CLA+ effector memory T Cells in circulation associate with DMARD non-response in psoriatic arthritis

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Background

Despite an expanding treatment landscape, only 40–60% of psoriatic arthritis (PsA) patients respond to first-line DMARD treatment, highlighting an unmet need for personalized treatment strategies.

Objective

To improve understanding of the immunologic mechanisms underlying differential treatment responses in PsA by comparing immune profiles of patients initiating conventional synthetic, biologic, and targeted synthetic DMARDs.

Methods

- **Study context:** Data from the ongoing **TOFA-PREDICT** randomized clinical trial using multi-omics to predict DMARD response (***Figure 1***)
- **Patient groups:**
  - *DMARD-naïve:* treated with methotrexate or tofacitinib
  - *DMARD-failure:* treated with etanercept or tofacitinib, + background csDMARDs
- **Primary outcome:**
  - Response at 16 weeks = **Minimal Disease Activity (MDA)**
- **Immune profiling:**
  - Baseline peripheral blood mononuclear cells analyzed via **flow cytometry** (***Figure 2***)
- **Statistical analysis:**
  - Comparisons: χ^2, *t*-test, Mann-Whitney U
  - Correlations: Spearman's ρ

Results

- 40 DMARD-naïve and 40 DMARD-failure patients were included. Overall response was 50%: 50% for methotrexate, 50% for tofacitinib, 60% for csDMARD+etanercept, and 40% for csDMARD+tofacitinib.
- Principal component analyses of immune profiling parameters revealed no distinct clustering between DMARD responders and non-responders (***Figure 3***).
- Non-responders had higher proportions of cutaneous lymphocyte antigen (CLA)+ CD8+ T effector memory cells (28% vs 21%, p = 0.002) (***Figure 4D***). CLA proteins are present on T cells that infiltrate inflamed skin. CLA expression by CD4+ and CD8+ T cells correlated with tissue homing receptor CCR10 (ρ 0.66-0.67, p < 0.05) (***Figure 4E-F***), suggesting an inflammatory response driven by tissue-resident mechanisms.
- Etanercept responders showed lower CD4+/CD8+ T cell ratios (2.3 vs 7.5, p = 0.002) and a higher proportion of terminally differentiated effector memory CD4+ (21% vs 7%, p = 0.015) and CD8+ T cells (64% vs 40%, p = 0.012), compared to etanercept non-responders (***Figure 4G-J***). Additionally, responders to etanercept had higher CD4+ T cell production of IFN-γ (14% vs 5%, p = 0.002) and TNF (39% vs 28%, p = 0.049) (***Figure 4K-L***).

Table 1. ***Baseline characteristics***

	DMARD-naive		DMARD-failure	
	Tofacitinib (n = 20)	Methotrexate (n = 20)	csDMARD+ Tofacitinib (n = 20)	csDMARD+ Etanercept (n = 20)
Age (years), mean ± SD *	49,2 ± 10,6)	47,8 ± 10,8	54,8 ± 13,8	53,4 ± 10,0
Female, n (%)	5 (25%)	12 (60%)	9 (45%)	6 (30%)
Years PsO diagnosis, median (IQR) *	7,9 (0,4 - 27,1)	1,6 (0,3 - 10,9)	13,1 (6,7 - 23,5)	11,2 (4,8 - 25,2)
Years PsA diagnosis, median (IQR)	0,1 (0,1 - 1,4)	0,1 (0,0 - 0,5)	11,3 (4,8 - 18,9)	5,5 (1,3 - 16,8)
Daily use of NSAID, n (%)	10 (50%)	11 (55%)	6 (30%)	12 (60%)
Methotrexate use, n (%) *	0 (0%)	0 (0%)	17 (85%)	15 (75%)
Leflunomide use, n (%) *	0 (0%)	0 (0%)	1 (5%)	4 (20%)
Sulfasalazine use, n (%)	0 (0%)	0 (0%)	2 (10%)	1 (5%)
BMI (kg/m^2), mean ± SD	29,1 ± 5,2	27,4 ± 5,6	29,0 ± 4,1	27,4 ± 4,3
PASI, median (IQR)	1,3 (0,6 - 4,5)	1,6 (0,6 - 5,0)	0,4 (0,0 - 1,4)	2,0 (1,1 - 4,0)
BSA, median (IQR)	1,0 (1,0 - 2,5)	2,0 (1,0 - 3,5)	1,0 (0,0 - 1,5)	1,0 (1,0 - 3,5)
Psoriasis nail abnormality, n (%)	14 (70%)	13 (65%)	10 (50%)	16 (80%)
TJC68, median (IQR)	6 (4 - 10)	7 (5 - 12)	4 (2 - 8)	6 (5 - 11)
SJC66, median (IQR)	3 (3 - 7)	6 (4 - 9)	4 (2 - 5)	5 (3 - 10)
Dactylitis, n (%) *	6 (30%)	4 (20%)	4 (20%)	6 (30%)
Enthesitis (LEI), n (%) *	4 (20%)	5 (25%)	8 (40%)	4 (20%)
ESR (mm/h), median (IQR)	9 (4 - 32)	8 (5 - 33)	13 (8 - 17)	8 (5 - 10)
CRP (mg/L), median (IQR)	2,5 (1,2 - 10,0)	5,3 (1,0 - 13,5)	3,0 (1,5 - 10,5)	3,7 (1,0 - 7,0)

Figure 2. ***Comprehensive immune profiling by flow cytometry***

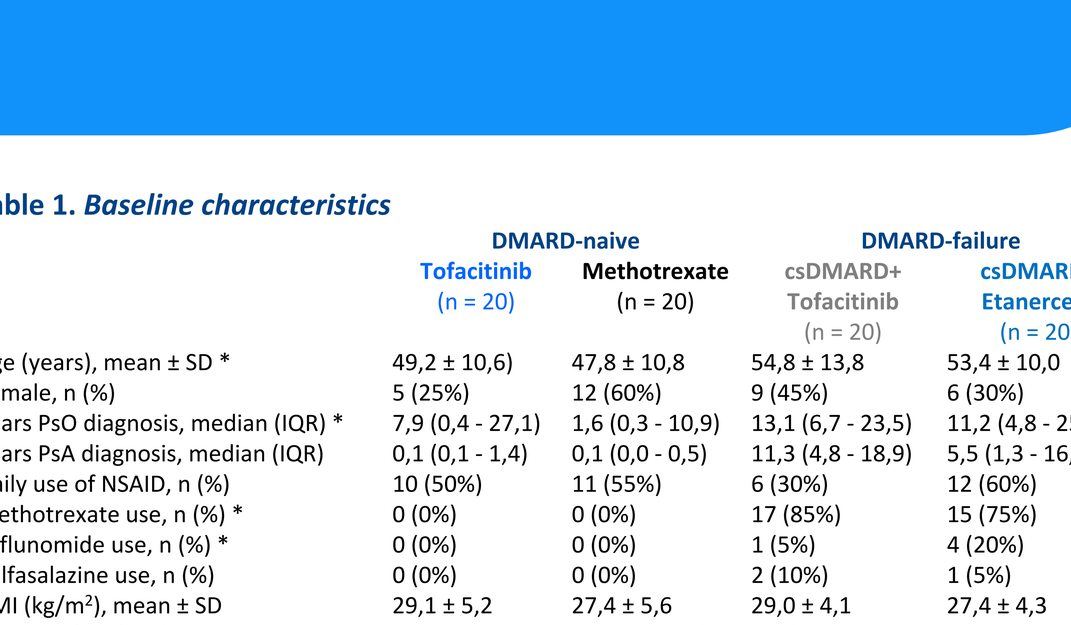

Figure 3. ***No distinct clustering in Principal Component Analyses of immune profiling parameters***

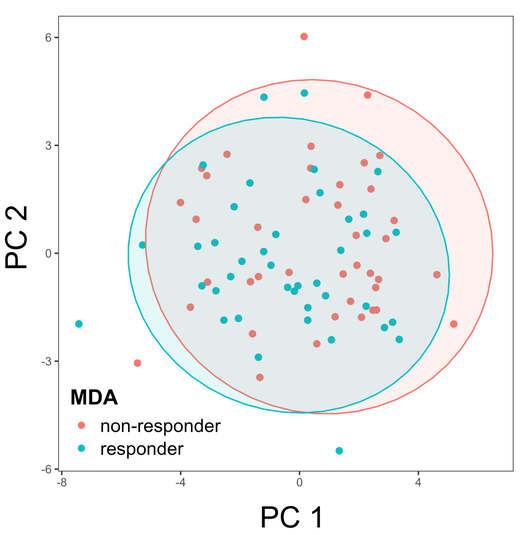

Figure 4. ***CLA expression by CD8+ T effector memory cells associates with DMARD non-response in PsA***

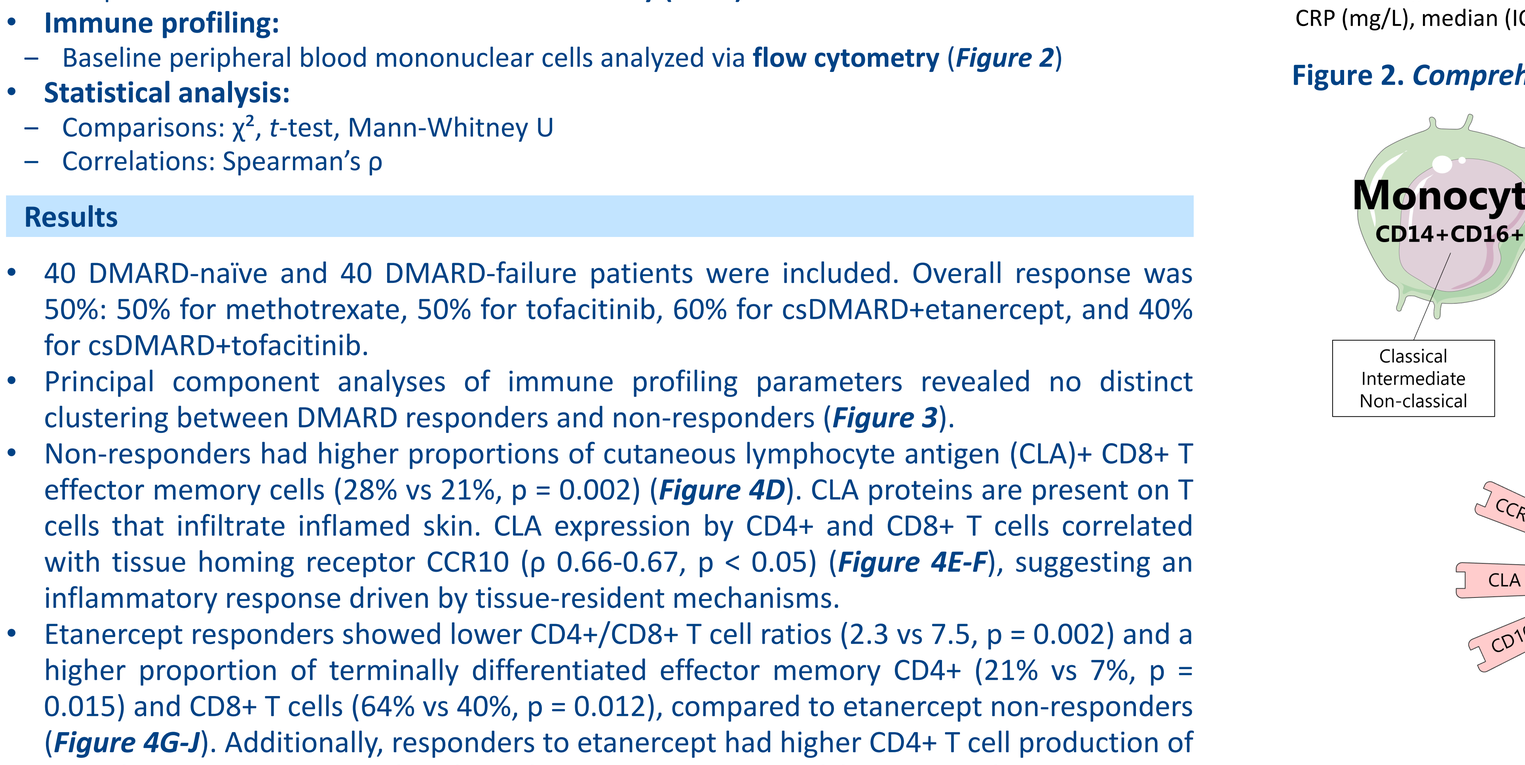

Figure 1. ***TOFA-PREDICT study protocol***

Conclusion

In PsA patients, high CLA expression by effector memory T cells associates with non-response to methotrexate, etanercept and tofacitinib. Additionally, a distinct immunologic phenotype in PsA patients may associate with susceptibility to etanercept therapy. Ongoing longitudinal studies of the TOFA-PREDICT cohort will further explore and validate these observations.

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