Ublituximab exerts a rapid B and T Cell depletion in multiple sclerosis: preliminary results

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INTRODUCTION

Anti-CD20 monoclonal antibodies are a well-established therapeutic approach in Multiple Sclerosis (MS). Among them, **Ublituximab** -a glycoengineered chimeric IgG1 drug (fig.1)- acts by depleting B cells through the activation of **ADCC** (antibody-dependent cell-mediated cytotoxicity) and **CDC** (Complement-dependent cytotoxicity) (fig.2)

Phase II studies demonstrated that B-cell depletion is achieved within 24 hours and such depletion is sustained at two weeks [1]

However, how early this effect occurs and the immune system depletes targeted lymphocytes is still unclear.

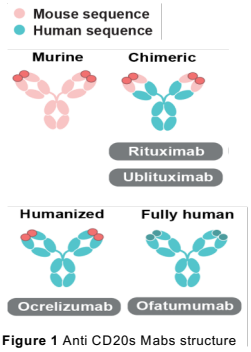

Figure 1 Anti CD20s Mabs structure

AIM

The aim of this study is to assess the rapidity of B and T cell subset depletion following the first infusion of Ublituximab in treatment-naïve relapsing remitting MS patients (RRMS).

	CDC	ADCC	
RTX	++	++	CDC > ADCC
OCR	+	+++	ADCC > CDC
OFA	+++	++	CDC > ADCC
UTX	+	++++	ADCC > CDC

Figure 2 Anti CD20 mechanism of action

METHODS

This pilot, monocentric, observational longitudinal study enrolled RRMS initiating Ublituximab as part of standard clinical care.

Blood samples were collected at baseline (w0) before infusion (T0), at mid-infusion (T1), and 30 minutes post-infusion (T2), and at week 2 (w2) at T0 and T2.

Flow cytometry was used to assess TBNK populations and B-cell maturation.

RESULTS

We enrolled 7 treatment-naïve RRMS patients (mean age 41 ± 12.8 years; 71,4% female). Main results are shown in table 1-2 graph 1-4. At baseline, T and B cell subsets were within normal ranges. A marked reduction was observed already at T1w0, persisting at T2w0. At w2, T cells partially repopulated at T0 but decreased post-infusion; B cells remained strongly suppressed. Considering B-cell sub-population analysis, at T0w0 naïve B cells (CD19+27−) represented the majority of total CD19+ followed by memory B cells (CD19+27+) and immature B cells (CD38++IgM++). By T1w0/T2w0, memory B cells dropped, while naïve cells increased, and immature cells were nearly absent. At T0w2/T2w2, memory B cells rebounded strongly, while naïve B cells fell below 10%, and immature cells remained undetectable.

Table 1 Mean values of T and B cells at different study timepoints

T and B subsets (cell/µL)	T0w0	T1w0	T2w0	T0w2	T2w2
CD3+CD4+ (mean, SD)	1281 ± 649	144 ± 81	93,7 ± 51	841 ± 509	276 ± 223
CD3+CD8+ (mean, SD)	579,4 ± 340	68,5 ± 54,2	62 ± 48	392,8 ± 209	225 ± 215
CD19+ (mean, SD)	298 ± 150	22 ± 12	18,7 ± 14	0,4	0

Table 2 Mean values of B cells subsets at different study timepoints

CD19 Subset (mean, %)	T0w0	T1w0	T2w0	T0w2	T2w2
Naïve (CD19+27−)	76,6 ± 12	85 ± 8	74 ± 31	7,5 ± 11	6,8 ± 8
Memory (CD19+27+)	23 ± 12	12,4 ± 9	12,4 ± 9	88,7 ± 10	83,6 ± 13
Immature (CD38++IgM++)	1,68 ± 1	0	0	0	0

Graph 1-4 T and B cells dynamics at different timepoints

CONCLUSIONS

Ublituximab induces very rapid B and T cell depletion mainly via ADCC, already evident during the first infusion after 3 hours.

As effect of treatment, a phenotypic shift in B-cell subsets composition, namely from naïve to memory, was observed from baseline by week 2, despite overall B-cell suppression. Such early and rapid B-cell depletion has a potential clinical relevance in highly active MS or in case of therapy switch requiring fast immune control (i.e. sequestering disease modifying treatments).

REFERENCES

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