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Belimumab for the Treatment of Early Diffuse Systemic Sclerosis:

Results of a Randomized, Double-Blind, Placebo-Controlled, Pilot Trial

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Abstract

Objective—To assess the safety and efficacy of treatment with belimumab in patients with early diffuse cutaneous systemic sclerosis (dcSSc) treated with background mycophenolate mofetil (MMF).

Methods—In this 52-week, investigator-initiated, single-center, double-blind, placebo-controlled, pilot study, 20 patients with dcSSc recently started on MMF were randomized 1:1 to additionally receive belimumab at 10 mg/kg intravenously or placebo. We assessed safety, efficacy, and differential gene expression.

Results—In the belimumab group, the median modified Rodnan skin thickness score (MRSS) decreased from 27 (interquartile range [IQR] 26.5, 31) to 18 (IQR 11, 23) ($P = 0.039$). In the placebo group, the median MRSS decreased from 28 (IQR 22, 28) to 21 (IQR 14, 25) ($P = 0.023$). The median change in MRSS was −10 (IQR −13, −9) in the belimumab group and −3.0 (IQR −15,

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AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Gordon had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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−1) in the placebo group ($P = 0.411$). There were no significant differences between the groups in the number of adverse events (AEs). A significant decrease in expression of B cell signaling and profibrotic genes and pathways was observed in patients with improved MRSS in the belimumab group but not in the placebo group.

Conclusion—Patients in both treatment groups experienced significant improvements in MRSS. The median difference was greater in the belimumab group but did not achieve statistical significance in this small pilot study. AEs were similar between the groups. Changes in gene expression were consistent with mechanism of action and showed that clinical response to treatment with belimumab is associated with a significant decrease in profibrotic genes and pathways. Additional studies are needed to determine the role of belimumab in the treatment of dcSSc.

Systemic sclerosis (SSc) is a multisystem connective tissue disease characterized by autoimmunity, fibrosis, and vasculopathy (1). Immune dysregulation in SSc is manifested by the presence of autoantibodies and alterations in phenotype and activation levels of B cells, T cells, cytokines, and other components of the immune system (2). Current treatment paradigms for SSc depend on the organ system involved and include immunosuppressive regimens such as methotrexate, mycophenolate mofetil (MMF), cyclophosphamide, and autologous stem cell transplantation for severe and rapidly progressive disease with poor prognostic features (3). Although these treatments are effective, improved therapies for SSc are needed (4).

Abnormalities in B cell function and homeostasis have been observed in SSc. Skin and lung samples from SSc patients show B cell infiltrates (5,6). Gene expression studies performed on SSc skin show high expression of immunoglobulin genes in patients from an inflammatory intrinsic molecular gene expression subset (7). B cell homeostasis is disrupted in SSc, with greater numbers of transitional and naive B cells and fewer memory B cells as well as altered expression of molecules involved in B cell regulation compared with healthy controls (8). Although reduced in number, memory B cells in SSc are hyperreactive, leading to increased antibody formation (9). BAFF, also known as B lymphocyte stimulator (BLyS), is increased in the serum of patients with SSc and correlates with the extent of skin fibrosis (10). Serum levels of APRIL, a homolog of BAFF, are also elevated in SSc patients and have been associated with an increased incidence of pulmonary fibrosis (11).

Anti-B cell strategies using rituximab, a monoclonal antibody directed against the CD20 antigen, have been studied for use in SSc in observational studies and small trials. In a retrospective study from the European League Against Rheumatism (EULAR) Scleroderma Trial and Research group, patients with diffuse cutaneous SSc (dcSSc) who were treated with rituximab had a greater decrease in modified Rodnan skin thickness score (MRSS) (12) and a smaller decline in forced vital capacity (FVC) compared with matched controls (13). Prospective studies have shown mixed results—some with benefit (14) and others without significant change (5).

Belimumab (Benlysta; GlaxoSmithKline) is a recombinant, fully human monoclonal antibody which is approved by the US Food and Drug Administration for the treatment of systemic lupus erythematosus (15). Belimumab binds to soluble human BLyS and inhibits

its biologic activity, leading to apoptosis of B lymphocytes and decreased autoantibody production (16). We report the first investigation of the use of belimumab in SSc.

PATIENTS AND METHODS

Study design and participants

This was an investigator-initiated, industry-supported, single-center, randomized, doubleblind, placebo-controlled, pilot study. Patients fulfilled both the American College of Rheumatology (ACR) preliminary criteria for SSc (17) and the ACR/EULAR 2013 criteria for SSc (18) and had dcSSc (19). Patients were included if they were age >18 years, had disease duration of <3 years since the first SSc-related symptom other than Raynaud's phenomenon (RP), and had a baseline MRSS of ≥16. Patients were excluded if their diffusing capacity for carbon monoxide (DLCO) was <30% predicted, if their ejection fraction was <50%, if they had been receiving MMF for >3 months, if they had previously received rituximab or belimumab, or if they required prednisone at >10 mg/day (full inclusion criteria are available in Supplementary File 1, available on the *Arthritis & Rheumatology* web site at http://onlinelibrary.wiley.com/doi/10.1002/art.40358/abstract). The protocol was approved by the Institutional Review Board at Hospital for Special Surgery. Patients provided written informed consent before enrollment, and the study was performed in accordance with the Declaration of Helsinki and Good Clinical Practice Guidelines. An independent data and safety monitoring board regularly reviewed safety data.

The primary objective was to assess the safety and tolerability of belimumab in patients with dcSSc receiving background MMF therapy, as assessed by the number of adverse events (AEs) and serious AEs (SAEs). The primary efficacy end point was the difference in the median change in MRSS after 52 weeks of treatment. Secondary efficacy end points included change in MRSS at 6 months as well as change at 52 weeks in FVC and DLCO on pulmonary function testing (PFT) and change at 52 weeks in the Short Form 36 (SF-36) health survey mental component summary (MCS) score and physical component summary (PCS) score (20), the Scleroderma Health Assessment Questionnaire disability index (SHAQ DI) score (21), and, post hoc, the ACR composite response index in dcSSc (CRISS) score (22). Skin biopsy samples were assessed using histopathology, immunohistochemistry, and differential gene expression analysis to evaluate change with treatment and to explore the biologic basis of the clinical changes observed. Serum BLyS levels were assessed at baseline using a custom enzyme-linked immunosorbent assay (ELISA) (see Supplementary File 2, http://onlinelibrary.wiley.com/doi/10.1002/art.40358/abstract).

Patients were assessed at monthly visits for AE ascertainment, interval history, physical examination, and clinical laboratory testing. AEs were listed according to the National Cancer Institute's common terminology (23). The MRSS was measured at screening, baseline, and every 3 months by the same physician (JKG or RFS). PFTs with measurement of FVC and DLCO were performed at baseline and after 6 and 12 months.

Dosing and visits

At baseline, 14 patients were naive to MMF and the other 6 had been receiving MMF at <2,000 mg/day for <3 months. The MMF-naive group was started on MMF at their first baseline visit, and this dose was up-titrated over the course of 2 weeks to 1,000 mg twice daily by mouth with weekly complete blood counts. All patients continued to receive MMF monotherapy for 3 months to ensure individual tolerability of MMF. MMF was chosen so that background therapy would be uniform and not a further source of variability in this small study. our preference is to use MMF over methotrexate in patients with interstitial lung disease (ILD), and such patients were included. Two patients withdrew during the wash-in period due to disease progression. After this wash-in period, patients were randomized to receive belimumab or identical placebo at the second baseline visit. Belimumab at 10 mg/kg or identical placebo (normal saline) was given intravenously at 2-week intervals for the first 3 doses and then at 4-week intervals until week 48 as patients maintained background MMF at 1,000 mg twice daily. The final assessment occurred 4 weeks following the final belimumab infusion at week 52. Adherence to MMF was assessed by pill count.

Randomization and blinding

Patients were randomly assigned (1:1) using block randomization performed by personnel in biostatistics and pharmacy. Investigators, patients, and study personnel were masked to treatment assignment.

Dermatopathology

Two 3-mm punch biopsies of lesional forearm skin were performed at the first baseline visit and at 52 weeks. The posttreatment biopsy samples were obtained 1-cm adjacent to baseline biopsy samples. At each time point, one specimen was formalin-fixed and paraffin-embedded, and the other was stored in RNAlater. Sections for histopathology were stained with hematoxylin and eosin (H&E), anti-α-smooth muscle actin (anti-α-SMA), CD34, procollagen, CD3, and CD79 using standard techniques. A dermatopathologist (CM) who was blinded with regard to treatment status compared each case. Slides were scored semi-quantitatively based on collagen density and degree of infiltrate on H&E staining as well as intensity of staining. Skin thickness was measured from the epidermis to the subcutis by a micrometer. Eccrine coils and hair follicles were counted per section.

Statistical analysis

This pilot trial was conducted to obtain initial safety and efficacy data in order to perform a power calculation for a larger study, so formal power calculation was not done to determine sample size. The efficacy analyses were performed using a modified intent-to-treat population, including all randomly assigned patients who received at least 1 dose of study drug and had at least 1 follow-up MRSS. This included 9 patients in each group. Comparative safety analyses included all patients who were randomized and received at least 1 infusion (n = 20). For subanalyses, we classified patients as clinical improvers if they individually demonstrated a 20% decrease in the MRSS, as in previous studies (24).

Comparisons were performed using Mann-Whitney U tests and Wilcoxon signed rank tests, as appropriate. All analyses were performed using SAS software version 9.3 for Windows

(SAS Institute) with a significance level of 0.05. Since this was a pilot trial, adjustment for multiple comparisons was not performed for the clinical outcomes.

Gene expression analyses by DNA microarray

Tissue samples stored in RNAlater were homogenized, and RNA was purified as previously described (25). Baseline and posttreatment biopsy samples from 18 patients were used for analyses. Expression data were imputed for missing values and collapsed to unique genes using GenePattern (26), median-centered in Cluster 3.0 (27), and visualized in Java TreeView (28). Data from this study are available from the NCBI GEO (accession no. GSE97248).

Differentially expressed genes (DEGs) were identified via Significance Analysis of Microarrays (29). DEGs with a false discovery rate (FDR) of ≤10% were treated as significant and were evaluated for significant functional enrichment via g:Profiler (30) ($P \leq 0.05$ corrected for multiple testing via default Gene Set Counts and Sizes method). We performed gene set enrichment analysis (GSEA) (31,32) in GenePattern. GSEA was run against Canonical Pathways database version 5.2. Pathways with a GSEA FDR of ≤5% were treated as significant.

Intrinsic subset assignment

Expression data and subset labels collected from GEO accession nos. GSE9285, GSE32413, and GSE45485 were used to train and test a multinomial elastic net (25,33,34). The glmnet (35) and caret (36) packages implemented in R (www.r-project.org) were used with repeated cross-validation (10×, 3-fold) to train the classifier and assess robustness (37). The inflammatory subset score was quantified as the probability of being assigned to the inflammatory molecular subset from the multinomial elastic net.

RESULTS

Primary and secondary efficacy analyses

Patients were recruited from August 17, 2012 until September 12, 2014. Of 25 patients screened, 22 patients enrolled in the MMF wash-in period (see Supplementary File 3, http://onlinelibrary.wiley.com/doi/10.1002/art.40358/abstract). Two patients withdrew prior to randomization—1 due to scleroderma renal crisis and 1 due to progressive myopathy. Twenty patients were randomized 1:1, and 9 patients in each group completed 52 weeks of treatment. One patient in the placebo group withdrew due to progressive cardiomyopathy, and 1 in the belimumab group withdrew due to progressive ILD after receiving 2 infusions. Both patients withdrew prior to the 12-week MRSS assessment. Baseline characteristics of randomized patients were balanced between groups with 2 exceptions. The baseline SHAQ DI score and RP score on a visual analog scale (VAS) were significantly worse in the belimumab group (Table 1).

Patients in both groups experienced significant improvements in the MRSS. In the belimumab group, the median MRSS decreased from 27 (interquartile range [IQR] 26.5, 31) to 18 (IQR 11, 23) ($P = 0.039$), while in the placebo group, the median MRSS decreased

from 28 (IQR 22, 28) to 21 (IQR 14, 25) ($P = 0.023$) (Figure 1A). The MRSS changed by a median of −10 (IQR −13, −9) in the belimumab group and by a median of −3.0 (IQR −15, −1) in the placebo group ($P = 0.411$) (Figure 1B). Because there was no statistically significant difference between the groups in the median change in MRSS, the primary efficacy end point was not met. In the belimumab group, 7 of 9 patients were clinical improvers compared to 3 of 9 patients in the placebo group ($P = 0.153$) (Figure 1C). FVC and DLCO remained stable during treatment (Table 2).

Multiple secondary outcome measures were assessed (Table 2). Significantly greater improvements were observed in the belimumab group for the SHAQ DI score and the VAS RP score. There were no significant differences seen in VAS pain score, VAS ulcers score, VAS breathing score, VAS overall score, physician's global assessment, SF-36 MCS score, or SF-36 PCS score. In a post hoc analysis, we assessed the CRISS score at baseline compared to 52 weeks. The median CRISS score at 52 weeks was 0.61 (IQR 0.34, 0.88) in the belimumab group and 0.03 (IQR 0, 0.80) in the placebo group ($P = 0.345$) (Figure 1D).

AEs

There was no difference between the groups in the total number of AEs (53 in the belimumab group and 56 in the placebo group; $P = 0.868$). There was no difference between the groups in the total number of infectious AEs (18 in the belimumab group and 16 in the placebo group; $P = 0.818$). There were 3 SAEs postrandomization, all of which occurred in the placebo group (Table 3). one patient was hospitalized with an anxiety attack. The 2 other SAEs were hospitalizations due to chest pain and dyspnea related to progression of SSc-related cardiomyopathy, both of which occurred in 1 patient. This patient was withdrawn from the study to receive treatment off protocol. Two SAEs occurred during the wash-in phase prior to randomization in 1 patient who experienced scleroderma hypertensive crisis resulting in 2 hospitalizations. No deaths occurred during the study period. All AEs occurring more than once are shown in Supplementary File 4 (http://onlinelibrary.wiley.com/doi/10.1002/art.40358/abstract).

Dermatopathology findings

The majority of biopsy samples from both groups demonstrated an overall improvement in microscopic morphology with a qualitative decrease in degree of sclerosis, hyalinization of collagen, thickness of collagen fiber bundles, and dermal thickness. There were no significant differences between the groups in skin thickness, collagen density, degree of infiltrate on H&E staining, number of follicles and eccrine structures, and staining intensity of α-SMA, trichrome, CD34, procollagen, CD3, or CD79. This complete analysis is included as Supplementary File 5 (http://onlinelibrary.wiley.com/doi/10.1002/art.40358/abstract).

BLyS levels

Baseline BLyS levels in our patients were higher than those in healthy controls, consistent with previous findings (10). The median BLyS level was 1.46 ng/ml (IQR 1.25, 2.05) in 15 patients versus 0.67 ng/ml (IQR 0.59, 0.87) in 50 healthy controls ($P < 0.001$). There was no

difference between improvers and nonimprovers in baseline BLyS levels (median 1.48 ng/ml [IQR 1.23, 1.95] versus 1.74 ng/ml [IQR 1.27, 2.08], respectively; $P = 0.66$).

Differential gene expression and intrinsic subset assignment

Differential expression analysis demonstrated that there were 43 significant DEGs that decreased posttreatment in the belimumab arm (Figure 2A; also see Supplementary File 6, http://onlinelibrary.wiley.com/doi/10.1002/art.40358/abstract). These genes were significantly enriched in immune system signaling including defense response, inflammatory response, and complement activation (see Supplementary File 7, http://onlinelibrary.wiley.com/doi/10.1002/art.40358/abstract). Significantly down-regulated pathways included B cell receptor activation and Toll-like receptor signaling as well as integrin signaling pathways (Figure 2B; also see Supplementary File 8, http://onlinelibrary.wiley.com/doi/10.1002/art.40358/abstract). In contrast, there were no significant DEGs in the placebo group; therefore, presentation of differential expression is limited to the belimumab arm.

We then examined DEGs specifically in belimumab improvers. There were 76 significant DEGs whose levels were decreased posttreatment (Figure 2C; also see Supplementary File 9, http://onlinelibrary.wiley.com/doi/10.1002/ art.40358/abstract). These genes were enriched in immune and fibrotic signaling (e.g., extracellular matrix [ECM] organization, vasculature development, and collagen metabolic process) (see Supplementary File 10, http://onlinelibrary.wiley.com/doi/10.1002/art.40358/abstract). Down-regulated pathways included both fibrotic signaling (transforming growth factor β [TGFβ]/TGFβ receptor [TGFβR] signaling and ECM regulators) and B cell signaling (B cell antigen receptor and B cell receptor signaling) (Figure 2D; also see Supplementary File 11, http://onlinelibrary.wiley.com/doi/10.1002/art.40358/abstract).

Finally, we examined the baseline differences between belimumab improvers and nonimprovers. There were 19 genes with higher expression in improvers (see Supplementary File 12 and Supplementary Figure 1A, http://onlinelibrary.wiley.com/doi/10.1002/art.40358/abstract) enriched in collagen metabolic process and ECM organization. Pathways enriched in improvers included ECM-receptor interaction and other ECM-related gene sets as well as TGFβR signaling (see Supplementary File 13 and Supplementary Figure 1B, http://onlinelibrary.wiley.com/doi/10.1002/art.40358/abstract). There were no significant DEGs in placebo improvers, although this could be attributed to sample size.

There was no difference between treatment groups in baseline frequency of intrinsic gene expression subsets. Molecular subset at baseline was not associated with clinical improvement in the belimumab arm (Figure 3A), the placebo arm (Figure 3B), or the pooled treatment arms ($P > 0.05$ by Fisher's exact test; data not shown). Fifteen patients were assigned to either an inflammatory or a proliferative molecular subset at baseline. In a pooled analysis, 9 of these patients (60%) changed their subset to normal-like, and this was accompanied by a decrease in MRSS for all 9 patients. Furthermore, 8 of 10 improvers were assigned to a normal-like molecular subset posttreatment.

We quantified an inflammatory subset score and tracked this change over the course of treatment. The change in inflammatory subset score correlated with the change in MRSS (Pearson's r = 0.51, $P = 0.03$), particularly for patients assigned to the inflammatory molecular subset at baseline (Pearson's r = 0.81, $P = 0.008$) (Figure 3C). These findings suggest that an overall reduction in inflammatory gene expression and movement toward the normal-like subset was associated with improvement in MRSS.

DISCUSSION

This is the first double-blind, randomized controlled trial of belimumab for the treatment of early dcSSc. We observed clinically and statistically significant improvement in MRSS in both treatment groups. Although the median difference in MRSS was greater in the belimumab group, the difference was not statistically significant in this small pilot study. A larger proportion of patients in the belimumab group were clinical improvers, although this did not reach statistical significance. The CRISS score, evaluated post hoc, favored the belimumab group, but the difference was not statistically significant. The SHAQ DI score and VAS RP score showed significantly greater improvements in the belimumab group. However, given that the baseline values for these measures were worse in the belimumab group, this may represent regression to the mean. There were no significant differences for the other secondary outcome measures.

Using differential gene expression analysis, we were able to detect differences between the groups. We observed significant changes in gene expression only in the belimumab arm, driven largely by the improvers. There were no significant DEGs in nonimprovers or in the placebo arm, despite the fact that the placebo patients were treated with MMF. The clinical improvers treated with belimumab and background MMF showed significant decrease of B cell signaling consistent with the mechanism of action of belimumab. This group also displayed high baseline levels and posttreatment down-regulation of fibrotic genes and pathways including collagens, ECM, and TGFβ/TGFβR signaling. The role of B cells in stimulating collagen synthesis and contributing to fibrosis in SSc via multiple mechanisms (including generation of interleukin-6 and CCL2, which were down-regulated in belimumab improvers in this trial) has been described (38–41). A recent study (42) demonstrated induction of collagen secretion and profibrotic cytokines in skin fibroblasts by B cells and particularly by BAFF. Our findings suggest that clinical response to belimumab is associated with a decrease in profibrotic genes and pathways. However, the use of MMF can also impact gene expression as well as intrinsic subset assignment (43). We found no association between baseline intrinsic subsets and clinical response. However, improvers were more likely to be assigned to a normal-like molecular subset following treatment, and decrease in inflammatory gene expression signatures accompanied decrease in MRSS.

Although our investigation has several strengths which will enable planning for future studies, there are limitations to the conclusions that can be drawn from this pilot study. As a pilot trial the sample size was small, and the study was underpowered to detect modest differences between treatment groups. Our use of MMF as an active comparator likely blunted our ability to detect a difference between the groups with regard to impact of belimumab on clinical outcomes. However, most patients with early progressive dcSSc are

treated with immunosuppressive therapies, and data suggest that such patients have improved survival (4). The use of an active comparator therefore not only provides an answer to a more clinically relevant question, but also improves recruitment and ability to carry out a trial. Future studies should include patients treated only with belimumab to assess direct effects of belimumab. Larger clinical trials will be needed to determine the role of belimumab in the treatment of early dcSSc, and this report suggests that such studies are warranted.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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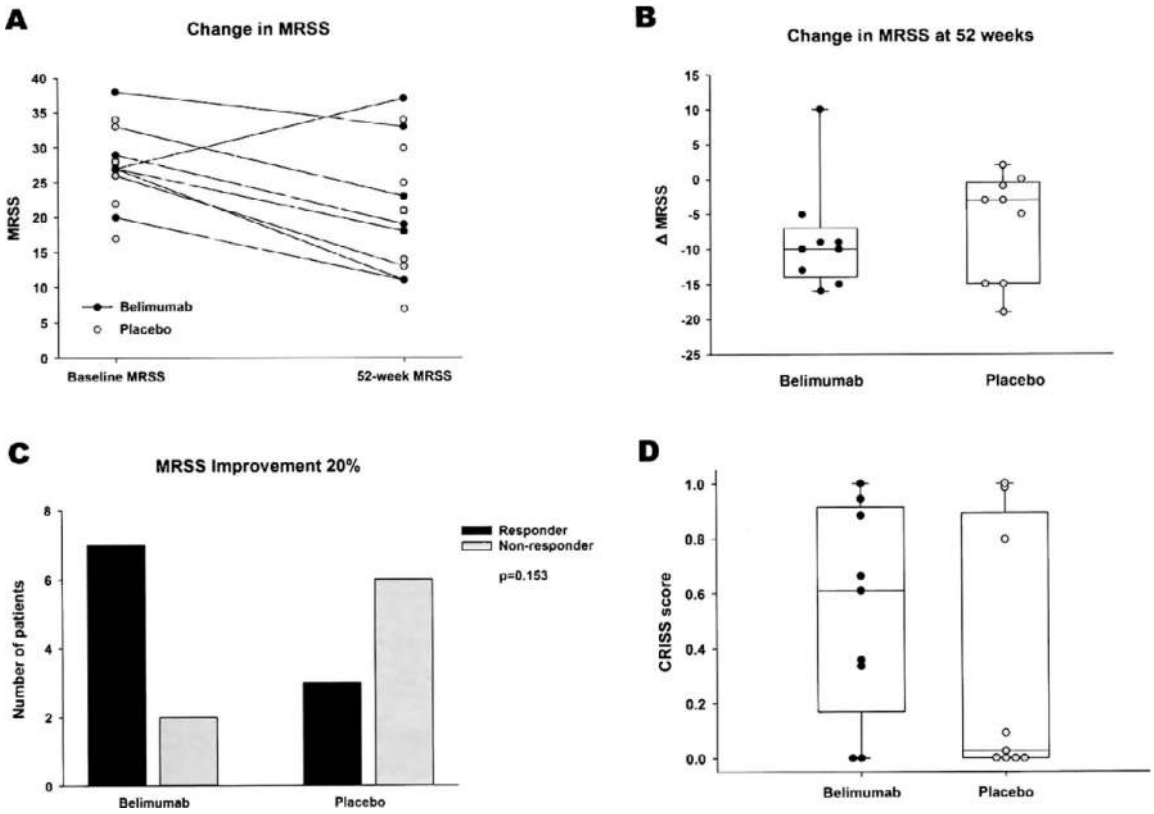

Figure 1.

Changes in modified Rodnan skin thickness score (MRSS) and composite response index in diffuse cutaneous systemic sclerosis (CRISS) score. **A**, MRSS at baseline and at week 52 in patients treated with belimumab and those treated with placebo. The median MRSS decreased from 27 (interquartile range [IQR] 26.5, 31) to 18 (IQR 11, 23) in the belimumab group ($P = 0.039$) and from 28 (IQR 22, 28) to 21 (IQR 14, 25) in the placebo group ($P = 0.023$). **B**, Median change in MRSS. The MRSS changed by a median of −10 (IQR −13, −9) in the belimumab group and by a median of −3.0 (IQR −15, −1) in the placebo group ($P = 0.411$). **C**, Proportion of patients achieving MRSS improvement of at least 20%. **D**, CRISS score at 52 weeks. The median CRISS score was 0.61 (IQR 0.34, 0.88) in the belimumab group and 0.03 (IQR 0, 0.80) in the placebo group ($P = 0.345$). Although CRISS scores in the belimumab group tended to be higher, statistical significance was not reached due to small sample size and distribution of placebo values. In **B** and **D**, data are presented as box plots, where the boxes represent the 25th to 75th percentiles, the lines within the boxes represent the median, and the lines outside the boxes represent minimum and maximum values. Circles represent individual patients.

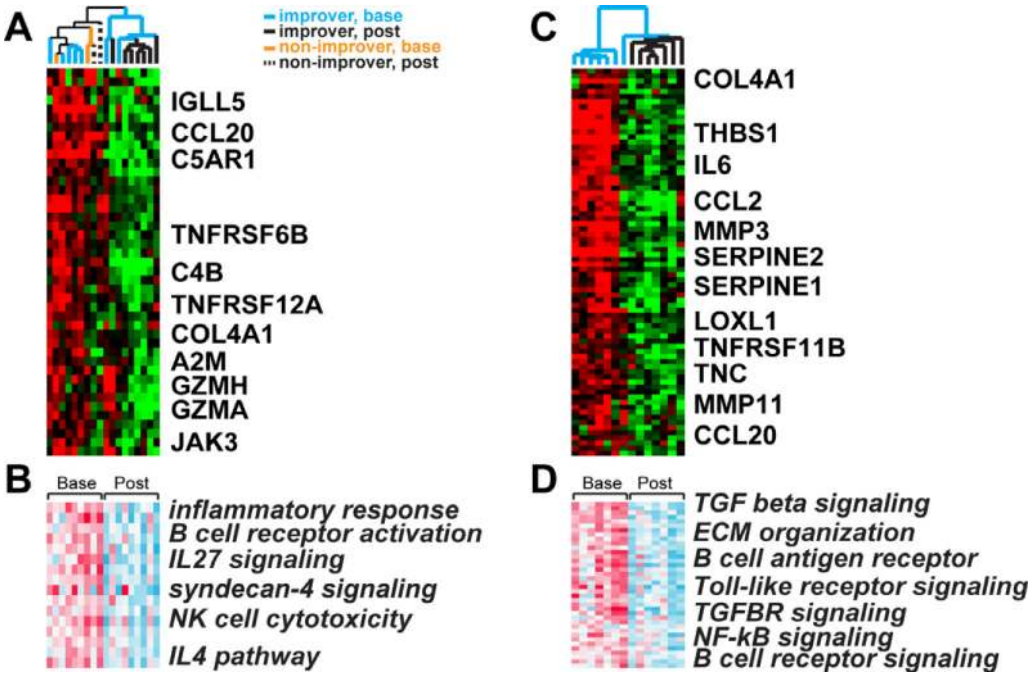

Figure 2.

Gene expression changes in the belimumab arm and in belimumab improvers (patients who individually demonstrated a 20% decrease in the modified Rodnan skin thickness score). **A**, Sample genes that were significantly down-regulated (false discovery rate [FDR] ≤10%) posttreatment in the belimumab arm. **B**, Sample pathways that were significantly down-regulated (FDR ≤5%) posttreatment in the belimumab arm. **C**, Sample genes that were significantly down-regulated posttreatment in belimumab improvers. **D**, Sample pathways that were significantly down-regulated posttreatment in belimumab improvers. Base = baseline; IL-27 = interleukin-27; NK = natural killer; TGF = transforming growth factor; ECM = extracellular matrix; TGFβR = TGFβ receptor.

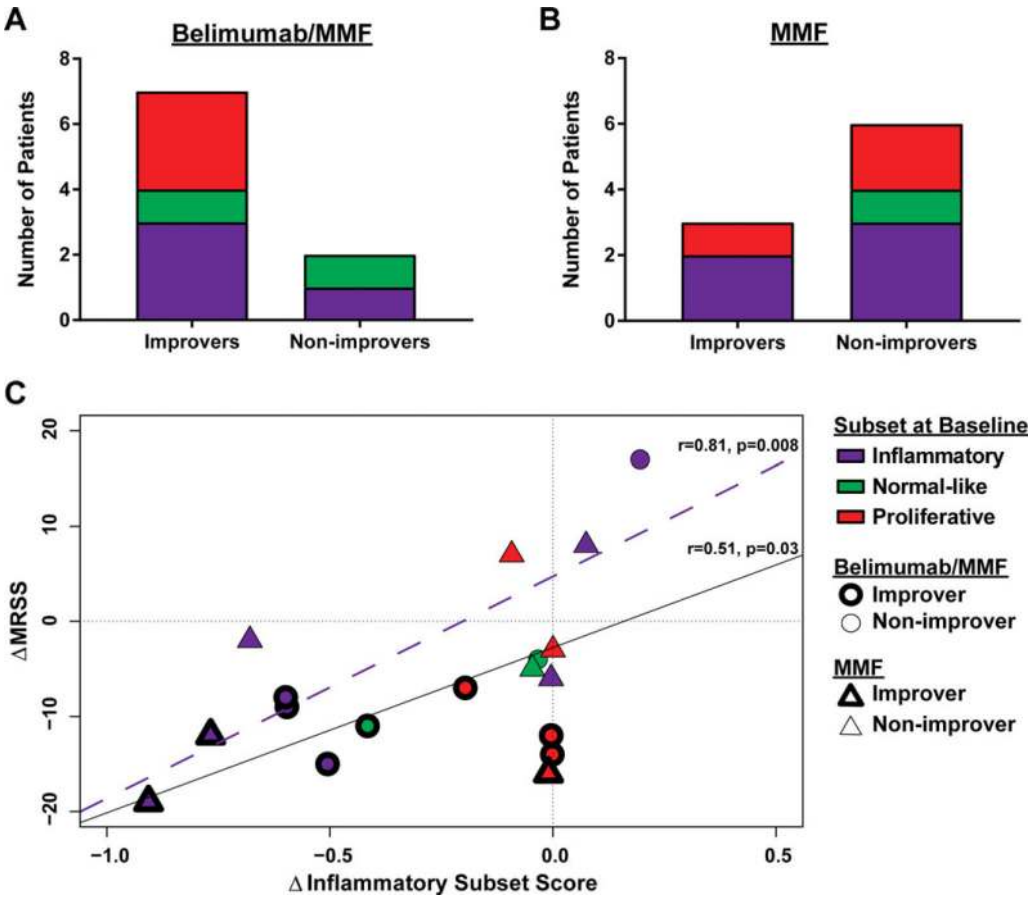

Figure 3.

Patients were assigned to one of the intrinsic molecular subsets based on gene expression signatures at baseline: inflammatory (purple), normal-like (green), or proliferative (red). **A**, In the belimumab/mycophenolate mofetil (MMF) treatment arm, improvers (patients who individually demonstrated a 20% decrease in the modified Rodnan skin thickness score [MRSS]) spanned all 3 subsets, while nonimprovers were assigned to an inflammatory or normal-like molecular subset. **B**, In the MMF treatment arm, improvers were assigned to either an inflammatory or a proliferative molecular subset, while nonimprovers spanned all 3 subsets. **C**, We used the inflammatory gene expression signature to quantify an inflammatory subset score for each patient at baseline and at 12 months, and we correlated changes in this score with changes in MRSS. Symbols represent individual patients. Regression lines are shown for all patients (solid) and for only those patients assigned to the inflammatory molecular subset (dashed).

Table 1.

Characteristics of the patients at baseline*

	Belimumab	Placebo
Age, mean ± SD years	56.7 ± 10.26	53 ± 12.1
Disease duration, mean ± SD months	11.7 ± 7.82	9 ± 4.03
Female, %	80	70
Caucasian, %	90	70
Hispanic, %	30	10
ILD, %	10	20
Anti-Scl-70 positive, %	20	30
Anti-RNA polymerase III positive, %	70	30
MRSS, 0–51	27 (26.5, 31)	28 (22, 28)
SHAQ DI score, 0–3	1.38 (1.13, 1.75)†	0.38 (0.13, 0.63)
VAS pain score, 0–150 mm	45.0 (42.0, 55.0)	30.0 (4.0, 49.0)
VAS RP score, 0–150 mm	63.0 (43.0, 74.0)‡	8.0 (0.0, 12.0)
VAS ulcers score, 0–150 mm	0.0 (0.0, 66.0)	0.0 (0.0, 3.0)
VAS breathing score, 0–150 mm	1.0 (0.0,11.0)	0.0 (0.0, 19.0)
VAS overall score, 0–150 mm	48.0 (33.0, 72.0)	47.0 (28.0, 53.0)
SF-36 MCS score, 0–100	66 (44, 77)	62 (34, 68)
SF-36 PCS score, 0–100	38 (31, 44)	45 (38, 66)
PGA, 0–10	6.3 (4.9, 7.3)	4.8 (4.2, 5.7)
FVC, % predicted	88 (81, 100)	95 (88, 101)
DLCO, % predicted§	85 (67, 94)	81 (81, 87)

*Values for age, disease duration, percent female, percent Caucasian, percent Hispanic, presence of interstitial lung disease (ILD), and autoantibody status are given for all patients randomized (n = 10 per group). All other values are given for treated patients (n = 9 per group). Except where indicated otherwise, values are the median (interquartile range). MRSS = modified Rodnan skin thickness score; SHAQ DI = Scleroderma Health Assessment Questionnaire disability index; VAS = visual analog scale; RP = Raynaud's phenomenon; SF-36 = Short Form 36 health survey; MCS = mental component summary; PCS = physical component summary; PGA = physician's global assessment; FVC = forced vital capacity; DLCO = diffusing capacity for carbon monoxide.

†$P = 0.021$ versus placebo.

‡$P = 0.004$ versus placebo.

§Adjusted for hemoglobin level.

Table 2.

Change in primary and secondary end points at 52 weeks*

	Belimumab + MMF (n = 9)	Placebo + MMF (n = 9)
MRSS, 0–51	−10 (−13, −9)	−3.0 (−15, −1)
SHAQ DI score, 0–3	−0.25 (−0.38, −0.25) †	0.00 (−0.13, 0.13)
VAS pain score, 0–150 mm	−10.5 (−40.5, 6.5)	−1.0 (−32.0, 0.0)
VAS RP score, 0–150 mm	−30.0 (−40.0, −14.0)‡	0.0 (−7.0, 22.0)
VAS ulcers score, 0–150 mm	−12.0 (−38.0, 1.0)	0.0 (−7.5, 4.0)
VAS breathing score, 0–150 mm	2.0 (0.0, 7.0)	0.0 (−7.0, 3.0)
VAS overall score, 0–150 mm	−14.0 (−29.0, −9.00)	−10.0 (−40.0, −6.0)
SF-36 MCS score, 0–100	7.50 (2.50, 18.50)	3.00 (0.00, 10.00)
SF-36 PCS score, 0–100	8.00 (−3.50, 19.00)	−3.00 (−3.00, 27.00)
PGA, 0–10	−4.43 (−8.05, −0.90)	−1.67 (−2.87, −0.90)
FVC, % predicted	5.00 (0.00, 8.00)	−2.00 (−6.00, 4.00)
DLCO, % predicted§	2.00 (−7.00, 7.00)	0.00 (−6.00, 7.00)
CRISS score	0.61 (0.34, 0.88)	0.03 (<0.001, 0.80)

* Values are the median (interquartile range). MMF = mycophenolate mofetil; CRISS = composite response index in diffuse cutaneous systemic sclerosis (see Table 1 for other definitions).

† $P = 0.042$ versus placebo + MMF.

‡ $P = 0.029$ versus placebo + MMF.

§ Adjusted for hemoglobin level.

Table 3.

Adverse events (AEs) in each treatment group*

	Belimumab + MMF (n = 10)	Placebo + MMF (n = 10)
Total AEs	53	56
Total infectious AEs	18	16
Serious AEs	0	3

* There were no significant differences between the groups. MMF = mycophenolate mofetil.