

Circulating follicular helper T cells (CD4⁺CXCR5⁺ICOS⁺) decrease in patients with rheumatoid arthritis treated with abatacept

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CD4⁺CXCR5⁺ICOS⁺ follicular helper T (TFH) cells promote the production of autoantibodies in rheumatoid arthritis, interacting with B cells in lymph node germinal centres. In our cohort of patients, TFH cells were significantly reduced after treatment for six months with abatacept, suggesting a central action of the drug.

In most cases, rheumatoid arthritis (RA) is characterised by autoantibodies, including rheumatoid factor (RF) and anti-cyclic citrullinated peptide antigen (ACPA). The capability of producing autoantibodies is acquired by B-cells after interaction with follicular helper T-cells (TFH), whose main functions are to maintain the germinal centres (GC) of secondary lymphoid tissues and promote B-cell differentiation into plasma cells and memory cells. TFH are characterised by a high expression of CXC-chemokine receptor 5 (CXCR5), which mediates their migration into GC, where its ligand CXCL13 is expressed. Expression of inducible co-stimulator (ICOS), a receptor structurally and functionally related to CD28, which can receive signals from B-cells expressing ICOS-Ligand, is required for GC formation (1): ICOS-deficient humans suffer from a form of common variable immunodeficiency characterised by reduced GC responses and selective loss of peripheral blood CXCR5⁺CD4⁺ T-cells, despite normal frequencies of CD4⁺ T-cells overall (2). The exclusive roles played by CD28 and ICOS in different stages of TFH development have been elucidated (3): while CD28 regulates the early differentiation steps of naive T-cells into TFH, ICOS is important to maintain the phenotype of already differentiated TFH and their correct localisation within GC.

Abatacept (ABA) is a soluble CTLA-4-Ig chimera, used to block CD28 in RA treatment. Data from animal models and phenotypic analysis of circulating T-cells in RA suggest that ABA may act in the secondary lymphoid organ, and not directly on the synovium (4,

5). While experimental models show that ABA can block the generation of TFH (6), not much is known on the effect of ABA on circulating TFH-like cells of RA patients (7). Recently, Fukuyo *et al.* reported that the proportions of total CD4⁺CXCR5⁺ (“TFH-like”) cells were increased in 34 RA patients as compared with 14 healthy controls (8). The proportions of TFH-like cells among CD4⁺CD28⁺ cells were significantly higher than those among CD4⁺CD28⁻ cells. Finally, in 15 RA patients evaluated for this purpose, the proportion of TFH-like cells among CD4⁺CD28⁺ cells was significantly reduced after ABA therapy (8).

We evaluated by flow-cytometry analysis the CD4⁺CXCR5⁺ T-cell population according to ICOS expression in 50 RA patients before ABA therapy, and in 32 of them also after 6 months of therapy (Table I). The CD4⁺CXCR5⁺ICOS⁺ population, but not the ICOS⁻ counterpart, was significantly increased in RA patients, as compared to 18 healthy controls. No difference was observed between patients with baseline proportions of CD4⁺CXCR5⁺ICOS⁺ T-cells higher than 95th percentile of healthy controls (1.1% of CD3⁺CD4⁺; n=20) as compared with other RA patients (n=30), as far as positivity or levels of ACPA or other clinical aspects of the disease. Only the CD4⁺CXCR5⁺ICOS⁺ population decreased after ABA therapy, both in patients with (n=25) or without (n=7) good EULAR response.

Our results extend those of Fukuyo *et al.* (8), allowing a better interpretation of the effect of ABA on total CD4⁺CXCR5⁺ (“TFH-like”) populations in RA. In these patients, the CD28⁺ subset, which is likely to include naive cells committed to TFH differentiation, is expanded: the blockade of CD28 costimulation by ABA inhibits the early differentiation steps preventing the generation of TFH (8). The efficacy of this preventive role is confirmed by our observations: the ICOS⁺ subset, which is likely to better reflect the “real” TFH population, including already differentiated CD4⁺ T-cells receiving signals within the GC (3), is expanded in RA, but its generation is reduced by the CD28 costimulation blockade. These results therefore confirm data suggesting that the main actions of ABA in RA are those in the secondary lymphoid organ (4, 5), and highlight the need of further investiga-

tions evaluating the role of TFH, their phenotype and functions in human autoimmune diseases.

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Table I. Clinical and demographic characteristics of 50 RA patients and proportions of peripheral blood T-cell subsets.

Clinical and demographic features of RA patients						
Gender	Females 41 (82%); Male 9 (18%)					
Age	60 (48-67) years					
Disease duration	72 (30-144) months					
ACPA+	37/48 (77%)					
FR+	39/50 (78%)					
Previous treatment with other biological agent(s)	21 (42%)					
DAS28-CRP at baseline (T0)	4.89 (4.11-5.48)					
Proportions of peripheral blood T-cell subsets						
	Healthy controls (n=18)	RA (n=50)	p	RA pre-ABA (T0) n=32	RA post-ABA (T6) n=32	p
CXCR5 ⁺ ICOS ⁺ (% of CD3 ⁺ CD4 ⁺)	0.5 (0.2-0.7)	1.05 (0.2-2.9)	0.02	0.7 (0.1-3.3)	0.2 (0-0.8)	0.008
CXCR5 ⁺ ICOS ⁻ (% of CD3 ⁺ CD4 ⁺)	0.9 (0.4-3.0)	2.5 (0.6-6.9)	0.07	3.1 (0.8-7.5)	1.6 (0.4-9.4)	0.8

Data are presented as the median (25th-75th percentile), if not otherwise specified. Comparisons were made with the Mann-Whitney or the Wilcoxon signed rank test when appropriated.