THE BLOOD B-CELL SUBSETS AND EFFECT OF TOCILIZUMAB THERAPY ON THEM IN PATIENTS WITH RHEUMATOID ARTHRITIS

E. Gerasimova, T. Popkova, A. Aleksankin, E. Aleksandrova

V.A. Nasonova Research Institute of Rheumatology, Moscow, Russian Federation

Background

The use of the IL-6 receptor antagonist, tocilizumab (TCZ), in rheumatoid arthritis (RA) produce pleiotropic effects that also involve circulating B-cells. Preliminary reports have suggested that B cell function and humoral immune responses might be modulated by TCZ treatments in RA pts [1, 2].

Objectives

To assess the effect of 12 months (mo) TCZ therapy on B-cell phenotype and gene expression in RA and to analyze the association between B-cell subsets and RA activity.

Methods

24 active RA pts (20F/4M); median age 55 [49; 64] years; disease duration 72 [24; 108]m; DAS28 score 5,8[5,3;6,3]; RF+100%, ACCP+ 87% were treated in an open-label study with tocilizumab (8 mg/kg every 4 weeks). Immunophenotyping was performed at baseline and 12 mo. Pts were assessed for B-cell subpopulations and laboratory data: ESR, RF, ACCP, CRP. The control group consisted of 29 volunteers (21F/8M, median age 58,5 [53; 62] years). CD19+B cells, memory B cells (CD19+CD27+), non-switched memory B cells (CD19+CD27+ IgD+), switched memory B cells (CD19+CD27+IgD-), naive (CD19+CD27-IgD+), double-negative (CD19+CD27-IgD-), transitional (CD19+CD38++CD10+IgD+CD27-) B cells, and plasmablasts (CD19+CD38+++CD27+IgD-CD20-) were analyzed using multicolor flow cytometry.

Results

At baseline, the absolute counts of memory B cells (CD19+CD27+) and switched memory B cells (CD19+CD27+IgD-) were lower in RA pts compared to healthy donors: 0,0015 (0,001–0,003)×10^9/1 vs 0,003 (0,001–0,007)×10^9/1 and 0,01 (0,005–0,02)×10^9/1 vs 0,02 (0,01–0,04)×10^9/1, respectively, p<0,01 for both cases (Table 1).

At baseline, a significant correlation was found in RA pts between absolute counts of memory B cells (CD19+CD27+) and CRP (r=0,50, p<0,05); the percentage and absolute counts of plasmablasts (CD19+CD38+++CD27+IgD-CD20-) and RF (r=0,41 and r=0,52, p<0,05) (Fig. 1).

After 12 mo of TCZ therapy, 54% of pts were categorized as good responders, 46% of pts – as moderate responders according to the EULAR response criteria. Reductions in the percentages and absolute counts of plasmablasts (CD19+CD38+++CD27+IgD-CD20-) were documented after 12mo of TCZ therapy: 0,15 (0,1–0,3)% vs 0,1 (0,01–0,1)% and 0,0003 (0,00007–0,004)×10^9/1 vs 0,0001 (0–0,0003)×10^9/1, respectively, p<0,05 (Table 2). The median percentages/absolute counts of switched memory B cells (CD19+CD27+IgD-) were 6,8 (3,6-11,6)%/0,01 (0,005–0,02)×10^9/1 at baseline; and 3,1 (1,1–4,2)%/0,003 (0,002–0,006)×10^9/1 after 12mo of TCZ therapy, p>0,05. After 12mo of TCZ therapy, the median percentages and absolute counts of memory B cells (CD19+CD27+) and switched memory B cells (CD19+CD27+IgD-) became lower in RA pts than in the controls: 1,0 (0,7–1,2)% vs 2,2 (1,1–3,0)%; 0,001 (0,006–0,003)×10^9/1 vs 0,003 (0,001–0,007)×10^9/1 ; 3,1% (1,1–4,2) vs 12,8% (9,3–17,0); 0,003 (0,002–0,006)×10^9/1 vs 0,02 (0,01–0,04)×10^9/1, respectively, p<0,05, respectively, for all cases. Other B-cell subpopulations did not changed after 12 mo of TCZ therapy as compared to baseline values.

Parameters, n (x10^9/l)	RA (n=24)	Control (n=29)
CD19+B cells	0,11 (0,1-0,2)	0,2 (0,1-0,2)
memory B cells (CD19+CD27+)	0,0015(0,001-0,003) *	0,003(0,001-0,007)*
non-switched memory B cells (CD19 +CD27+ IgD+)	0,01 (0,006-0,01)	0,01 (0,005-0,02)
switched memory B cells (CD19+ CD27 +IgD-)	0,01(0,005-0,02)*	0,02(0,01-0,04)*
naive B cells (CD19+CD27-IgD+)	0,095 (0,07-0,1)	0,1 (0,06-0,1)
double-negative B cells (CD19+CD27-IgD-)	0,02 (0,01-0,03)	0,02 (0,01-0,02)
transitional B cells (CD19+CD38++CD10 +IgD+CD27-)	0,00009 (0-0,00028)	0,0001 (0-0,0003)
plasmablasts (CD19+CD38+++CD27+IgD-CD20-)	0,0003 (0,0001-0,0004)	0,0002 (0,0001-0,0004)

* p< 0,001

Table 1. Levels of the blood B-cell subsets in RA pts and in control.

Parameters, % / n.10^9/l	At baseline	12 months
CD19+B cells	8,4 (6,0-10,2) / 0,11 (0,1-0,2)	8,7 (7,7-12,1) / 0,15 (0,1-0,3)
memory B cells (CD19+CD27+)	1,3 (0,9-1,7) / 0,0015(0,001-0,003)	1,1 (0,7-1,2) / 0,001 (0,01006-0,003)
non-switched memory B cells (CD19 +CD27+ IgD+)	7,5 (5,1-11,4) / 0,01 (0,006-0,01)	7,0 (4,8-9,9) / 0,01 (0,006-0,01)
switched memory B cells (CD19+ CD27 +IgD-)	6,8 (3,6-11,6) / 0,01(0,005-0,02)	3,1 (1,1-4,2) / 0,003(0,002-0,006)
naive B cells (CD19+CD27-IgD+)	70,9 (62,5-75,6) / 0,095 (0,07-0,1)	76,9 (69,3-82,9) / 0,1 (0,07-0,2)
double-negative B cells (CD19+CD27-IgD-)	15,1 (11,9-18,1) / 0,02 (0,01-0,03)	11,4 (7,7-18,4) / 0,02 (0,01-0,03)
transitional B cells (CD19+CD38+ +CD10+IgD+CD27-)	0,01 (0-0,1) / 0,00009 (0-0,00028)	0,05 (0-0,1) / 0,00003 (0-0,0001)
plasmablasts (CD19+CD38+++CD27 +IgD-CD20-)	0,15 (0,1-0,3) * / 0,0003 (0,00007-0,004)*	0,1 (0,01-0,1)* / 0,0001(0-0,0003)*

* p< 0,05

Table 2. Levels of the blood B-cell subsets in RA pts at baseline and after 12months of TCZ therapy.

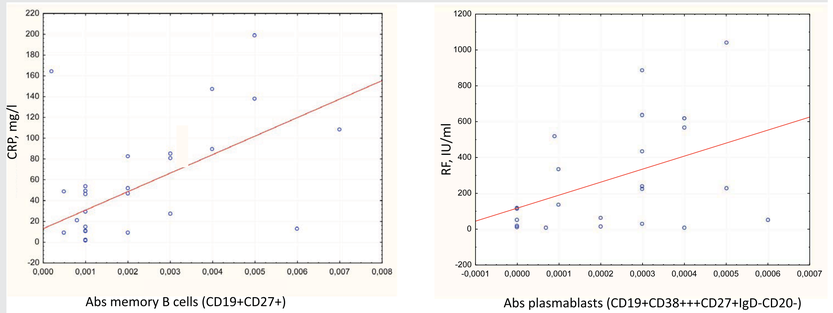

Fig. 1. Correlations of absolute counts of memory B cells (CD19+CD27+) and CRP, the percentage and absolute counts of plasmablasts (CD19+CD38+++CD27+IgD-CD20-) and RF in RA pts at baseline.

Conclusions

Immunophenotyping in pts with active RA showed the decrease in the absolute counts of memory B cells (CD19+CD27+), switched memory B cells (CD19+CD27+IgD-) as compared to healthy subjects. Positive correlation between the counts of memory B cells and plasmablasts and values of laboratory indicators of RA (CRP, RF) suggests that B-lymphocytes may be involved in RA pathogenesis. The reduction in the levels of plasmonoblasts after 12mo of TCZ therapy was observed.

References

1. Roll P, Muhammad K., Schumann M. et al. In vivo effects of the anti-interleukin-6 receptor inhibitor tocilizumab on the B cell compartment. *Arthritis Rheum.* 2011 May;63(5):1255-64. doi: 10.1002/art.30242.

2. Moura RA, Quaresma C, Vieira AR. et al. B-cell phenotype and IgD-CD27- memory B cells are affected by TNF-inhibitors and tocilizumab treatment in rheumatoid arthritis. *PLoS One.* 2017 Sep 8;12(9):e0182927. doi: 10.1371/journal.pone.0182927.