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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

significantly associated with a higher probability of non-REM at 6 months (OR: 5.0; 95% CI: 1.1-21.7) (Figure 1).

Table 1. The table shows mean±SD, median (IQR) or absolute number (percentage) for all patients included (n=62). RF, rheumatoid factor; ACPA, anti-citrullinated protein antibodies; DAS28, Disease Activity Score-28; csDMARD, conventional synthetic disease-modifying anti-rheumatic drug; MTX, methotrexate; OD, other conventional synthetic disease-modifying anti-rheumatic drugs than methotrexate. The differences between DAS28 groups were analysed considering p-value<0.05 as statistically significant result.

Baseline patients' characteristics	Total patients (n=62)	DAS28>2.6 (n=32; 52%)	DAS28≤2.6 (n=30; 48%)	p-value
Age (years)	53±12	53±13	52±10	0.8
Female	55 (89)	30 (94)	25 (83)	0.2
Disease duration (years)	8 (4-11)	8 (4-12)	7 (3-11)	0.7
RF positive	49 (79)	23 (72)	26 (87)	0.1
ACPA positive	54 (87)	26 (81)	28 (93)	0.2
Smoking habit (n=55)				0.2
Non-smokers	26 (47)	16 (55)	10 (38)	
Smoker	29 (53)	13 (45)	16 (51)	
Body mass index (kg/m ²)	25.9±5.6	25.8±5.7	26.0±5.6	0.9
DAS28	4.9±1.0	5.4±0.9	4.3±0.9	<0.0001
Concomitant csDMARDs	60 (97)	32 (100)	28 (93)	0.3
MTX [±OD]	46 (74)	26 (81)	20 (67)	0.3
Only OD	14 (23)	6 (19)	8 (26)	0.3
Prednisone	36 (58)	19 (59)	17 (57)	0.9

Conclusion: Our results show that the proinflammatory IL10 B/TNF CD4 ratio is associated with non-REM status. It could be useful to analyse the success of TNFi treatment in patients with RA.

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POS0624

EFFICACY AND SAFETY OF LEVILIMAB IN COMBINATION WITH METHOTREXATE IN SUBJECTS WITH ACTIVE RHEUMATOID ARTHRITIS: PHASE III, DOUBLE-BLIND, PLACEBO-CONTROLLED, RANDOMIZED TRIAL

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Background: Previously, the results of phase II AURORA clinical study of levilimab in subjects with active rheumatoid arthritis (RA) have been reported¹. Here we report topline 24-weeks results of preliminary primary efficacy and safety analysis of phase 3 double-blind, placebo-controlled randomized clinical study (SOLAR).

Objectives: To confirm that levilimab in combination with methotrexate is superior to placebo in combination with methotrexate in achieving ACR20 at week 12 and low disease activity (LDA) at week 24 in subjects with methotrexate (MTX) resistant active RA.

Methods: The study is ongoing at 21 clinical sites in Russia and Belarus. All randomized subjects have completed 24 weeks of study between November 2019 and January 2021.

154 adults, aged ≥18 years with the diagnosis of RA (ACR 2010) for at least 24 weeks, and confirmed disease activity at screening despite treatment with MTX for the last 12 weeks (in a stable dose 15-25 mg/week, for at least 4 weeks) were randomly assigned (2:1) to receive either levilimab (162 mg, SC, QW) + MTX (n=102) or placebo + MTX (n=52). The randomization and treatment allocation were carried out by a central computer-based system. Subjects, caregivers, and those assessing the outcomes were blinded to group assignment.

The hypothesis of superiority of levilimab over placebo was tested for two co-primary efficacy outcomes: proportion of subjects who achieved ACR20 at week 12 and proportion of subjects who achieved LDA of RA (DAS28-CRP <3.2) at Week 24 of the study.

For ethical reasons, subjects who haven't achieved minimal clinical response at week 12 (≥20% reduction in the number of tender/swollen joints; 66/68) received rescue therapy at the discretion of the Investigator, and all subsequent efficacy assessments for those were considered missing.

For the primary efficacy analysis, subjects with missing data due to study discontinuation or rescue therapy prescription were considered non-responders (non-responder imputation, NRI). Otherwise, the analysis was performed on observed cases.

Safety was assessed through monitoring of adverse events (AEs).

Results: The primary analysis was based on 149 randomized subjects (n=99 and n=50) for ACR20 and 154 randomized subjects (n=102 and n=52) for LDA. 70/99 (71%) of subjects who received levilimab and 20/50 (40%) who received placebo achieved ACR20 response at week 12. The difference in proportion was 30% with a lower bound of 97.5% CI 12.8%; p=0.0003 (Pearson's chi-squared test).

53/102 (52%) of subjects received levilimab and 3/52 (6%) received placebo achieved LDA at week 24. The difference in proportion was 46% with a lower bound of 97.5% CI 31.2 %; p<0.0001 (Pearson's chi-squared test).

The safety population included all subjects, who received investigational product (n=154).

The most common adverse events (reported in ≥5% of subjects) in levilimab and placebo arms, respectively were: blood cholesterol increase (19% vs. 10%), ALT increase (11% vs. 8%), lymphocyte count decrease (9% vs. 8%), blood bilirubin increase (11% vs. 0%), blood triglycerides increase (9% vs. 2%), AST increase (7% vs. 4%), IGRA with *M.tuberculosis* antigen positive (5% vs. 6%), ANC decrease (8% vs. 0%). No deaths were occurred.

Conclusion: The study confirmed superior efficacy of levilimab + MTX over placebo + MTX in subjects with MTX resistant active RA. No new safety signals were detected.

Trial registration: Clinicaltrials.gov identifier NCT04397562