IL-23 AS BIOMARKER OF CLINICAL RESPONSE TO APREMILAST IN PATIENTS WITH PSORIATIC ARTHRITIS

Antonio Tonutti[1,2], Maria De Santis[1,2], Natasa Isailovic[2], Francesca Motta[1,2], Rita Ragusa[2], Giacomo M. Guidelli[2], Marta Caprioli[2], Angela Ceribelli[1,2], Nicoletta Luciano[1,2], Carlo Selmi[1,2]

[1]*Department of Biomedical Sciences, Humanitas University, Pieve Emanuele, Italy;* [2]*Rheumatology and Clinical immunology, IRCCS Humanitas Research Hospital, Rozzano, Italy*

BACKGROUND

- **IL-23** is a major **driver of IL-17 production**, both being central to the pathogenesis of psoriaric arthritis (PsA).
- **Apremilast inhibits PDE4** and modulates the inflammation underlying PsA; however, the immunological mechanisms are largely unclear.
- **Predictors of response** to apremilast **would be clinically most relevant**.

OBJECTIVES

a. To define the ***ex vivo* effects of apremilast** on cytokine production by peripheral blood **monocyte-derived macrophages**, **T** cells, and **innate-like lymphocytes** in PsA patients, based on clinical response;

b. To explore the role of **serum IL-23** in **predicting** clinical **response** to apremilast in PsA patients.

METHODS

23 patients with **PsA starting apremilast**: age 55±14 years; 10/23 women; median baseline DAPSA 16.3.
21 controls with **knee osteoarthritis** (**OA**): age 63 ± 8.7 years; 10/21 women.

Peripheral blood samples: at baseline (**BSL**) from all subjects, and after one (**T1M**) and four months (**T4M**) in PsA cases.

Monocytes: isolated and differentiated into **M1-**macrophages to assess **IL-23**, **TNF-α**, and **IL-1β** through:
- gene expression (**qPCR**);
- production levels (**ELISA**).

Flow cytometry used to assess the **phenotype** (T, γδT, NK, NKT-like, ILC1, ILC3, MAIT cells) and **cytokine production** (IFNγ, IL-17, IL-9) of **lymphocytes**.

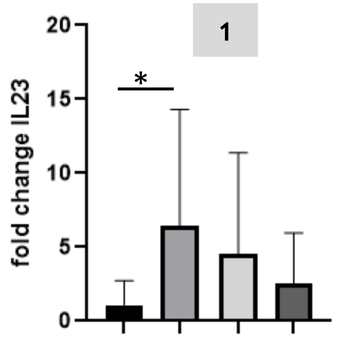
ELISA used to assess **serum IL-23** at **baseline**.

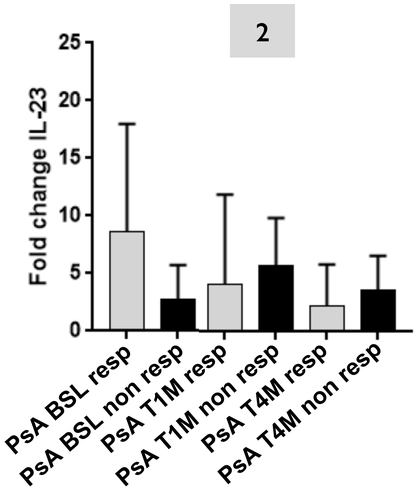
RESULTS

17/23 patients with PsA **were responders** after 4 months of apremilast treatment, according to:
a. ACR20;
b. A reduction of DAPSA > 4 points;
c. TJC=0 and SJC≤1.

Monocyte-derived M1-macrophages

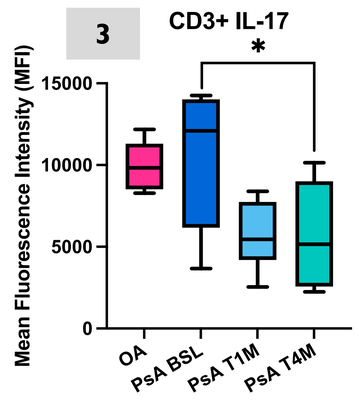
- Baseline gene expression of IL-23 was higher in PsA than OA and decreased at T4M in PsA (**1**).
- Responders had higher baseline expression of IL-23 than non-responders; at T4M, IL-23 decreased only in responders (**2**).





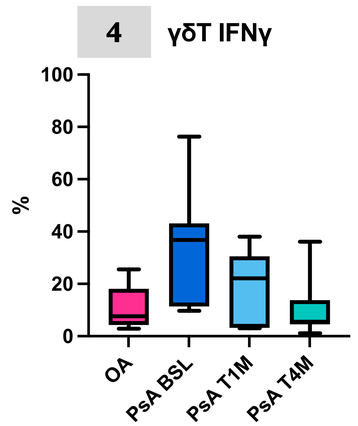
Lymphocyte modulation: IL-17

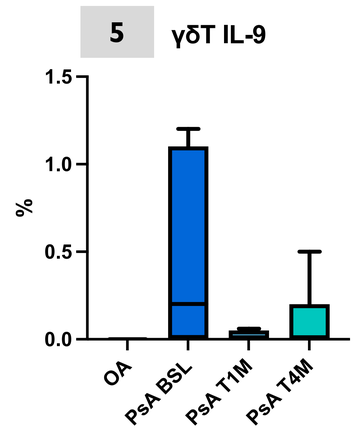
- Apremilast reduced the expression of IL-17 from T cells in responders (**3**), but not in non-responders.
- Similar results were observed with ILC3, but only at an early time-point (*not shown*).



Lymphocyte modulation: IFNγ and IL-9

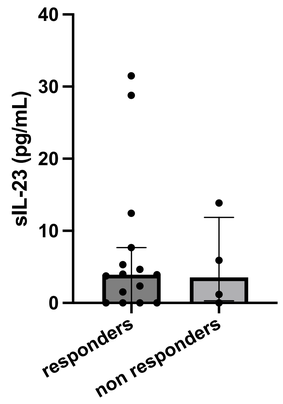
- Apremilast reduced the expression of IFNγ from γδT cells only in responders; similar results were observed in ILC1 only at an early time-point (**4**).
- Apremilast reduced the expression of IL-9 from γδT cells (**5**).

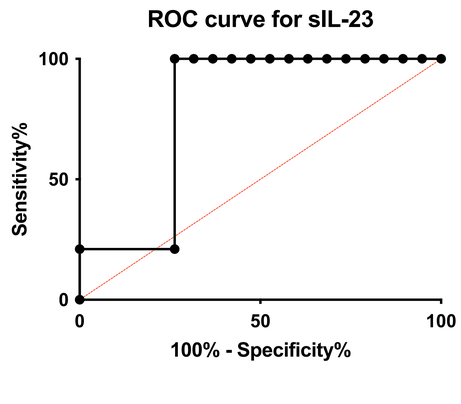




Serum IL-23 predicts the response to apremilast

- Baseline serum IL-23 >1.4pg/mL predicted the response to apremilast at T4M (AUC_{ROC} 0.79; Sensit.100%, Specif. 68%).
- No correlation with clinical features, CRP, concurrent treatments.





- **Higher serum IL-23 at baseline**, reflecting a **myeloid** signature, identify PsA patients **responding** to apremilast.
- **Responders** manifest a significant **reduction** in:
  - **IL-23** expression by monocyte-derived M1-macrophages;
  - **IL-17** production by T lymohocytes;
  - **IL-9** and **IFN-γ** production by **γδT cells**.