Type I interferon signature may influence the effect of belimumab on immunoglobulin levels, including rheumatoid factor in Sjögren’s syndrome

Sirs,
B-lymphocyte stimulator (BLyS, or BAFF), a survival factor for B cells, has been implicated in the pathogenesis of Sjögren’s syndrome (SS) and SS-related lymphoproliferation (1-2). BAFF is induced by both type I and II Interferons (IFNs) (3). Targeting BAFF, by belimumab, appears a promising therapy for SS (4-7). The objective of this study is to explore the possible effect of belimumab on IFN-induced peripheral blood gene expression and to evaluate whether baseline IFN signature predicts clinical and serological responses to belimumab.

Twelve patients who were enrolled in the BELISS trial (4, 5) were evaluated. They were all patients for whom the samples of peripheral blood were available. Peripheral blood IFN signature was studied at baseline in all (12/12), at w28 in 10/12, and at w52 in 4/12. Peripheral blood mononuclear cells (PBMC) from all study participants were subjected to Real-Time PCR for 3 interferon inducible genes (MX1, IFIT1, IFI44) preferentially induced by type I IFN and 2 interferon inducible genes preferentially induced by type II IFN (MIG-1, GBP1). Both type I and II IFN scores were determined, as previously described (3). The data are presented as mean (standard error, SE) or median (range), according to the variable distribution. Statistical comparisons by parametric or non-parametric tests were then performed. Patients were all females, with mean (SE) age of 51 (4) years, and mean (SE) disease duration of 6.8 (1.7) years. At baseline, they showed a median (range) ESSDAI score of 7 (2-27) and a mean (SE) ESSPRI score of 6.1 (3.9). All were positive for anti-SSA/SSB and for rheumatoid factor (RF).

Baseline, w28 and w52 type I IFN levels were 17.8 (3.2), 19.9 (3.7), and 20.2 (1.2), respectively. No statistically significant changes in type I IFN score were observed between baseline (visit 0) and w28 (visit 1) or w52 (visit 2) (p=0.05 for all comparisons by paired sample t-tests). Baseline type I IFN significantly correlated with the overall change of RF, from baseline to w52 (r=0.76, p=0.007, by Pearson’s test) (Fig. 1). When patients were subdivided into two groups, i.e., low IFN score (n=7) and high IFN score (n=5), based on the baseline median of IFN score, patients in the high IFN group showed greater changes from baseline to w52 in IgG (Fig. 2A), IgA (Fig. 2B), IgM (Fig. 2C), and RF levels (Fig. 2D). Of note, the two groups were comparable as regards age, disease duration, baseline ESSDAI score, and baseline serum levels of IgG, IgA, IgM and RF (by Mann-Whitney U test). No correlation was found between type I IFN and ESSDAI changes (data not shown). Finally, no significant changes or associations with type II IFN scores were observed (data not shown).

Based on these preliminary data, type I IFN signature may affect the magnitude of biological effect of belimumab on immunoglobulin production, including RF. Since increased RF titre could be a risk factor for lymphoma, as recently proposed (8), and for a higher disease activity in SS (9), patients showing higher IFN signature may be the best target for belimumab in SS. Secondly, belimumab could not affect type I IFN signature, consistently with the worsening of SS after drug suspension (10).

Fig. 1. Correlation between type I IFN score at baseline and decrease of serum rheumatoid factor from baseline to w52 (4 weeks after last infusion of belimumab). Data were available for 11/12 patients, since one patient interrupted the treatment at w28.

Fig. 2. Error bar graphs shows the differences between low and high IFN groups as regards baseline to w52 changes of serum levels of IgG (A), IgA (B), IgM (C), and rheumatoid factor (D). Data were available for 11/12 patients, since one patient interrupted the treatment at w28.

References
5. DE VITA S, QUARTUCCIO L, SEROR R et al.: Efficacy and safety of belimumab given for 12
Letters to the Editors


