

Short Washout from sequestering to depleting agents in Multiple Sclerosis: The FAST experience

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INTRODUCTION

Anti-CD20 monoclonal antibodies (Ocrelizumab, Ofatumumab, Ublituximab) are increasingly used in Multiple Sclerosis (MS) as second-line agents when switching from sphingosine-1-phosphate modulators (S1Pm), but recommendations regarding the **S1Pm washout period (WP)** are currently lacking. Current **practice balances the need for peripheral immune reconstitution** before starting anti-CD20 treatment with the **risk of disease rebound** associated with longer WPs (1-2 months)¹. However, clinical practice evidence showing whether cutting short the wash-out period is a safe and effective strategy to reduce the risk of clinical/radiological relapses without increasing the risk of adverse events is still lacking.

OBJECTIVES

This ongoing study investigates whether a shorter WP could minimize the risk of disease activity as rebound effect after S1Pm discontinuation, without compromising the efficacy and safety of anti-CD20 therapy.

METHODS

We conducted a **prospective observational study** (from June 2024) including consecutively MS patients who started intravenous (IV) or subcutaneous anti-CD20 after treatment with S1Pm, with a **WP shorter than 14 days (FAST group)**. Data collected included clinical and MRI disease activity, adverse events (AEs), and weekly total, CD4, CD8, and CD19 lymphocyte counts during the first month for the FAST group. A retrospective control cohort of patients with a **longer WP (>14 days, LONG group)** was included as a control group. In the latter group, haematological data were obtained shortly before and one week after anti-CD20 initiation, as per clinical practice. Figure 1 displays the study design.

RESULTS

We included **10 patients in the FAST** and **10 in the LONG** group. Patients were predominantly relapsing-remitting (85%), and 80% were switched to anti-CD20 due to clinical or radiological activity. 19 patients shifted from fingolimod and 1 from Siponimod; 55% started IV Ocrelizumab, 45% Ofatumumab. **The WP was 8.7±1.6 days in the FAST-group and 72.7±33.7 days in the LONG-group (<0.001)**. During the WP, 3 patients experienced MRI activity, all in the LONG-group, but no relapses were observed in the first 30 days after the switch in either group. Mean total lymphocyte count at anti-CD20 start was significantly lower in the FAST group (502 vs 1584 cells/uL, p=0.007). **No difference was observed at week one**. In the FAST-group, mean CD3 and CD4 increased from the start of anti-CD20 to week 4 (CD3: 309 vs 774 cells/uL, p=0.029; CD4: 113 vs 412 cells/uL, p=0.015) (figure 2). CD19 decreased from week 2 to week 4 (p=0.001) (Figure 2). **3 patients developed AEs (mild upper respiratory infections) after the switch (2 FAST, 1 LONG)**.

DISCUSSION

The extensive use of anti-CD20 monoclonal antibodies in the treatment of MS patients is rising issues about how to manage shift from a previous therapy. **Stopping an S1Pm is associated with high risk of rebound** of the inflammatory disease activity, but the best timing of the switch is still unclear. **The right washout period has to balance the risk of relapse and safety**. In the present study we demonstrated that a **short washout period (<14 days) does not affect peripheral immune reconstitution** after S1Pm discontinuation **nor does affect safety, and it is associated with a lower risk of rebound relapses**. In the **FAST-group** a lower total lymphocyte count was observed immediately after the start of the therapy, with a **restoring comparable** to that observed in the **LONG-group**. According to our preliminary results, the faster shift did not have any major effect on immune reconstitution also considering immune subtypes. These results reflect the very few and mild adverse events we observed. Inflammatory activity was recorded during the inter-shift period only in the LONG-group, confirming the impact of a long waiting time after the S1Pm stop on the disease activity rebound. Our results are in line with a previous study by Gassama et al.² We also showed evidence that peripheral immune reconstitution is preserved by early beginning of antiCD20 treatment after S1Pm discontinuation, together with the antiCD20 efficacy and safety.

CONCLUSION

Rapid switch within 14 days from S1Pm to anti-CD20 therapies is an effective strategy to minimize the risk of rebound and does not negatively affect peripheral immune reconstitution of total lymphocytes and lymphocyte subtypes, nor seems to impact the safety of immunomodulatory therapies. Longer and larger studies are needed to confirm the findings of this study and to broaden the implementation of this strategy in clinical practice.

REFERENCES

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²Gassama S, Garmenia A, Lajene FV, Baudouin M, Lohrapour C, Dupuy C, Mallat E, Roux T. A short washout period from fingolimod to anti-CD20 therapy is safe and decreases the risk of reactivation. *Rev Neurol (Paris)*. 2023 Nov;179(9):1035-1038.

DISCLOSURES

Dr. Creta and all the authors have nothing to disclose. Dr. Crisafulli has nothing to disclose. Dr. Perugini has nothing to disclose. Dr. Tomas Roldan has nothing to disclose. Dr. Torri Clerici has nothing to disclose. Dr. Antozzi has nothing to disclose. Dr. Dinoto has nothing to disclose. Dr. Brambilla has nothing to disclose. Dr. Confalonieri has nothing to disclose.

Figure 1

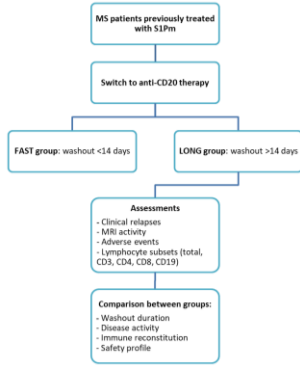
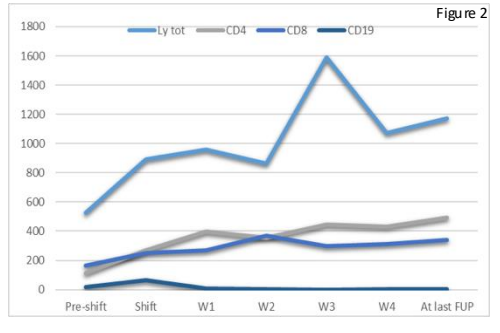


Figure 2



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