19-21 GIUGNO ROMA
UNIVERSITA' CATTOLICA DEL SACRO CUORE CENTRO CONGRESSI EUROPA
RESEARCH and CARE: FROM BENCH, TO BEDSIDE, TO COMMUNITY
Promosso da SIMIT
16° CONGRESSO NAZIONALE ICAR Italian Conference on AIDS and Antiviral Research
P 107
POSTER 4 YOU ICAR 2024

Cytomegalovirus specific T-cell response in people with multiple sclerosis under different disease-modifying therapies

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Introduction

The risk of reactivation of latent herpesvirus infection, such as cytomegalovirus (CMV), is increased by therapies that affect cellular immunity, such as disease-modifying therapies (DMTs) that can reduce multiple sclerosis (MS) activity and progression [1,2,3].
In this context, our study aimed to characterize CMV T-cell-specific response in people with MS (pwMS) under different DMTs.

Materials and methods

At the Neuroinfectious unit of Policlinico Umberto I, Sapienza University of Rome, pwMS under differ DMTs were enrolled. As control group, healthy donors (HD) were enrolled as well.
On blood samples, the IFNg, IL2 and TNFa production by T-cells upon CMV peptides library stimulation was investigated and T-cells were defined as "responding" T-cells, those producing any of IFNg, IL2 and TNFa, and "triple-positive"T-cells, those simultaneously producing all the three cytokines (Fig.1).
pwMS were stratified according DMT into those treated with anti-CD20 (anti-CD20), with anti-alpha-4-integrin (anti-a4), and with sphingosine-1-phosphate (S1P) antagonist or T-cell interfering drugs (Other).

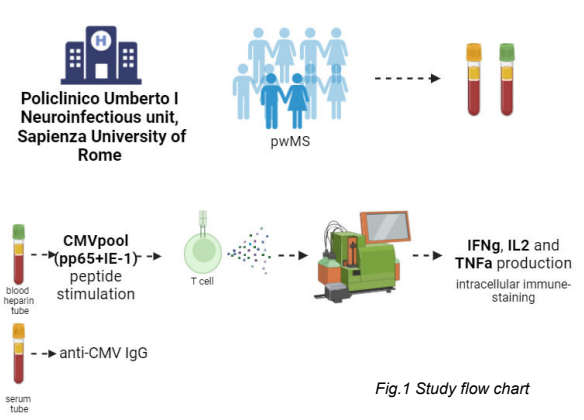


Fig.1 Study flow chart

Results

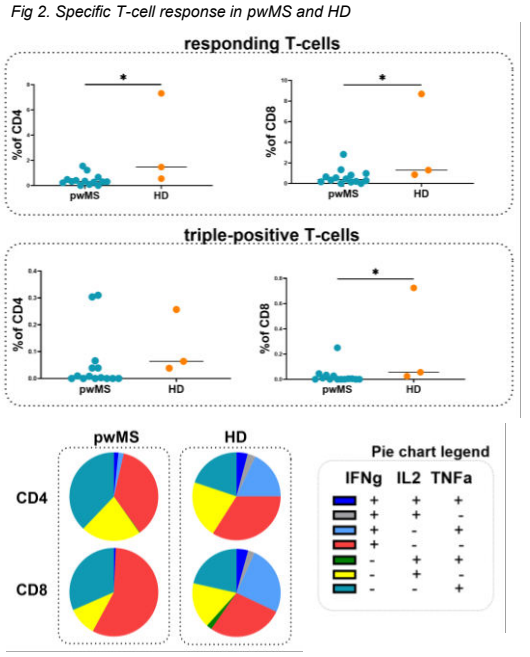
Among the 254 pwMS (female/male:152/102; median age [IQR]: 51[42-60] years) routinely followed at the Neuroinfectious unit, a CMV seroprevalence of 50% (127/254) was observed.
Among them, 22 pwMS were enrolled. 12/22 pwMS were under anti-CD20, 2 on anti-a4, 5/22 on T-cell interfering drugs, and 3/22 on S1P antagonists. Three HD were enrolled as control group (Table 1).

Demographic and clinical characteristics	HD (n=3)	pwMS (n=22)	anti-CD20 (n=12)	anti-a4 (n=2)	other (n=8)
female/male	3/0	17/5	10/2	1/1	6/2
age, median (IQR) years	41 (40-61)	48 (42-61)	50 (41-61)	52 (45-59)	47 (39-51)
years of disease, median (IQR) years	-	7 (4-27)	8 (4-28)	28 (28-28)	5 (4-8)
EDSS score	-	3 (1-6)	5 (3-6)	3 (3-3)	1 (1-3)
years of current treatment, median (IQR) years	-	4 (1-5)	4 (2-6)	-	3 (1-5)
treatments:					
anti-CD20	-	12	12	-	-
anti-a4 integrin	-	2	-	2	-
S1P antagonist	-	3	-	-	3
T-cell interfereing drugs	-	5	-	-	5
CMV serostatus					
CMV positive	2	13	5	2	6
CMV negative	1	9	7	0	2

HD, healthy donors; MS, multiple sclerosis; pwMS, people with multiple sclerosis; n, number; IQR, interquartile range; EDSS, expanded disability status scale; anti-a4 integrin, anti-alpha 4 integrin; S1P antagonist, sphingosine-1-phosphate antagonist; % of, percentage of; anti-CD20, anti-CD20-treated pwMS; anti-a4, anti-a4 integrin-treated pwMS; other, sphingosine-1-prhosphate antagonist and T-cell interfering drugs-treated pwMS.

An evaluation on specific T cell response was performed between pwMS and HD. Lower percentages of responding CD4+ and CD8+ T-cells were seen in pwMS compared to HD (CD4+: 0.32[0.19-0.54] and 1.47[0.55-7.31], respectively, p=0.0294; CD8+: 0.39[0.16-0.86] and 1.30[0.86-8.69], respectively, p=0.0441). While, lower percentages of only CD8+ triple-positive T-cells were observed in pwMS compared to HD (0.0[0.0-0.03] and 0.06[0.03-0.73], respectively, p=0.0235). Moreover, looking at the different T-cell subsets upon stimulation, a more heterogeneous cytokine production was observed in HD, while in pwMS a predominance of only IFNg and aìonly TNFa was observed (Fig.2).

Fig 2. Specific T-cell response in pwMS and HD



pwMS were then stratified according to DMT use. Although not statistically significant, a lower percentage of CD4+ responding T-cells was observed in anti-CD20 subgroup compared to HD (0.29[0.17-0.32] and 1.47[0.55-7.31], respectively, p=0.0572). While no differences were observed in the other subgroups, as well as no difference were observed among the subgroups in the percentages of CD8 responding and CD4+ and CD8+ triple positive T-cells.
Moreover, a prevalence of only IFNg producing T-cell was observed in both anti-CD20 and Other subgroups, compared to anti-a4 in which a polarization toward only IL2 production was found (Fig. 3).

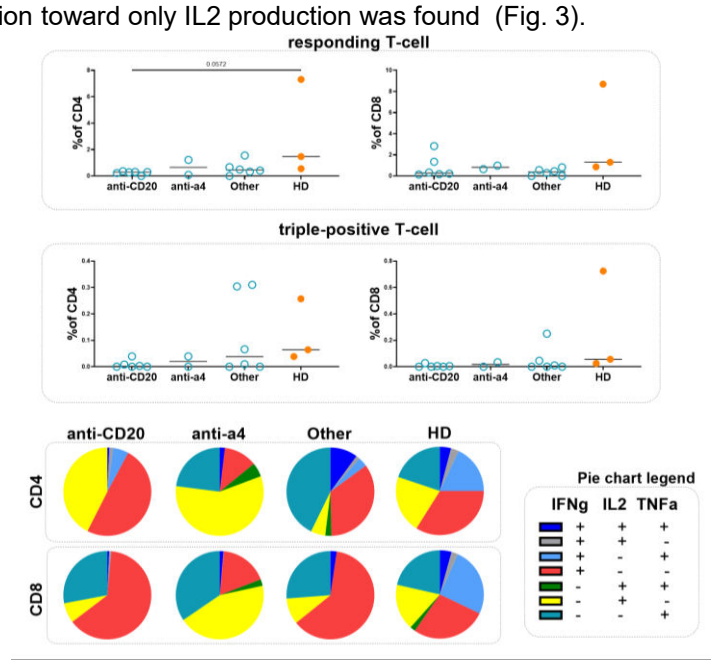


Fig 3. Specific T-cell response in anti-CD20, anti-a4 and Other groups compared to HD.

Conclusions

Our preliminary data showed a polarization toward only IFNg production by T-cell after specific stimulation by CMV peptides in pwMS. After stratifying according to DMT use, no differences were observed, although a polarization toward IFNg production was found in both anti-CD20 and Other groups. These findings suggest that a potential dysfunction in CMV T-cell specific response might be seen in pwMS, supporting the possible correlation to frequent CMV reactivations in pwMS following starting of immunosuppressive treatments [2,3].

References

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