle (day 14), one month after the initial infusion (day 30), and then every 30 days.

Longitudinal trajectories were modelled with subject-specific random-intercept linear mixed-effects models. To identify determinants of early residual depletion, linear regression models were built.

RESULTS

A total cohort of 16 patients completed the first cycle of ublituximab infusion, 5 (31.2%) female, median age 47 (41-58), median EDSS 4.5 (3.5-5.0). Demographic, clinical and radiological characteristics are shown in Table 1.

At baseline, mean **Symbol Digit Modalities Test (SDMT)** Z-score was -0.6±1.2. Mean time to complete the **9HPT** was 27.8±7.5 seconds for the dominant hand and 30.7±8.0 seconds for the non-dominant hand. Mean **T25FW** score was 31.4±19.1 seconds (median: 21.8; Q1-Q3: 19.1-44). Mean **Lower Extremity Functional Scale (LEFS)** score was 37.9±23.6 (median: 33; Q1-Q3: 20.5-62), mean **Arm Function in Multiple Sclerosis Questionnaire – Short Form (AMSQ-SF)** score was 23.9±16.7 (median: 16; Q1-Q3: 11-34.5).

The lymphocyte subset data were **available for all 16 patients** (100%) **up to 60 days following therapy initiation**. At 90 days, data were available for 11/16 (68.8%) patients. At 120 days, the subset data were available for 8/16 patients (50%). Beyond 120 days, follow-up data were available for 6/16 (37.5%) patients at both 150 and 180 days. These follow-up rates are influenced by the average duration of patient follow-up after starting therapy, reflecting the natural variability in patient retention over time.

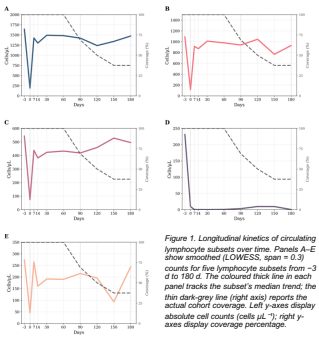

Figure 1. Longitudinal kinetics of circulating lymphocyte subsets over time. Panels A–E show smoothed (LOWESS, span = 0.3) counts for five lymphocyte subsets from −3 d to 180 d. The coloured thick line in each panel tracks the subset's median trend; the thin dark-grey line (right axis) reports the actual cohort coverage. Left y-axes display absolute cell counts (cells µL⁻¹); right y-axes display coverage percentage.

CD3⁺ T cells; B. CD3⁻CD4⁺ T cells; C. CD3⁻CD8⁺ T cells; D. CD19⁺ naive B cells; E. CD16⁺CD56⁺ Natural Killer cells.
Legend (common to all panels): Coloured thick line= LOWESS trend for the indicated subset; Grey thin line = Observed cohort coverage (%); Vertical dotted lines at 0 d, 90 d, 180 d = reference time-points. d=Days

Variable*	
Age at start of Ublituximab (years)	47 (41-58)
Sex, n(%)	
Male	11 (68.8)
Female	5 (31.2)
Comorbidities, n(%)	
Yes	12 (75)
No	4 (25)
Smokers, n(%)	
Yes	7 (43.8)
No	9 (56.2)
Education, (years)	13 (8-13)
BMI (kg/m²)	26.9 (24.4-28.8)
Disease duration (years)	21.5 (5.3-153)
Naïve to DMTs, n(%)	9 (56.3)
N. of prior DMTs	0 (0-2)
N. of relapses within 12 months before enrollment	2 (1-2)
N. of Spinal Cord lesions at baseline MRI	1 (1-3)
Lesion volume on T2 weighted sequences (baseline MRI) (mm³)	2,360.2 (1,484-5,348.7)
N. of Patients with Gadolinium enhancing lesions at baseline MRI, n(%)	6 (37.5)
EDSS at the time of Ublituximab start	4.5 (3.5-5.0)
Time on Ublituximab (months)	3.5 (2-5.5)

*Table 1. Baseline demographic, clinical and radiological characteristics of the enrolled cohort. *Data are presented as median (Q1-Q3) for continuous variables. BMI, Body Mass Index; DMTs, disease modifying therapies; N. number; MRI, magnetic resonance imaging; EDSS, Expanded Disability Status Scale*

All five lymphocyte subsets displayed a significant effect of time in the mixed-effects models (Type-III F-tests, all p <.05). Between-patient stability, as measured by the ICC, varied substantially across cellular subsets, with values ranging from very low to moderate (ICC = 0.017–0.70), indicating that reproducibility was highly dependent on the specific subset analysed. **The amplitude of change ranged from modest fluctuations in total T-cell counts to profound, sustained depletion of CD19⁺ B cells** (Fig. 1).

The linear regression analysis for CD19⁺ naive B cell counts at day 30 after ublituximab infusion indicated that **none of the baseline variables**—age, BMI, number of prior DMTs, gadolinium-enhancing lesions, or sex—**significantly predicted early lymphocyte reconstitution** (Tab. 2).

Predictor	Beta (Unstd.)	SE	Beta (Std.)	95% CI (Lower, Upper)	p-value
Intercept	−0.51	4.09	—	−11.01, 9.99	0.906
Sex¹	−0.694	0.863	−0.379	−2.912, 1.523	0.457
Age at start of Ublituximab, years	0.007	0.040	0.083	−0.097, 0.110	0.878
BMI (kg/m²)	0.044	0.141	0.148	−0.319, 0.406	0.769
N. of previous DMTs	−0.269	0.319	−0.365	−1.089, 0.550	0.437
Gadolinium enhancing lesion at baseline MRI	−0.438	1.164	−0.192	−3.430, 2.553	0.722

Table 2. Linear regression model Predicting Day 30 CD19+ naive B cell count (cells/µL). Model statistics: R^2 = 0.239; Adjusted R^2 = −0.522; F (5, 5) = 0.31; p = 0.885. 1 : male as reference; BMI, Body Mass Index; DMT, disease modifying therapies; MRI, magnetic resonance imaging; N. number.

CONCLUSIONS

In our cohort **ublituximab induced rapid, durable CD19⁺ naive B cell depletion** with only transient, reversible effects on other lymphocyte subsets and preserved immunoglobulin levels.

This signature extends to older and high-BMI patients, supporting ublituximab as a versatile therapeutic option across heterogeneous MS populations.

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DISCLOSURES

The authors have nothing to disclose.

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