The impact of biologic therapy for moderate-to-severe psoriasis on the immune responses to SARS-CoV2 infection and vaccination

Dear Editor, We explored the impact of biologics and conventional therapies for psoriasis on humoral and T-cellular responses to SARS-CoV-2 infection[1] and vaccine [2]. The study (EUDRA 2020-004965-37 Humanitas ICH Ethic Committee) was conducted at the Istituto Clinico Humanitas-Rozzano, Milan, and at the University of Verona, Italy. The enrolled patients were affected by moderate-to-severe psoriasis and were divided into two groups: those who had developed COVID-19 infection (group 1, n=95) and those who underwent COVID-19 vaccination (group 2, n=77). The patients enrolled in group 1 were treated with anti-IL-23 or IL-12/23 (n=46), anti-IL-17 (n=14), anti-TNFα (n=2), methotrexate (n=2), cyclosporin (n=2) or were receiving no treatment (n=27). In group 2, patients were treated with anti-IL-23 or IL-12/23 (n=21), anti-IL-17 (n=17), anti-TNF-α (n=20), methotrexate (n=2) and apremilast (n=3), and 14 psoriatic patients were untreated. Healthy donors (HD) were also included for comparison.

Regarding humoral responses, in group 1 there were no differences in the production of virus-specific anti-S1 and anti-N IgG following COVID-19 infection across psoriasis-treated, psoriasis-untreated patients, and HD. When we analyzed the responses based on the therapy, only patients that were treated with methotrexate or cyclosporin showed a significantly lower level of both anti-S1 and anti-N IgG compared to untreated patients and HD (Figure 1A). In group 2, psoriasis-treated patients responded to the mRNA vaccine [3] producing a level of anti-S1 IgG comparable to the untreated psoriatic patients and HD. Patients treated with anti-TNF-α showed a significantly lower titer compared to all other categories, interestingly, anti-IL23-treated patients produced a higher level of IgG compared to the anti-IL17 and untreated

cohorts (Figure 1A). Anti-S1 IgG antibody titer is time-modulated and correlates with days post-vaccine ($P < 0.001$ data not shown).

Then, we tested the presence of reactive T-cells to SARS-CoV-2 S1 and N antigens. The stimulation index (SI) of activated virus antigen-specific $CD4^+$ and $CD8^+$ T-cells for both the antigens was comparable across all three categories: psoriasis-treated, psoriasis-untreated, and HD (CD4 in Figure 1B). The frequency of activated $CD4^+$ and $CD8^+$ SARS-CoV-2 specific T-cells was stable months after infection suggesting that a long-lasting pool of memory T-cells was also present in biologic-treated patients as assessed by previous studies (not shown) [4].

Considering that anti-IL-23 patients presented the highest humoral response, we hypothesized that IL-23 inhibition may shift T-cell development towards the follicular T helper cells (Tfh) phenotype [5]. Therefore, we tested three anti-IL-23 patients and three anti-IL-17 patients for the presence of activated ($CD134^+$ $CD137^+$) T-cells with the characteristics of Tfh cells ($CD4^+CXCR5^+PD1^+$). After S1 stimulation, the percentage of activated Tfh cells in the anti-IL-23 patients was higher than in the anti-IL-17 treated patients. (Figure 1B). The subject with no antibody response (empty magenta) does not activate Tfh cells.

Since Th1 cells mediate response to COVID-19 infection [6], we tested the production of *in vitro* stimulated PBMC for Th1-associated cytokines IFN-γ and IL-2. In psoriatic-untreated patients and HD, S1 peptide induced significantly higher levels of both IFN-γ and IL-2 compared to unstimulated cells, while N induced a significantly higher level of IFN-γ, but not IL-2. We notice that in psoriasis-treated patients, the exposure to both antigens, induced significantly higher levels of both IFN-γ and IL-2 (Figure 1C), suggesting an enhanced immune response in biologic-treated patients. $CD4^+CD134^+CD137^+$ antigen-activated T-cells contribute directly to the production of IFN-γ and IL-2 (not shown).

HLA-Cw*06:02 is one of the major susceptibility loci in psoriasis with a frequency of 36.88% (149/404) in psoriatic patients in our hospital compared with the 11,2% of the Italian population [7]. In the COVID-19-infected group 1, the presence of the HLA-Cw*06:02 allele is negatively associated with the COVID-19 infection with an ODD ratio of 0.5898 (P =.02, 95% 0.355-0.979): allele positivity 28.26% (23/90) significantly lower than 36.88% (χ2 4.16 P=0.04).

In conclusion, we can assess that conventional immunomodulating (methotrexate /cyclosporin) drugs have a significant negative influence on the humoral response after SARS-CoV-2 infection, while biologics anti-IL-23 and anti-IL-17 do not impact the immune response to SARS-CoV-2 virus and psoriatic untreated patients do have a good response to infection. We observed that anti-TNF-α agents significantly decrease the titer of antibodies directed against the S1 antigen following vaccination confirming data of Aringer *et.al.*[8] and it is advisable to discontinue TNF-α inhibitors before administering SARS-CoV-2 vaccines. While IL-23 inhibitors increase the antibody titer, it suggests an enhancing effect on the humoral response via Tfh-cells. Our results highlight that biologics treatment as IL-23 and IL-17 inhibitors does not alter the adaptive immune response of T-cell and Th1-mediated responses to SARS-CoV-2 infection.

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Figure legends

Figure 1

A) Humoral responses: COVID-infected patients under treatment with conventional drugs had a lower level of IgG (anti-S1, anti-N) compared to all the other categories. After vaccination, anti-TNF-α treated patients showed a significantly lower level of anti-S1 IgG compared to all; the anti-IL-23 treated performed higher level of IgG.

B) Cellular adaptive immune response in treated patients (24-hours-stimulation with antigen S1 or N) is not affected. Anti-IL-23 treatment (green) enhances the frequency of activated virus-specific Tfh cells ($CD34^+$ $CD37^+CXCR5^+PD1^+$) with respect to anti-IL-17 (magenta).

C) Th1 interleukins IFN-γ and IL-2 levels in the supernatant of COVID-19 antigen-stimulated PBMC. *p-value <.05;**p-value<.01;***p-value<.001;****p-value< .0001.

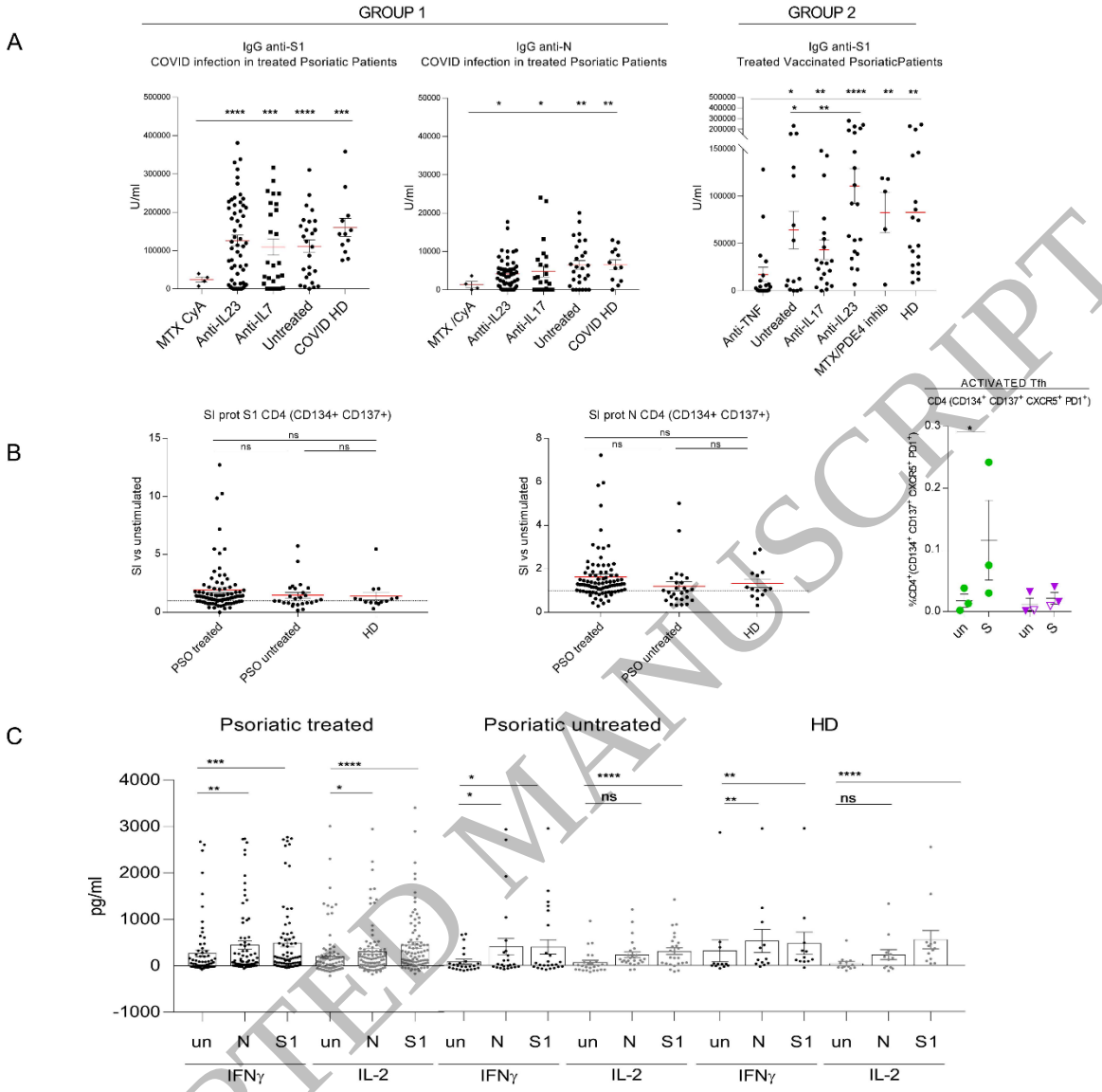

Figure 1
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