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POS0622

THE BLOOD T-CELL SUBSETS IN RHEUMATOID ARTHRITIS PATIENTS ON LONG-TERM IL-6 RECEPTOR BLOCKER THERAPY

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Background: Pleiotropic effects of IL-6 receptor antagonist tocilizumab (TCZ) in rheumatoid arthritis (RA) involve circulating T-cells. Preliminary reports have suggested that TCZ therapy can modulate T cell function and humoral immune responses in RA [1,2]. According to other studies, TCZ had no influence on T-lymphocyte subdifferentiation [3].

Objectives: To assess the effect of 12 months (m) TCZ therapy on T-cell phenotype, and to analyze the association between T-cell subsets and RA activity.

Methods: 36 active RA pts (29F/7M); median age 55[46; 64] years; disease duration 120[72; 1928]m; DAS28 score 6,3[5,7;6,7]; RF+100%, ACCP+ 86% were treated with TCZ (8mg/kg every 4 weeks) in an open-label study. Immunophenotyping was performed at baseline, 6m and 12m. T-cell subpopulations and key laboratory parameters (CRP, RF, ACCP, MCV, MMP-3) were assessed.

Results: At baseline, the absolute counts of T cell subpopulations in RA pts - (CD3+), Th (CD3+CD4+), Tc (CD3+CD8+), NK cells (CD3-CD56+) - were comparable with counts in healthy donors (table1). At baseline, the absolute NK cells (CD3-CD56+) count correlated with MCV ($r=0,35$, $p<0,05$) and with MMP-3 ($r=0,57$, $p<0,05$) in RA pts. After 6m of TCZ therapy, 34% of pts were classified as good responders, 66% - as moderate responders; after 12m of TCZ therapy 68% of pts - as good responders, 32% - as moderate responders, according to the response criteria of the EULAR. Tc (CD3+CD8+) absolute count reductions were documented after 6m of TCZ therapy, absolute of T cells (CD3+) count and Th (CD3+CD4+) count - after 12m of TCZ therapy (table1). A positive correlation between Tc (CD3+CD8+) absolute counts and RF ($r=0,50$, $p<0,05$) was found after 6m of TCZ therapy. A negative correlation of Δ CRP was established with Δ T cells (CD3+) ($r=-0,45$), Δ Th (CD3+CD4+) ($r=-0,47$), and Δ Tc (CD3+CD8+) ($r=-0,59$, $p<0,05$ in all cases) after 12m of TCZ. The median absolute counts of T cells (CD3+), Th (CD3+CD4+) was lower than on healthy donors after 12m of TCZ therapy. NK cells (CD3-CD56+) counts and Th/Tc index did not change after 12 m of TCZ therapy vs healthy donors and baseline values.

Conclusion: Immunophenotyping in pts with active RA showed no difference in the absolute counts of T-cell subpopulations (T cells (CD3+), Th (CD3+CD4+), Tc (CD3+CD8+), NK cells (CD3-CD56+)) compared to healthy donors. T cells (CD3+), Th (CD3+CD4+) and Tc (CD3+CD8+) T cell counts dropped after 6 or 12m of TCZ therapy. Significant correlation between the T-cell subpopulations

counts and values of RA laboratory indicators (CRP, MCV, RF, MMP-3) suggest potential T-lymphocytes involvement in RA pathogenesis.

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Table 1. Absolute counts of T-cell subpopulations at baseline, after 6 and 12 m of TCZ therapy

	Donors	Baseline	6m	12m
T cell (CD3+)	1,3 (1,2-1,8)*	1,2 (0,9; 1,7)*	1,1 (0,7; 1,4)	1,0 (0,7; 1,5)**
Th (CD3+CD4+)	0,9 (0,7-1,2)*	0,8 (0,6; 1,0)*	0,7 (0,5; 1,0)	0,6 (0,4; 1,1)**
Tc (CD3+CD8+)	0,4 (0,3-0,5)	0,4 (0,2; 0,5)**	0,3 (0,2; 0,4)**	0,3 (0,3; 0,5)
Th/Tc	2,5 (1,9-3,1)	2,3 (1,4; 3,0)	2,3 (1,5; 3,6)	2,3 (1,4; 4,0)
NK (CD3-CD56+)	0,2 (0,2-0,5)	0,2 (0,1; 0,2)	0,2 (0,1; 0,3)	0,2 (0,1; 0,3)

Note: * - $p<0,05$ between pts at baseline and after 12 m of TCZ therapy; ** - $p=0,02$ between pts at baseline and after 6 m of TCZ therapy; ** - $p<0,05$ between donors and pts after 12 m of TCZ therapy.

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POS0623

CYTOKINE PRODUCTION BY BLOOD LYMPHOCYTES DEFINES A PROFILE ASSOCIATED WITH NON-REMISSION IN PATIENTS WITH RHEUMATOID ARTHRITIS TREATED WITH TNF INHIBITORS

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Background: In clinical practice no more than 50% of the patients treated with TNF inhibitors (TNFi) achieve remission (REM). Previous investigations suggested that peripheral blood mononuclear cells (PBMC) may be markers associated with the TNFi treatment success¹.

Objectives: This study aims to analyse the intracellular cytokine production by PBMC and its association with REM achievement after 6 months (m) of TNFi treatment in patients with RA.

Methods: This was a prospective study including 62 patients with RA starting the 1st TNFi. PBMC were isolated from patients at baseline and after 6m of treatment with TNFi and cryopreserved until studied. In vitro stimulation and intracellular cytokine production by PBMC was performed as follow: in the presence of 2µg/mL brefeldin and 2µmol/L monensin monocytes were stimulated with 20ng/mL LPS during 4h whereas lymphocytes were stimulated with 50ng/mL phorbol 12-myristate 13-acetate and 750ng/mL ionomycin for 4h at 37°C. To identify IL10-producing B cells, PBMC were pre-incubated with 3µg/mL of CpG oligonucleotide during 20h at 37°C prior to stimulation. Intracellular cytokine production (TNF α , IL6, GM-CSF, IL10) by the different cell subsets (monocytes, CD4⁺ and CD8⁺ T cells, naïve and memory B cells) was analysed by flow-cytometry. Clinical activity at baseline and after 6m was assessed by DAS28-ESR. REM was defined as DAS28 $\leq$ 2.6 at 6m. The association between cytokine production by each PBMC subset and REM was analysed through univariable and multivariable logistic regression models. Receiving operating curve (ROC) analysis was used to select the optimal ratio of cytokine production associated with REM status.

Results: After 6m of TNFi treatment, 30 (48%) patients achieved REM. No significant differences between REM and non-REM groups were observed for patients' characteristics at baseline except for DAS28, which was lower in the REM group (non-REM: 5.4 $\pm$ 0.9; REM: 4.3 $\pm$ 0.9; $p<0.0001$) (Table 1). Therefore, further analyses were adjusted by baseline DAS28. A lower ratio between calculated with the IL10 and TNF α production by B cells and by CD4⁺ T cells (IL10 B/TNF CD4) at 6m was found for non-REM patients (non-REM: 0.31 vs REM: 0.54; $p=0.007$). Based on a ROC analysis, we found that a (IL10 B/TNF CD4)<0.54 at 6 m was