Abatacept Affects the T Cell Repertoire in Rheumatoid Arthritis Patients with Low Disease Activity

Barbara Dreo[1], Barbara Prietl[2,3], Selina Kofler[2,3], Harald Sourij[2,3], Angelika Lackner[1], Florentine Moazedi-Fürst[1], Monica D'Orazio[1], Martin Stradner[1], Winfried Graninger[1] and Hans-Peter Brezinsek[1], [1]Division of Rheumatology and Immunology, Medical University Graz, Graz, Austria, [2]CBmed GmbH – Center for Biomarker Research in Medicine, Graz, Austria; [3]Division of Endocrinology and Diabetology, Medical University of Graz, Graz, Austria

INTORDUCTION

Under physiological conditions, T regulatory cells (Tregs) are responsible for the downregulation of the immune response. In autoimmune diseases, such as rheumatoid arthritis (RA), auto-inflammation is driven by an imbalance of activation and downregulation of immunological pathways. Thus, treatment plans for autoimmune diseases often involve the enhancement of immunoregulatory pathways by administering inhibitors of co-stimulation, i.e. CTLA-4-Ig (abatacept, ABA). ABA binds specifically to CD80 and CD86 on antigen presenting cells (APC). Consequently, T cell activation via the CD28 receptor is blocked. Thus, administration of CTLA-4Ig can be considered inhibition of a positive checkpoint for T cell stimulation. Previous studies have demonstrated surprising effects of abatacept on Tregs, specifically decreased frequency of these cells but enhancement in their function[1]. Whether these alterations can only be found in patients with ABA treatment, or whether they are also present in patients receiving other anti-inflammatory drugs is currently unknown.

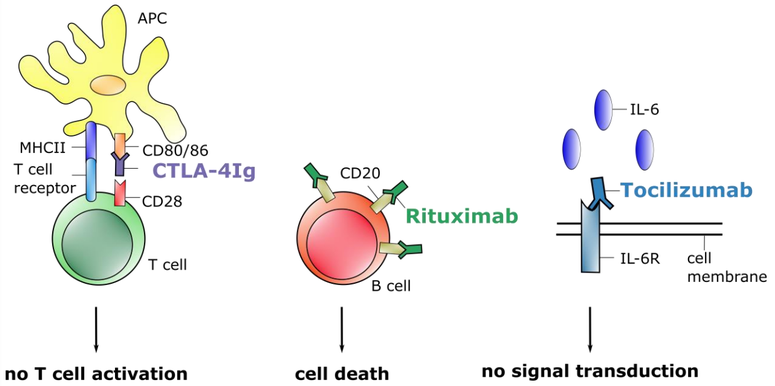

Figure 1 bDMARDs mechanisms of action

OBJECTIVE

The aim of our research was to delineate the impact of ABA on the different subsets of effector and regulatory T cells in RA and compare these findings with patients receiving an IL-6 receptor inhibitor (tocilizumab, TCZ) or an antibody against CD20 (rituximab, RTX).

1. Álvarez-Quiroga C, Abud-Mendoza C, Doníz-Padilla L, et al. CTLA-4-Ig therapy diminishes the frequency but enhances the function of treg cells in patients with rheumatoid arthritis. J Clin Immunol. 2011;31(4):588-595. doi:10.1007/s10875-011-9527-5

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MATERIAL AND METHODS

Peripheral blood samples from 56 RA patients (median ± SE; age: 60.5 ± 1.3 years, female ratio: 0.7, disease duration: 17.9 ± 2.1 years; respectively) were drawn over a sampling period of 2 years. Freshly isolated PBMCs of RA patients were stained with fluorochrome-labelled antibodies and T cell subsets were identified by flow cytometric means. $CD3^+CD4^+$ T cells were further classified using different T cell markers (CD25, CD127, CD39, CD95). All cytometric measurements were performed using a standardized BD LSR-Fortessa platform. RA patients were compared according to their treatment with ABA, TCZ or RTX.

Table 1 Patient characteristics

	bDMARDs		
	CTLA-4Ig	**IL-6Ri**	**RTX**
patient characteristics			
sample size	18 (32.1%)	25 (44.6%)	13 (23.2%)
female ratio	0.72	0.84	0.38
Age, years ± SD	63.5 ± 0.4	59 ± 9.5	62.5 ± 8.1
disease duration, years ± SD	5 ± 0	10 ± 8.7	14.6 ± 12.4
clinical parameters, n (%)			
disease activity, cDAI			
Remission	2 (11.1%)	6 (24%)	2 (15.4%)
low	16 (88.%)	19 (76%)	11 (84.6%)
other medication, n (%)			
Glucocorticoides	4 (22.2%)	4 (16%)	6 (46.2%)
NSARs	7 (38.9%)	6 (24%)	2 (15.4%)
MTX	8 (44.4%)	8 (32%)	6 (46.2%)
Leflunomide	3 (16.7%)	2 (8%)	1 (7.7%)
Hydroxychloroquin	-	-	2 (15.4%)

RESULTS

Eighteen out of 56 RA patients (32%) received ABA, 25 patients (45%) received TCZ and 13 patients (23%) were under $CD20^+$ cell depletion therapy with RTX. RA patients receiving ABA displayed a significant decrease in $CD3^+CD4^+CD25^+CD127^{dim}$ Tregs (3.7% ± 0.4) compared to patients with TCZ (5.4% ± 0.4, p = 0.041) and patients under RTX treatment (7.52% ± 0.93, p = 0.026).

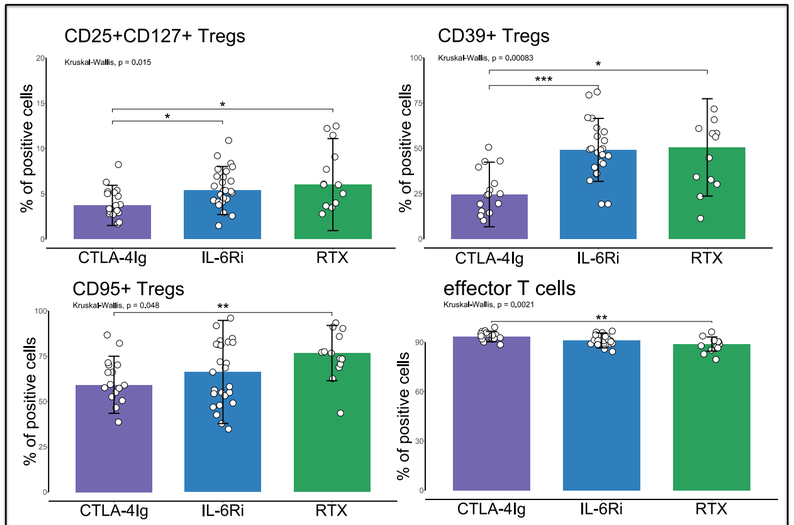

Figure 2 T cell profile in RA patients receiving bDMARDs. Percentages of Tregs and T effector cells were extracted from FACS data and comparisons of group means for patients receiving CTLA-4Ig, an IL-6Ri (TCZ) or RTX were calculated using Wilcoxon Rank-Sume test. Tests were corrected using Bonferroni corrections. Group medians are displayed as bars; interquartile ranges are displayed as error bars. Significance levels: * p ≤ 0.05, ** p ≤ 0.01, *** p ≤ 0.001

$CD39^+$ Tregs were significantly higher in RA patients treated with TCZ (49.5% + 3.2, p = 0.000) or RTX (50.5% ± 5.3, p = 0.026) compared to patients receiving ABA (24.5% ± 3.1).
In addition, the frequency of $CD95_+$ Tregs was significantly reduced in ABA patients compared to RTX patients (59.2% ± 3.1 vs.76.7% ± 3.6, p = 0.014; respectively). Interestingly, T cells displaying an effector T cell phenotype ($CD3^+CD4^+CD25^{+/-}CD127^+$) were increased in ABA treated patients compared to RTX treated patients (93.7% ± 0.6 and 88.9% ± 1.2, p = 0.002). Since none of our patients were a non-responder or had high disease activity, we could not analyze whether these changes are associated with treatment outcome.

CONCLUSION

Our data demonstrate that blockage of T cell stimulation via ABA leads to characteristic alterations in different regulatory and effector T cells not seen in patients treated with TCZ or RTX. Further studies must clarify whether the analysis of regulatory and effector T cell subpopulations before treatment initiation can be used as biomarker for treatment response.