JAK/STAT inhibition modifies the ILC1 immune response in patients with rheumatoid arthritis

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Abstract

Objective

Recent evidence suggests that innate lymphoid cells (ILCs) might be involved in rheumatoid arthritis (RA) pathogenesis and individuals at risk of RA exhibited an increased frequency of ILC1. JAK3 participates in ILC1 and ILC3 differentiation. Tofacitinib and the Janus Kinase (JAK) 3 inhibitor, PF-06651600, impair the ability of human intraepithelial ILC1 (iILC1) to produce IFN-γ and the proliferation of ILC1 and ILC3. Our study aims to evaluate the ex vivo effects of tofacitinib in RA patients and to investigate if ILC1s and ILC3s are specific targets of tofacitinib in RA.

Methods

Twenty RA patients starting tofacitinib and 10 RA patients starting anti-TNFα were enrolled. Peripheral blood mononuclear cells (PBMCs) from RA patients, collected before and three months after therapy, were cultured to evaluate ILC1 and ILC3 frequencies and the respective production of IFN-γ and IL-17 by flow cytometry analysis. PBMCs of RA patients were in vitro cultured with tofacitinib to evaluate the dose effects on ILC frequencies.

Results

RA patients showed a significant expansion of ILC1 but not ILC3. Unlike anti-TNFα treated patients, in whom no reduction in ILCs was reported, after three months of tofacitinib therapy the overall ILC frequency was reduced, as well as the ILC1 ability to release IFN-γ. In vitro treatment of PBMCs with tofacitinib demonstrated a dose-dependent reduction in the frequency of ILCs compared to untreated cells.

Conclusion

Our preliminary results demonstrate that tofacitinib modulates the innate immune response by reducing the frequency of ILC1 cells and their production of IFN-γ.

Key words

innate lymphoid cells, rheumatoid arthritis, JAK inhibitor, tofacitinib, innate immunity

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Introduction

RA is a chronic inflammatory disease, characterised by altered innate and adaptive immune responses, that can cause cartilage and bone damage as well as disability (1). Although the pathogenesis of RA has always been assumed to be dominated by a predominant activation of adaptive immunity, recent evidence suggests a relevant role of innate immunity.

In this regard, ILCs are the most recently identified cell subset to be added to the complex cellular map of the immune system that may also be involved in the pathogenesis of RA (2-4). It has been recently demonstrated that RA patients have lower numbers of lymphoid tissue-inducer (LTi) cells (c-Kit+NKp44- ILCs) and increased ILC1s (c-Kit-NKp44- ILCs) and ILC3s (c-Kit+NKp44+ ILCs) compared with controls (3). In addition, individuals at risk of RA exhibited a higher frequency of ILC1s than controls ($p<0.01$).

While they were first identified at barrier surfaces, in both humans and mice, it is now clear that ILCs populate almost every tissue thus far examined.

ILCs do not express rearranged antigen receptors that recognise 'non-self' structures, but they do exhibit a functional diversity similar to that of T cells. Innate counterparts for each T cell subset, such as cytotoxic ILCs for $CD8^+$ T cells, and non-cytotoxic ILCs for the T helper (Th) cells (Th1, Th2, and Th17) have been identified.

Th1 cells and their innate counterparts, ILC1s, express T-bet and produce IFN-γ. GATA-3^{hi} ILC2s, like Th2 cells, secrete IL-5, IL-13 and the epidermal-growth-factor-like molecule amphiregulin. RORγt^+ ILC3s correspond to Th17 cells and are heterogeneous in mice and humans (5).

JAK3 has been demonstrated to be functionally relevant in the differentiation of ILC1 and ILC3 (6). Loss-of-function mutations in JAK3 cause autosomal recessive severe combined immunodeficiency (SCID) (7) and the B6.Cg-Nr1d1tm1Ven/LazJ mice (Jackson Laboratories), harbouring a spontaneous mutation in JAK3, display a SCID phenotype with the inability to generate antigen-independent professional cytokine-producing ILCs. Mechanistically, JAK3 deficiency blocks ILC differentiation in the bone marrow at the ILC precursor and the pre-NK cell progenitor (6).

Based on this evidence, we main aim to study the *ex vivo* effects of tofacitinib, in order to understand if the clinical efficacy of tofacitinib can also be attributable to changes in frequency and function of ILC1 and ILC3 in the peripheral blood (PB) of RA patients and to further investigate if ILC1s and ILC3s are specific targets of the JAK inhibitor tofacitinib in RA patients.

Materials and methods

Patients

Twenty RA patients starting treatment with tofacitinib and 10 RA patients starting anti-TNF-α therapy were enrolled in this discovery study. All patients presented active disease defined as a disease activity score 28 C-reactive protein (DAS28CRP) >5.1 and were not treated with previous biologic agents. Ten healthy donors (HD) matched for age and sex were also enrolled as controls. The baseline demographic and clinical features of the patients are shown in Table I.

Methods

Baseline characteristics of patients were recorded at T0. Clinical parameters, including clinical disease activity index (CDAI), were assessed at baseline (T0) and after 3 months (T1) of tofacitinib and anti-TNFα treatment.

Peripheral blood of HD and RA patients was collected at baseline (T0) and after 3 months (T1) of treatment. PBMCs were isolated by Ficoll Hypaque density gradient centrifugation (Pharmacia Biotech, Uppsala, Sweden) from patients, at T0 and T1, and controls. Cell viability (trypan blue dye exclusion) was always >95%.

PBMCs were resuspended in RPMI 1640 medium (Euroclone, MI, Italy) supplemented with 10% fetal cow serum (FCS), L-glutamine (Euroclone, MI, Italy) and antibiotics (Euroclone, MI, Italy), and were incubated, for the functional assay, with medium alone or with ionomycin (Sigma, St. Louis, MO, US, 1μg/mL final concentration),

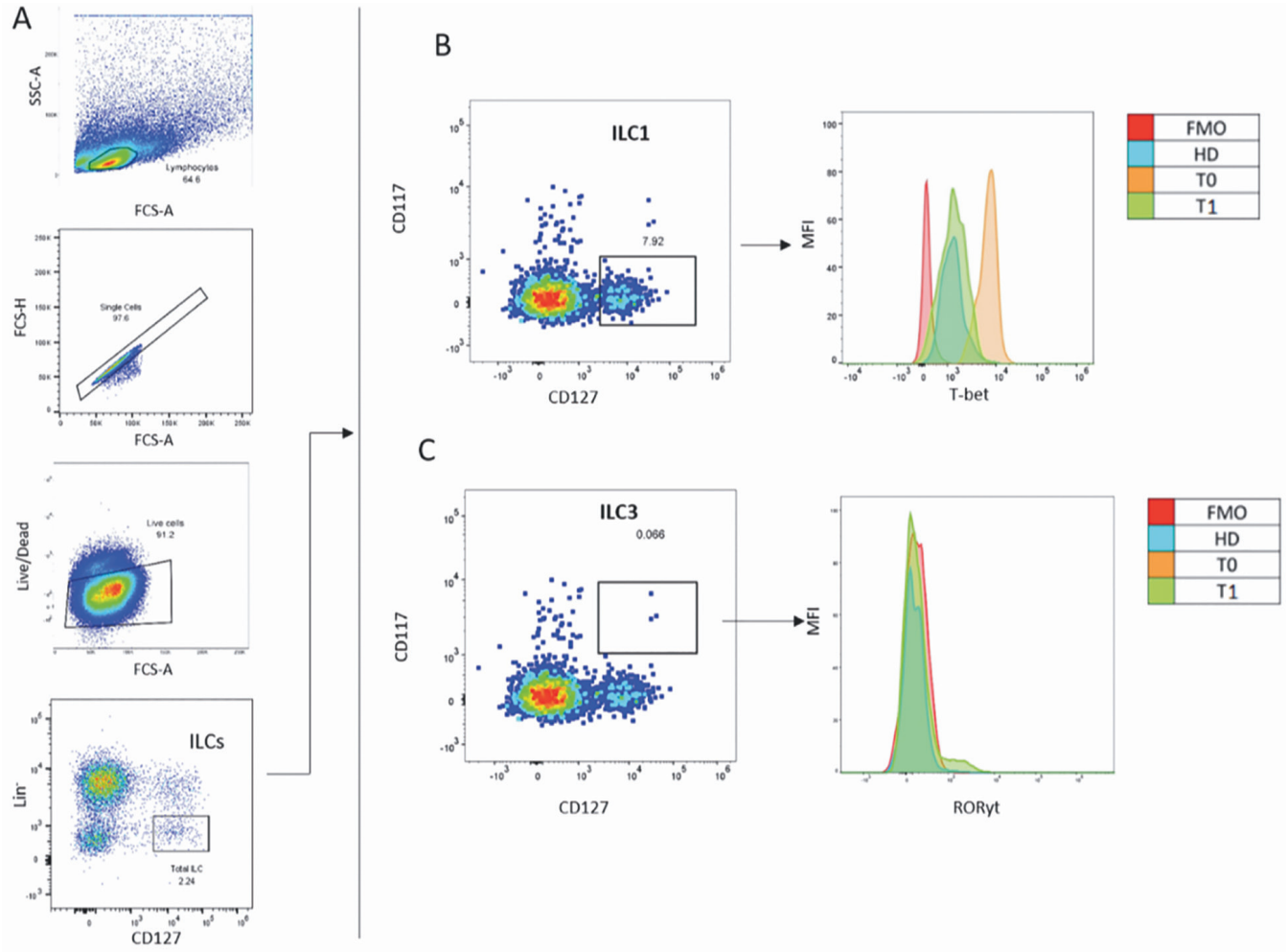

Fig. 1. Representative gating strategy used to identify ILC population.
A: Total ILCs (Lin$^-$ CD127$^+$) gated on live and single lymphocytes.
B: ILC1 subset gated as CD127$^+$ CD117$^-$ and relative T-bet expression (MFI). Legend show FMO: negative T-bet expression (red colour); T0: T-bet expression before tofacitinib treatment (orange); T1: T-bet expression 3 months after tofacitinib treatment (green); HD: T-bet expression on Healthy donor (blue).
C: ILC3 cells gated as CD127$^+$CD117$^+$ and relative RORγt expression (MFI). Legend show FMO: negative RORγt expression (red); T0: RORγt expression before tofacitinib treatment (orange); T1: RORγt expression 3 months after tofacitinib treatment (green); HD: RORγt expression on Healthy donor (blue).
FMO: fluorescence minus one; HD: healthy donor; ILC: innate lymphoid cells; T0: RA patients before treatment; T1: RA patients 3 months after treatment.

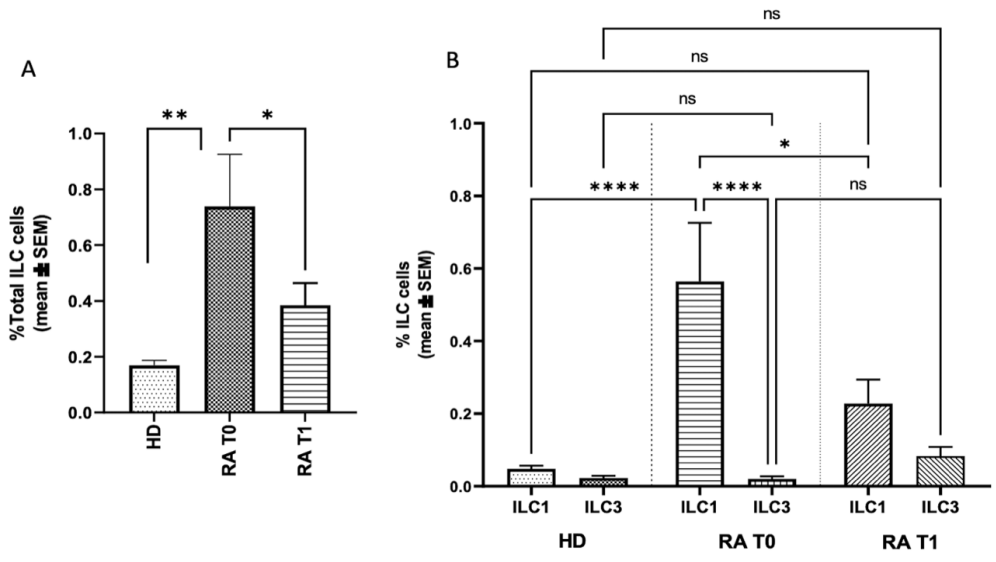

Fig. 2. Frequencies of Total ILCs and relative subsets ILC1 and ILC3 in RA patients treated with tofacitinib.
A: Comparison of peripheral total ILC frequency between HD and RA patients before starting tofacitinib treatment (T0) and 3 months after (T1). Ordinary one way-ANOVA $^{**}p<0.01$, $^{*}p<0.05$.
B: Frequency of ILC1 and ILC3 in the groups of subjects HD and RA patients before starting tofacitinib treatment (T0) and 3 months after (T1). Ordinary one-way ANOVA $^{****}p<0.0001$, $^{*}p<0.05$.
Ratio ILC1/ILC3 at T0: 28; Ratio ILC1/ILC3 at T1: 1.

Table I. Baseline characteristics of patients and controls

	RA (n=30)	HC (n=10)
Age, mean (range)	48 (20-71)	40 (30-60)
Female sex, n (%)	24 (80)	6 (60)
Disease duration, months (range)	8.5 (3-18)	-
RF +, n (%)	17 (56.6)	
ACPA +, n (%)	16 (53.3)	
CRP mg/l, mean (range)	12.6 (5-32.2)	-
DAS28CRP, mean (range)	5.36 (5.2-5.8)	-
Methotrexate (%)	80	-
Oral glucocorticoid dose*, mean (mg/die)	7	-

*prednisone or prednisone equivalent dose
ACPA: anticitrullinated peptides antibodies; CRP: C-reactive protein; DAS28: Disease Activity Score 28; HC: healthy control; MTX: methotrexate; n: number; RA: rheumatoid arthritis; RF: rheumatoid factor.

and phorbol myristate acetate (PMA, Sigma, St. Louis, MO, 150 ng/mL final concentration) for 6 h at 37°C in 5% CO2 in the presence of 10 mcg/ml of monensin (Sigma, St. Louis, MO) to inhibit cytokine secretion.

Following incubation, intracellular staining (ICS) was performed for each patient at T0 and T1 and each HD with appropriate monoclonal antibodies (mAbs).

PBMCs were stained with Zombie Aqua™ Fixable Viability Kit (Biolegend, San Diego, CA, USA) for 15 minutes and then with Pacific Blue™ anti-human Lineage Cocktail (CD3, CD14, CD16, CD19, CD20, CD56) (UCHT1; HCD14; 3G8; HIB19; 2H7; HCD56 Biolegend, San Diego, CA, USA), PE/Cyanine7 anti-human CD127 (IL-7Rα) Antibody (A019D5 Biolegend, San Diego, CA, USA), APC anti-human CD117 (c-kit) Antibody (S18022G Biolegend, San Diego, CA, USA), PerCP/Cyanine5.5 anti-T-bet Antibody (4B10 Biolegend, San Diego, CA, USA), Human ROR gamma /RORC/NR1F3 PerCP-conjugated Antibody (Clone no. 600214 R&D Systems, Inc.), PE anti-human IFN-γ Antibody (B27 Biolegend, San Diego, CA, USA), PE anti-human IL-17A Antibody (BL168 Biolegend, San Diego, CA, USA).

PBMCs of three RA patients, never treated with MTX and biological drugs, were also incubate with RPMI (complete medium alone) and with tofacitinib at 25 nM, 100 nM and 400 nM to evaluate the *in vitro* dose-effects on ILC frequency for 48 hours at 37°C in 5% CO_2 in the presence of 10 mcg/ml

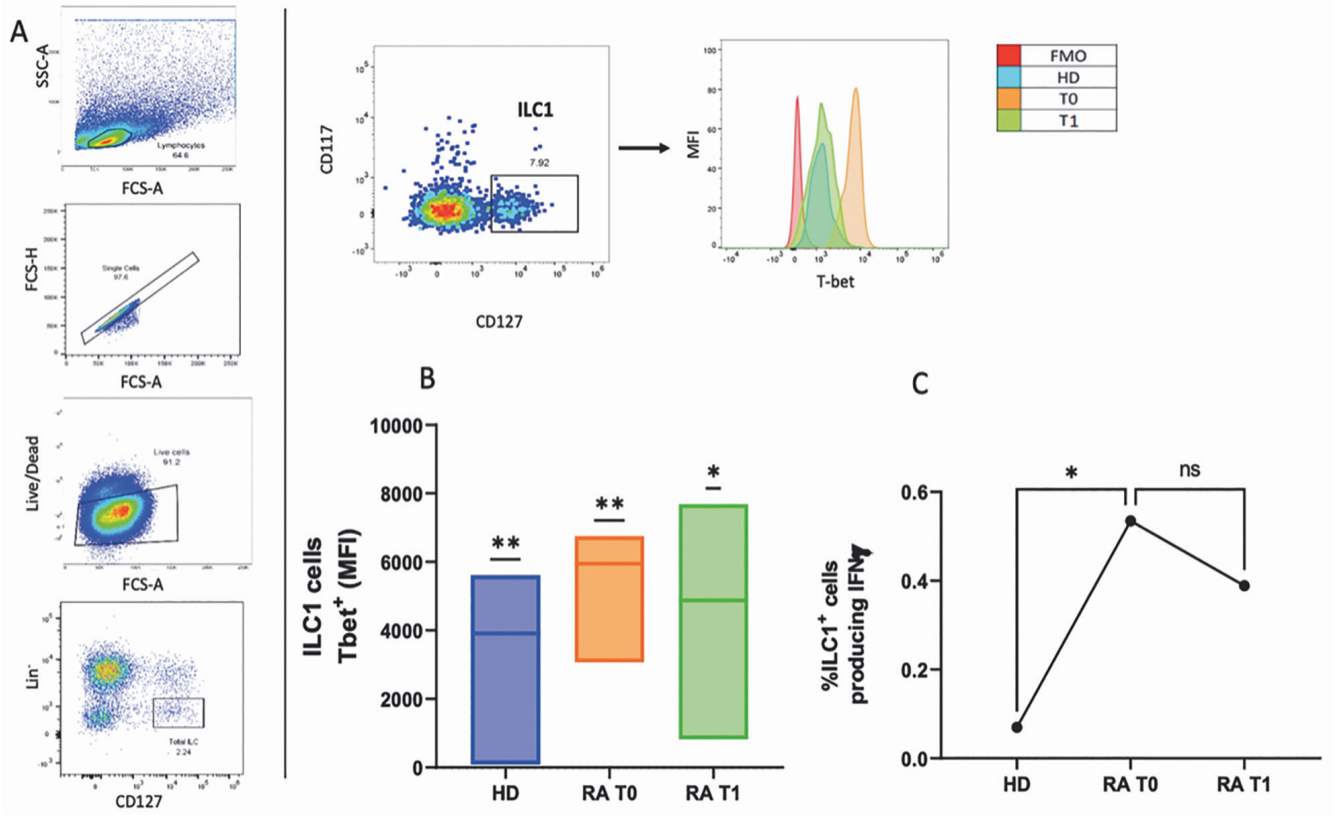

Fig. 3. Frequency and functional activity of ILC1s in RA patients treated with tofacitinib.
A: Representative gating strategy for ILC1 identification and T-bet expression (MFI). Histogram showing overlay of FMO (negative T-bet expression (red)); T0 (T-bet expression before tofacitinib treatment (orange)); T1 (T-bet expression 3 months after tofacitinib treatment (green)) and HD (T-bet expression on healthy donor (blue)).
B: Box plot showing comparison between median values of T-bet MFI for the HD and RA patients before starting tofacitinib treatment (T0) and 3 months after (T1). Wilcoxon Signed Rank test $^{**}p<0.01$, $^{*}p<0.05$.
C: IFNγ production by ILC1s in the HD group and RA patients before starting tofacitinib treatment (T0) and 3 months after (T1). Kruskal-Wallis test $^{*}p<0.05$.

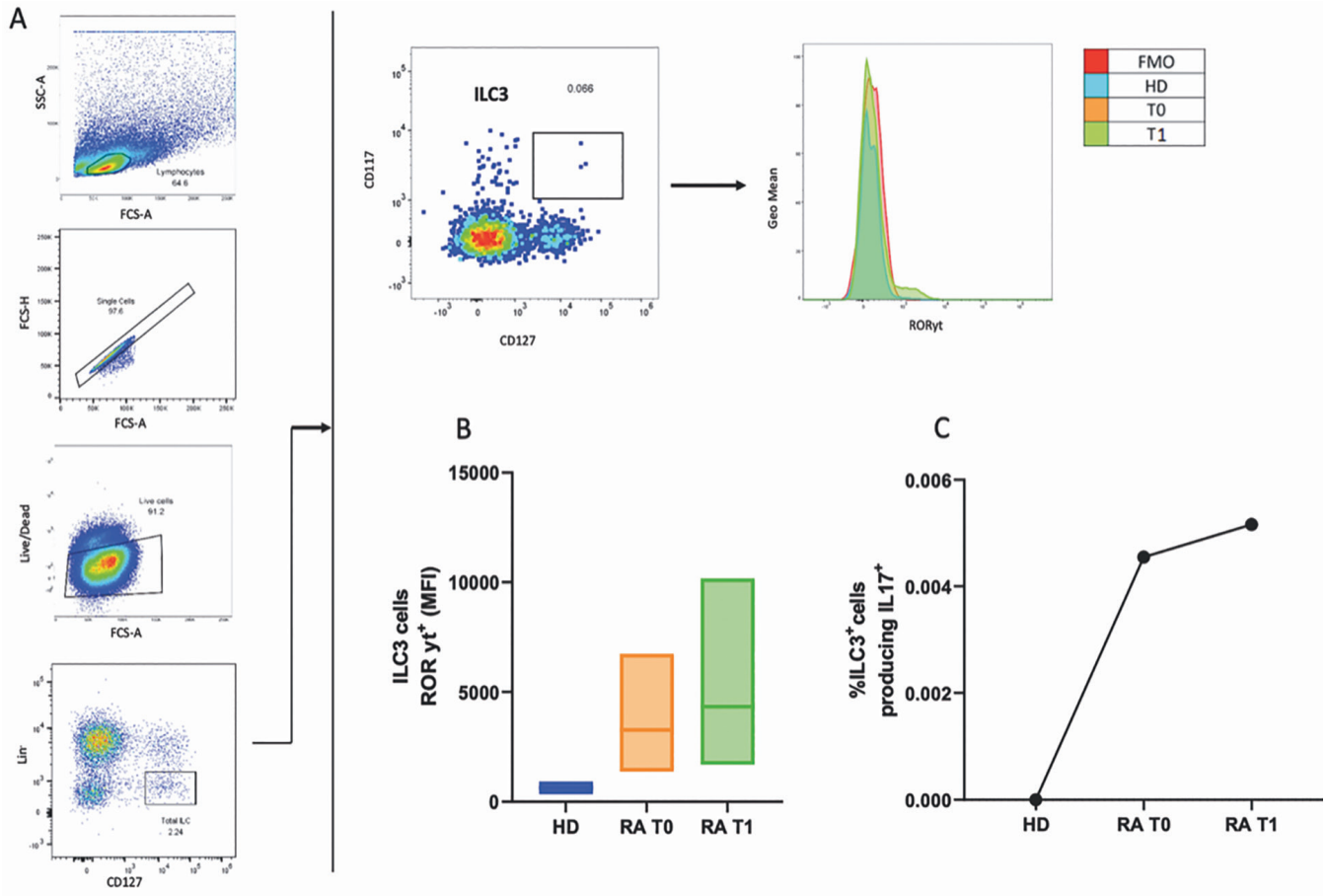

Fig. 4. Frequency and functional activity of ILC3s in RA patients treated with tofacitinib.
A: Representative gating strategy of for ILC3 identification and RORγt expression (MFI).
Histogram showing FMO (negative RORγt expression (red)); T0 (RORγt expression before tofacitinib treatment (orange)); T1 (RORγt expression 3 months after tofacitinib treatment (green)); HD (ROR γt expression on Healthy donor (blue)).
B: Box plot showing median values of RORγt MFI in the HD groups and RA patients before starting tofacitinib treatment (T0) and 3 months after (T1).
C: IL-17 production by ILC3s in the HD group and in the RA patients before starting tofacitinib treatment (T0) and 3 months after (T1).

of monensin (Sigma). After the incubation time, the cells were washed and the ICS was performed as described above.

The effects of tofacitinib in modulating the innate immune response were assessed through the frequency analysis of ILC1 and ILC3 and the respective production of IFN-γ and IL-17A.

Figure 1 shows the gating strategy used during cytometric analysis to identify the ILC1 and ILC3 population by the expression of lineage markers Lin$^-$, CD127, CD117, transcriptional factors T-bet and RoRγt and cytokines production IFN-γ and IL-17A.

At least 100.000 cells (events) were acquired by FACSAria (BD Biosciences, CA, USA) and data were analysed using FlowJo™ v. 10 software (BD Biosciences, CA, USA). Graphs and statistical analysis were performed by GraphPad Software. The correlation between the frequency of ILC1 and the clinimetric score CDAI was also assessed.

Cytometric analysis was chosen because it is a quantitative method that allows us to demonstrate whether the ILCSs population was modulated by tofacitinib treatment. This would enable us to observe the beneficial therapeutic effect and the role of these populations in RA pathogenesis.

The study was designed and performed by the authors; each sample, both for patients and HD, was processed at the time of collection.

Statistical analysis

Data were analysed using GraphPad Prism v. 8.0.1 (GraphPad). Ordinary one-way ANOVA was used to highlight statistical significance. For skewed distribution and small sample size, the non-parametric alternative tests were used (One sample Wilcoxon test or Mann-Whitney U or Kruskal-Wallis). Only p-values <0.05 were considered significant.

The Ordinary one-way ANOVA was used to determine significant frequency differences between ILC1s and ILC3s in the three groups grafted in the study. The non-parametric alternative tests (One sample Wilcoxon test or Mann-Whitney U or Kruskal-Wallis) were used to define significant differences in the cytokine production between the T0 and T1 groups.

Ethical considerations

We confirm that there are no known conflicts of interest associated with this investigation; we further confirm that any aspect of the work has

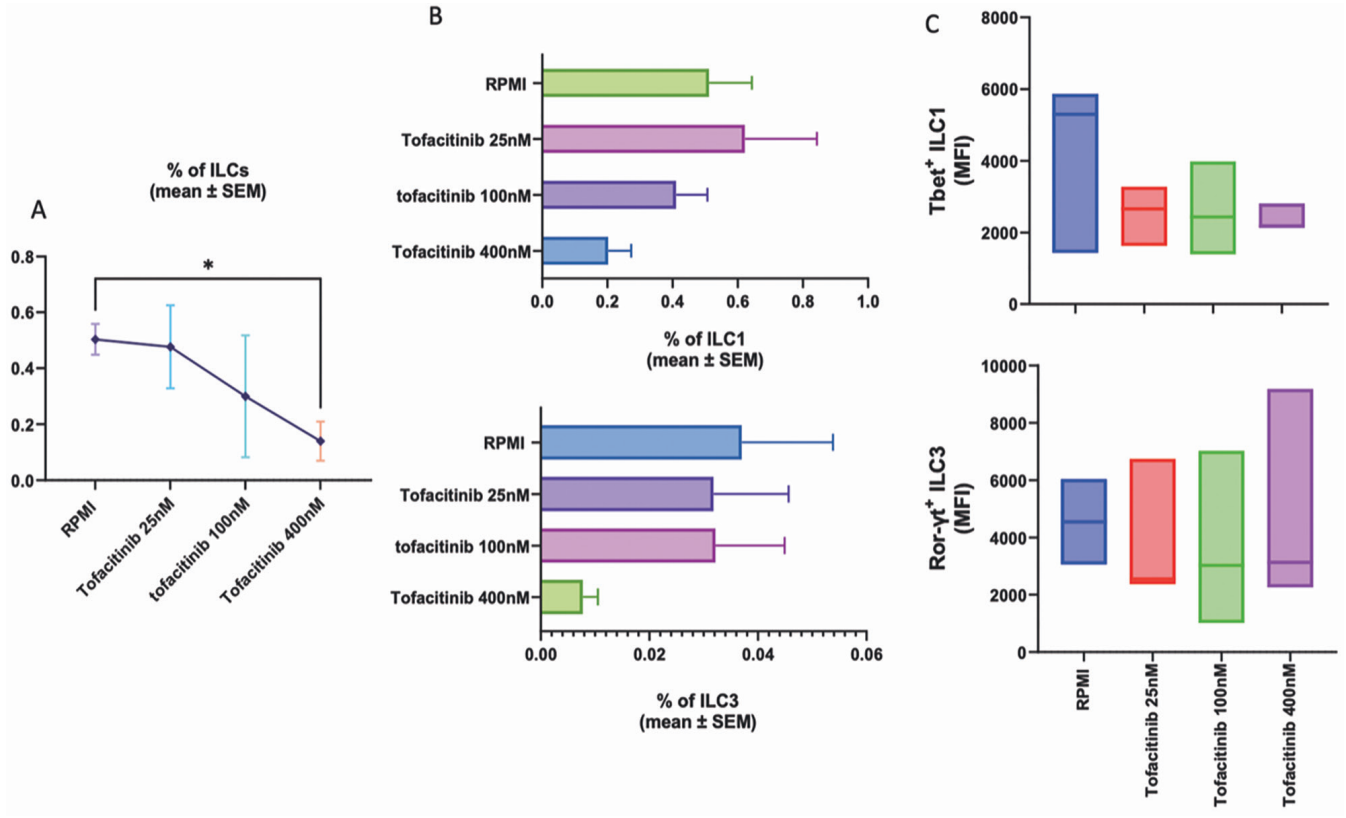

Fig. 5. Effects on ILC frequency of *in vitro* tofacitinib treatment.
A: Total ILC frequency, gated as Lin^-CD127^+. Ordinary one way-ANOVA *$p<0.05$.
B: Frequency of subpopulations ILC1 and ILC3, gated respectively as $Lin^-CD127^+CD117^-$ and $Lin^-CD127^+CD117^+$.
C: Box plot showing MFI expression of T-bet on ILC1s and RoRγt on ILC3s.
Cells were cultured for 48 hours with complete medium alone (RPMI) and with tofacitinib at 25 nM, 100 nM and 400 nM.

been conducted with ethical approval (ethics committee n. 08/2021 dated 09/15/2021) and has been performed accordingly Helsinki Declaration of 1964, and its later amendments. A consent for all subjects was obtained before enrolment in the study.

Results

Modulation of ILC frequency after treatment with tofacitinib in RA patients

In the present study we analysed the frequencies of total peripheral ILCs followed by a further description of ILC1 and ILC3 subsets in RA patients treated with tofacitinib. ILC frequency and function were compared at baseline (T0) and 3 months after (T1) treatment with tofacitinib. The gating strategy used to identify ILC populations is shown in Figure 1.

The total ILC frequency was assessed in HD and RA patients treated with tofacitinib at T0 and T1. At T0 RA patients showed a higher rate of total ILCs compared with HD; and at T1 a reduction of total ILC frequency was evidenced in the tofacitinib group (Fig. 2A).

To better understand the effect of tofacitinib treatment on ILC subsets, we analysed ILC1 and ILC3 frequencies in patients and controls. Before starting tofacitinib treatment, RA patients showed a significantly higher frequency of peripheral ILC1 but not ILC3, compared to controls (Fig. 2B).

Treatment with tofacitinib induced a significant reduction of peripheral ILC1 without a statistically significant change in ILC3s frequency (Fig. 2B)

The Figure 3A shows the representative gating strategy used to identify ILC1 and the effect of tofacitinib on T-bet expression in HD and RA patients at T0 and T1. Cumulative data of mean fluorescence intensity (MFI) of T-bet indicated that the reduction of ILC1 frequency after the treatment was associated with a reduction of T-bet expression; T-bet MFI in the HD group was lower than in RA patients at T0 and T1 (Fig. 3B). Next, as ILC1s produce IFN-γ we decided to evaluate its production before and after treatment to assess a possible effect of tofacitinib on ILC1 cytokine production.

We observed that ILC1s of RA patients produced a higher amount of IFN-γ than HD. However, we observed a slight reduction, not statistically significant, in IFN-γ production after treatment (Fig. 3C).

Regarding ILC3 we assessed the possible effect of tofacitinib on their function through the assessment of RoRγt expression and IL-17 production. Figure 4A shows the representative gating strategy used to identify ILC3s and the histogram displays RoRγt MFI in each analysed group. Cumulative MFI data of RoRγt showed that ILC3 at T0 exhibited a higher RoRγt MFI than HD, however the therapy did not significantly change its expression (Fig. 4B).

As for ILC1, we evaluated the functional activity of ILC3 assessing IL-17 production; IL-17 was more expressed

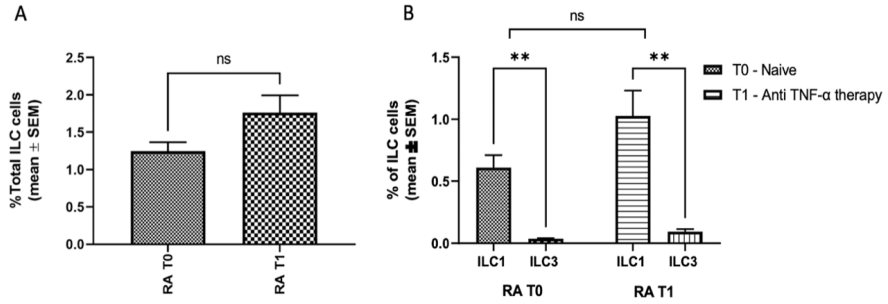

Fig. 6. Total ILCs and relative subsets ILC1 and ILC3 in RA patients treated with anti-TNF-α.
A: Comparison of total peripheral ILC frequency before (T0) and 3 months after (T1) starting anti-TNF-α treatment in RA patients.
B: Frequency of ILC1 and ILC3, in RA patients, before (T0) and 3 months after (T1) starting anti-TNF-α treatment. ** Ordinary one-way ANOVA $^{**}p<0.01$, $^{*}p<0.05$

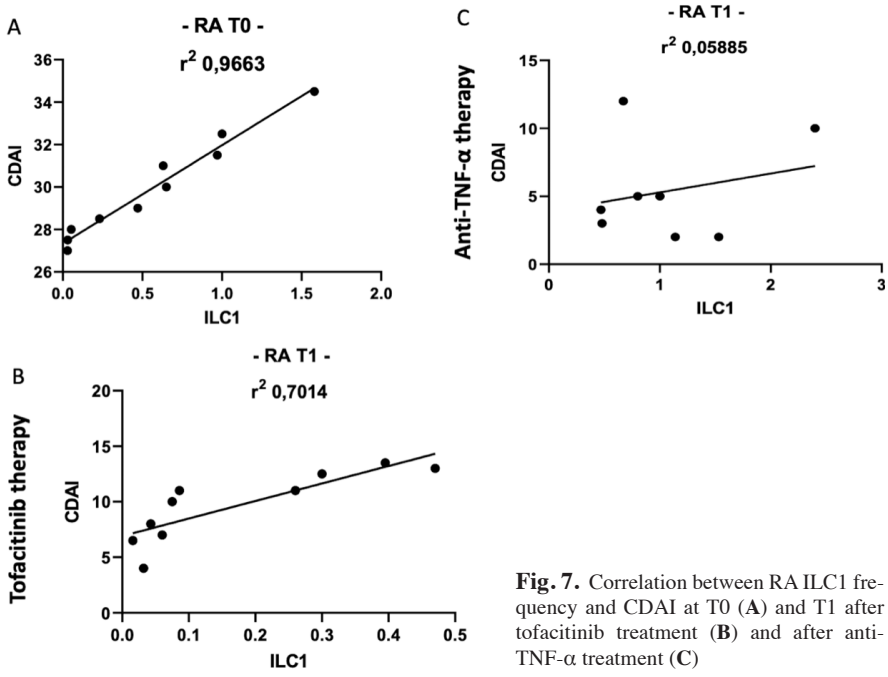

Fig. 7. Correlation between RA ILC1 frequency and CDAI at T0 (**A**) and T1 after tofacitinib treatment (**B**) and after anti-TNF-α treatment (**C**)

by ILC3 in RA patients than in HD, but the production was not modified by treatment (Fig. 4C).

Finally, we checked for tofacitinib dose dependent effects. We stimulated the PBMCs of three RA patients, *in vitro,* with three different tofacitinib concentrations: 25 nM, 100 nM and 400 nM for 48 hours. At the same time, a proportion of PBMCs were not treated with the drug. Tofacinib induced a dose-dependent reduction of total peripheral ILC frequency with a significant effect at 400nM (Fig. 5A). Furthermore, the analysis on the drug-dose effect was extended to ILC1 and ILC3 subpopulations. ILC1s resulted more affected, by the *in vitro* treatment, both in terms of frequency (Fig. 5B) and transcription factors expression (Fig. 5C) compared to ILC3, supporting our *ex vivo* results. The reduction of ILC1 was higher at 400 nM than that observed at 100 nM and 25 nM.

In order to evaluate whether the effect on the reduction of ILC1 frequency was a direct and specific effect of tofacitinib and not due to the reduction of disease activity, we analysed patients treated with another biologic agent (anti-TNF-α). In contrast to the tofacitinib group, patients starting anti-TNF-α showed an increasing trend of the total ILC frequency after three months of treatment (Fig. 6A), and analysing the ILC subpopulations, we did not report a reduction of ILC1 and ILC3 at T1 (Fig. 6B).

Evaluating the clinical response to the treatment regimen, assessed by CDAI, a positive correlation between reduction of ILC1 frequency and improvement of CDAI was reported in patients treated with tofacitinib compared with the anti-TNF-α group (Fig. 7).

Discussion

The role of the JAK/STAT pathway has recently been extended to several aspects of ILC biology, and recent evidence suggests that ILCs may also be involved in the pathogenesis of RA (3). ILCs have been reported to be crucial arbiters involved in immunity and tissue remodelling, also driving inflammation, innate and adaptive responses, and homeostatic processes around the body (8). Their alterations in number or function have been observed in autoimmune diseases such as systemic lupus erythematosus, systemic sclerosis, spondyloarthritis and RA (8, 9).

The pan-JAK inhibitor tofacitinib impairs the ability of human intraepithelial ILC1 (iILC1) to produce IFN-γ, as well as the proliferation and *in vitro* differentiation of ILC1 and ILC3 (6).

Since JAK inhibitors have been developed for RA therapy and considering the critical role of ILCs as a bridge between innate and adaptive immune systems and their implications in RA, we aimed to evaluate the *ex vivo* tofacitinib effects on both expansion and function of ILC1 and ILC3 in patients with active disease, naive to biological agents.

In this study we focused on whether tofacitinib could change the frequency of peripheral ILCs in our cohort of RA patients. Our results demonstrated that, before tofacitinib treatment, RA patients had a significant higher frequency of peripheral ILC1 (Lin-, CD127+, CD117-, Tbet+) than ILC3 (Lin-, CD127+, CD117+, RoRγt+), as previously reported in the literature. Regarding cytokine production, the two subsets were shown to produce IFN-γ and IL-17, respectively.

Tofacitinib induced a reduction of peripheral ILC1 frequency and decreased the expression of the transcriptional factor T-bet as well as IFN-γ release. Instead, for ILC3 not significant modifications in frequency, RoRγt expression and IL-17 production were detected after treatment, suggesting a predominant role for ILC1. To confirm that the

ILC changes were specific to tofacitinib treatment and not secondary to the reduction in disease activity, we tested a control group of patients receiving anti-TNF-α treatment. Despite the reduction of disease activity, clinically evaluated with the CDAI, no reduction of ILC1 was found in the anti-TNF-α group, validating the direct action of the JAK inhibitor tofacitinib on ILCs in RA. Certainly, our study presents some limitations such as the reduced sample size, the presence of only 2 time-points and the use of PB samples rather than tissue samples, thus our future goals include increasing the number of enrolled patients and studying the downstream and upstream mechanisms underlying the modulation of ILC by tofacitinib.

In conclusion our study confirms the role of ILC1 in driving inflammation in RA and demonstrates the efficacy of tofacitinib in modulating the innate immune response elicited by ILC1. Given the potent pro-inflammatory role played by these cells, our data may suggest that the clinical efficacy of tofacitinib may also be achieved through ILC1 blockade. Further studies are required to elucidate the precise contribution of innate immunity in patients with RA.

Acknowledgements

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