A CYTOKINE SIGNATURE FROM MONOCYTE-DERIVED MACROPHAGES PREDICTS THE RESPONSE TO APREMILAST IN PATIENTS WITH PSORIATIC ARTHRITIS

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BACKGROUND

- **Apremilast** is a **PDE4-inhibitor** approved for the treatment of psoriatic arthritis (PsA).
- The mechanisms of action of apremilast remain elusive, although data support the regulation of **innate immune cells**.
- The role of **macrophages** in the pathogenesis of PsA remains largely enigmatic

OBJECTIVE

- To investigate the ***ex vivo*** effects of **apremilast** on **monocyte-derived macrophages** in patients with PsA.

METHODS

Patients

- **23 PsA patients starting apremilast**
  - mean age 55±14.3; 10/23 women
  - disease duration 82 ± 95 months; 6 on MTX
- **21 knee osteoarthritis** (OA) controls
  - mean age 63 ± 8.7; 10/21 women

Peripheral blood (PB) **monocytes**

- isolated at **baseline** in subjects and after **4 months** of **apremilast** therapy in PsA
- differentiated into **M1- or M2-macrophages**

Gene expression (**RT-qPCR**) and supernatant levels (**ELISA**):

- **IL-1β**, **IL-23**, and **TNF-α** → **M1**-macrophages
- **IL-10**, **IL-1Ra**, and **TGF-β** → **M2**-macrophages.

Patients with PsA were coined as ***responders*** if at 4 months a decrease ≥4 points of DAPSA and any reduction in TJC or SJC occurred compared to baseline.

RESULTS

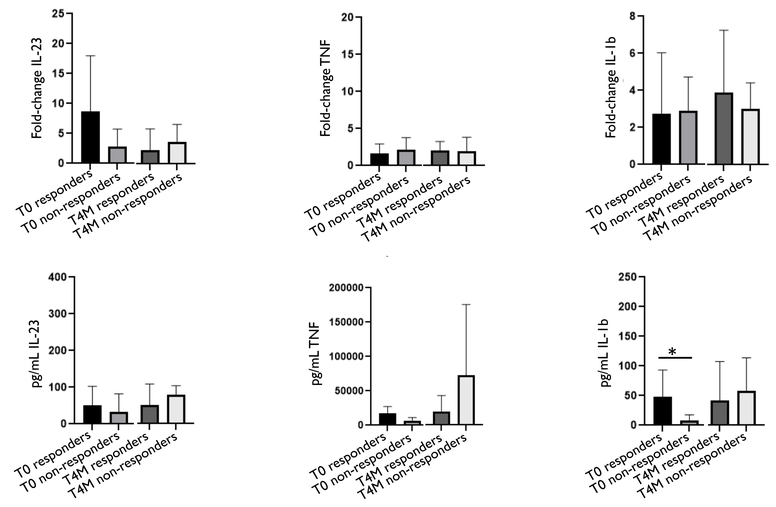
After receiving apremilast for 4 months:

- 17/23 patientswere responders; 10/17 had DAPSA down-stage
- Response was independent of concomitant MTX, systemic glucocorticoids or baseline DAPSA

M1-macrophages

	OA		PsA baseline	PsA 4 months
IL-23 expression (fold change)	1.09 (1.63)		6.43 (7.88)*	2.50 (3.46)
		Responders	8.68 (9.31)	2.26 (3.60)**
		Non-responders	2.83 (2.89)	3.64 (2.96)
IL-23 ELISA (pg/mL)	89.0 (101.1)		43.9 (49.6)	54.4 (54.5)
		Responders	50.4 (52.3)	50.8 (57.3)
		Non-responders	32.5 (49.5)	79.35 (24.34)
TNF-α expression (fold change)	1.36 (1.30)		1.86 (1.38)	2.03 (1.28)
		Responders	1.68 (1.27)	2.04 (1.21)
		Non-responders	2.14 (1.65)	1.97 (1.87)
TNF-α ELISA (pg/mL)	17 262 (23 479)		13 252 (9 483)	18 285 (22 854)
		Responders	17 844 (9 629)	19 007 (23 667)
		Non-responders	6 824 (4 435)#	72 112 (103 168)
IL-1β expression (fold change)	2.33 (2.46)		2.80 (2.72)	3.74 (3.10)
		Responders	2.75 (3.28)	3.89 (3.38)
		Non-responders	2.88 (1.84)	3.02 (1.40)
IL-1β ELISA (pg/mL)	20.6 (33.8)		31.1 (39.8)	44.7 (62.9)
		Responders	47.7 (45.5)	41.9 (65.6)
		Non-responders	7.74 (9.90)#	58.4 (55.4)

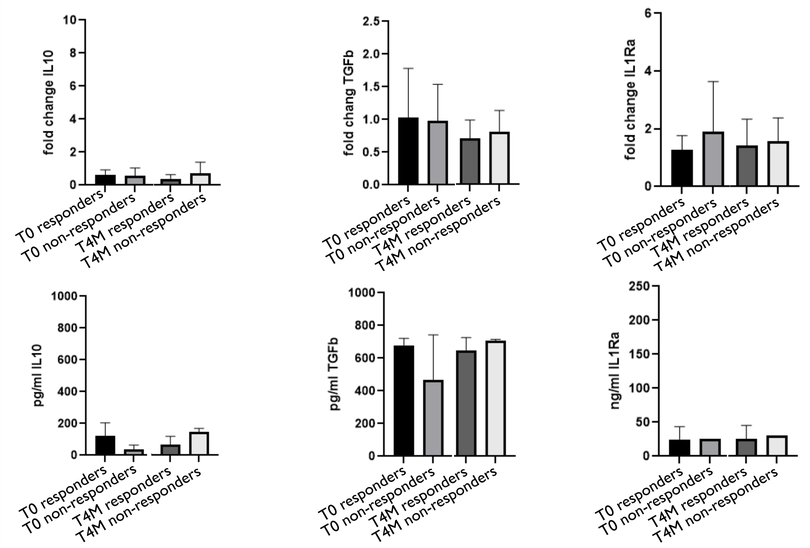
** p < 0.05 PsA baseline vs. OA; ** p < 0.05 PsA at 4 months vs. PsA baseline; # p < 0.05 non-responders vs. responders at baseline*



M2-macrophages

	OA		PsA baseline	PsA 4 months
IL-10 expression (fold change)	4.03 (9.24)		0.62 (0.35)	0.46 (0.34)
		Responders	0.64 (0.29)	0.40 (0.24)
		Non-responders	0.58 (0.46)	0.73 (0.65)
IL-10 ELISA (pg/mL)	91.1 (82.6)		84.4 (79.2)	77.4 (56.8)
		Responders	120.7 (83.0)	66.5 (52.6)
		Non-responders	36.1 (27.6)	148.1 (20.3)
TGF-β expression (fold change)	1.34 (1.30)		1.01 (0.66)	0.72 (0.28)
		Responders	1.03 (0.75)	0.70 (0.28)
		Non-responders	0.98 (0.56)	0.80 (0.33)
TGF-β ELISA (pg/mL)	578.1 (70.9)		592.2 (199.3)	656.7 (74.5)**
		Responders	679.8 (41.1)	649.3 (76.9)
		Non-responders	469.7 (273.0)	708.7 (6.32)
IL-1Ra expression (fold change)	2.62 (7.00)		1.52 (1.11)	1.46 (0.87)
		Responders	1.27 (0.49)	1.43 (0.91)
		Non-responders	1.91 (1.73)	1.58 (0.80)
IL-1Ra ELISA (ng/mL)	32.2 (31.6)		25.0 (16.7)	25.5 (19.6)
		Responders	24.8 (18.7)	25.2 (20.3)
		Non-responders	26.1 (0)	30.2 (0)

*** p < 0.05 PsA at 4 months vs. PsA baseline*



CONCLUSIONS

- An **IL-23 signature** characterizes PsA PB-derived M1 macrophages;
- Baseline **IL-1β**, **TNF-α**, **IL-23** predict **response** to apremilast
- IL-23 decreases in responders; **lack of response** is linked to an **increased myeloid** inflammatory **signature**