

BRIEF REPORT

Safety and Tolerability of Omalizumab: A Randomized Clinical Trial of Humanized Anti-IgE Monoclonal Antibody in Systemic Lupus Erythematosus

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Objective. Autoreactive IgE antibodies have been implicated in the pathogenesis of systemic lupus erythematosus (SLE). We hypothesize that omalizumab, a monoclonal antibody binding IgE, may improve SLE activity by reducing type I interferon (IFN) production by hampering plasmacytoid dendritic cells and basophil activation. This study was undertaken to assess the safety, tolerability, and clinical efficacy of omalizumab in mild to moderate SLE.

Methods. Sixteen subjects with SLE and a Systemic Lupus Erythematosus Disease Activity Index 2000 (SLEDAI-2K) score of ≥ 4 and elevated autoreactive IgE antibody levels were randomized to receive omalizumab or placebo (2:1) for 16 weeks, followed by 16 weeks of open-label treatment and a 4-week washout period. The SLEDAI-2K score, British Isles Lupus Assessment Group index (BILAG 2004) score, and physician's global assessment of disease activity were recorded at each visit. The type I IFN-induced gene signature was determined using quantitative polymerase chain reaction.

Results. Omalizumab was well tolerated with no allergic reactions, and mostly mild adverse events comparable to those experienced with placebo treatment. SLEDAI-2K scores improved in the omalizumab group compared to the placebo group at week 16 ($P = 0.038$), as well as during the open-label phase in subjects initially receiving placebo ($P = 0.02$). No worsening in BILAG scores or the physician's global assessment was detected. There was a trend toward a reduction in IFN gene signature in subjects treated with omalizumab ($P = 0.11$), especially in subjects with a high baseline IFN signature ($P = 0.052$).

Conclusion. Our findings indicate that omalizumab is well tolerated in SLE and is associated with improvement in disease activity. Larger randomized clinical trials will be needed to assess the efficacy of omalizumab in patients with SLE.

INTRODUCTION

The immune system in patients with systemic lupus erythematosus (SLE) is characterized by abnormal activation of

immune responses and the production of autoantibodies. While until recently most of the pathogenic autoantibodies in SLE were considered to be of the IgG subclass (1), we recently showed that Lyn- and Fcγ receptor II-deficient mice develop autoreactive

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IgE antibodies against anti-double-stranded DNA (dsDNA) as well as lupus-like nephritis that is amplified by basophils in an IgE-dependent manner (2,3). SLE patients also have serum self-reactive IgE and an increased number of activated basophils in the lymph nodes and spleens that can activate both T and B lymphocytes (2). The presence of IgE antibodies against dsDNA, Sm, and SSA was associated with active SLE and hypocomplementemia, suggesting that these autoantibodies may contribute to lupus pathogenesis (4,5). Furthermore, IgE autoantibody levels do not correlate with total serum IgE levels and show only a modest correlation with serum IgG autoantibody levels (5).

Additional studies have found that IgE immune complexes (IgE ICs) activate plasmacytoid dendritic cells (pDCs) upon binding cell surface Fcε receptors (FcεRI). These ICs induce type I interferon (IFN) production in a Toll-like receptor 9-dependent manner (6). When compared to IgG ICs, lower concentrations of IgE ICs are required to trigger proinflammatory responses. Hence, IgE ICs may be involved in the maintenance and amplification of autoimmunity in SLE by inducing heightened activation of autoreactive immune responses (3,6).

Omalizumab is a humanized IgG1 monoclonal antibody against human IgE that blocks the ability of IgE to bind FcεRI. It has been approved by the Food and Drug Administration for the treatment of asthma and chronic idiopathic urticaria (7,8). It effectively depletes circulating IgE and decreases basophil activation (9,10). We hypothesized that depleting IgE autoantibodies with omalizumab in SLE patients with elevated levels of autoreactive IgE would hamper type I IFN production and reduce autoantibody levels, possibly by reducing basophil and pDC activation, and could potentially reduce disease activity. Herein we report the results of a phase Ib study designed to evaluate the safety and tolerability of omalizumab in SLE. We also assessed clinical efficacy and the effects of IgE blockade on the type I IFN gene signature.

PATIENTS AND METHODS

Trial design and interventions. The study was approved by the Institutional Review Board at the NIH and was conducted in accordance with the International Conference on Harmonization Good Clinical Practice requirements. The trial was monitored by an independent Data Safety Monitoring Committee for ongoing safety and predefined stopping rules. Participants were evaluated and all data collection occurred at the NIH Clinical Center in Bethesda, Maryland. The study was designed to be conducted in 3 phases (see Supplementary Figure 1, available on the *Arthritis & Rheumatology* web site at <http://onlinelibrary.wiley.com/doi/10.1002/art.40828/abstract>). In the first phase, the double-blind phase, subjects were randomized at a 2:1 ratio to receive monthly subcutaneous omalizumab or placebo for 16 weeks. In the second, open-label, phase, all subjects received subcutaneous omalizumab for 16 weeks. In the third phase, subjects were followed up for an

additional 4 weeks after stopping the study drug. Subcutaneous omalizumab was administered as a 600 mg loading dose followed by 300 mg every 4 weeks, based on simulation models created from data obtained from previous studies of the use of omalizumab in subjects with asthma and healthy volunteers. This dosing regimen can suppress >90% of circulating free IgE and significantly down-regulates basophil high-affinity FcεRI along with membrane surface IgE (11). The model was qualified as fit for purpose by confirming that simulations reproduced experimental data (12).

Participants. Adult patients who were diagnosed as having SLE and fulfilled at least 4 of the American College of Rheumatology criteria (13) were eligible to participate. Additional inclusion criteria were increased levels (>2 SD above the mean in healthy controls) of IgE anti-dsDNA, anti-Sm, and/or anti-SSA autoantibodies measured by enzyme-linked immunosorbent assay, as previously described (2), and moderately active nonrenal, non-central nervous system lupus, defined as a Systemic Lupus Erythematosus Disease Activity Index 2000 (SLEDAI-2K) (14) score of 4–14. Subjects were maintained on a regimen of stable background immunosuppressive agents and prednisone ≤20 mg/day or equivalent throughout the study, with the option of a one-time intramuscular injection of methylprednisolone for disease flare (defined as an increase in SLEDAI-2K score of ≥5 compared to baseline). Any subject who continued to have disease activity (defined as an increase in SLEDAI-2K of >4 compared to study entry) despite a one-time intramuscular dose of methylprednisolone was withdrawn from the trial. Subjects were excluded if they were taking biologic agents, had a history of asthma, anaphylaxis, known or suspected helminthic infection/infestation, weight >105 kg, total serum IgE level >700 IU/ml, or serum creatinine level >2.0 mg/dl (see Supplementary Table 1, available on the *Arthritis & Rheumatology* web site at <http://onlinelibrary.wiley.com/doi/10.1002/art.40828/abstract>).

Clinical end points. Adverse events (AEs) were graded according to National Cancer Institute Common Toxicity Criteria version 4.0, and the relatedness of AEs to the intervention was determined according to predefined criteria. Disease activity measures included the SLEDAI-2K and the British Isles Lupus Assessment Group (BILAG) 2004 index (15). Global disease activity was rated by the physician's global assessment of disease activity. The severity of cutaneous involvement was documented on the Cutaneous Lupus Erythematosus Disease Area and Severity Index (16). A 28-joint count for swelling and tenderness was performed as specified by the Disease Activity Score in 28 joints (17). Patient-reported outcomes were measured using a visual analog scale (VAS), the Multidimensional Assessment of Fatigue (MAF) questionnaire (18), and the Short Form 36 (SF-36) (19).

Assessment of type I IFN gene signature. The IFN gene signature was determined using a previously validated 4-gene

score by assessing the levels of *IFI27*, *IFI44*, *IFI44L*, and *RSAD2* in whole blood by quantitative polymerase chain reaction (PCR) using a TaqMan gene expression assay (ThermoFisher Scientific) (20,21). Peripheral blood was drawn by venipuncture into PAXgene Blood RNA tubes (BD Diagnostics) and stored at -20°C . RNA was isolated using a PAXgene Blood RNA kit (Qiagen) following the manufacturer's instructions. Reverse Transcription Supremix for quantitative reverse transcriptase-PCR by iScript (Bio-Rad) was used to synthesize complementary DNA. GAPDH was used as a housekeeping gene to normalize gene expression. The $\Delta\Delta C_t$ value was calculated by subtracting the mean determined in a set of healthy controls ($n = 30$) for that particular gene. An IFN score was calculated as the average of the fold inductions for the 4 genes. A high IFN score was defined as an IFN gene signature >2 SD above the mean in healthy controls.

Statistical analysis. This was a pilot, phase Ib study of the tolerability/toxicity of omalizumab. The number of subjects enrolled in this study was based primarily on the conventional number used in similar studies. Baseline clinical characteristics were summarized as the median (interquartile range) for continuous outcomes and as proportions for categorical outcomes, and were compared using Wilcoxon's rank sum test for continuous variables and exact chi-square tests for categorical variables. The percent change (or difference) from baseline in the outcome of interest was calculated at each time point. A linear mixed model was used to take into account the correlation among repeated measures per subject, in order to assess the difference between placebo and omalizumab using either percent changes or differences. Significant differences between treatment groups obtained using a linear mixed model were summarized using estimated least squares means with corresponding standard errors. For univariate analysis, placebo and omalizumab were compared using Wilcoxon's rank sum test. All analyses were 2-tailed tests based on $\alpha = 0.05$. Statistical analyses were conducted using SAS version 9.4 (SAS Institute).

RESULTS

Subject characteristics. Sixty-two subjects were screened, 46 were excluded, and 16 were randomized to receive omalizumab ($n = 10$) or placebo ($n = 6$) (Figure 1 and Supplementary Table 2, available on the *Arthritis & Rheumatology* web site at <http://onlinelibrary.wiley.com/doi/10.1002/art.40828/abstract>). Baseline demographics and disease activity were similar in the 2 groups, except that subjects randomized to receive omalizumab had a longer disease duration compared to those randomized to receive placebo ($P = 0.02$), and none of the patients in the placebo group were white (Supplementary Table 3, online at <http://onlinelibrary.wiley.com/doi/10.1002/art.40828/abstract>). All subjects were receiving hydroxychloroquine, and 80% of the subjects were receiving

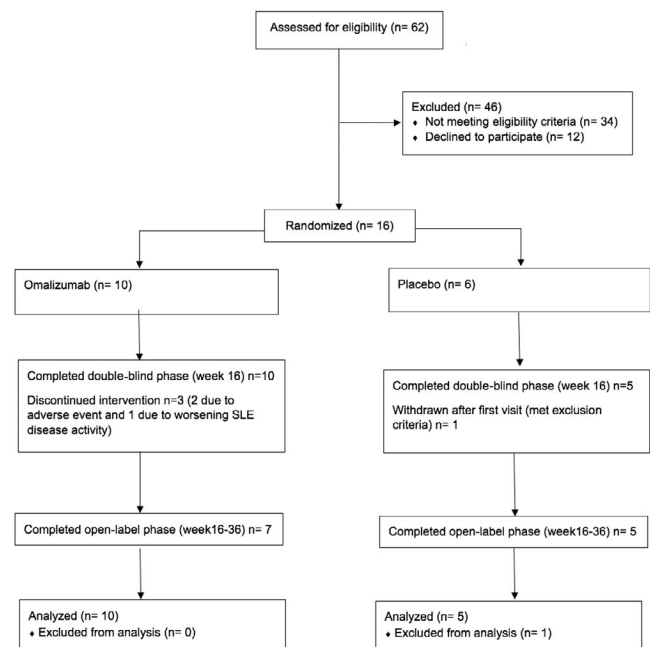


Figure 1. Flow diagram showing the distribution of patients through the enrollment, intervention allocation, and data analysis phases. Details are given according to the Consolidated Standards of Reporting Trials (CONSORT) statement for reporting randomized controlled trials. SLE = systemic lupus erythematosus.

prednisone, with an average prednisone dosage of ~ 7 mg/day in both groups (Supplementary Table 4, online at <http://onlinelibrary.wiley.com/doi/10.1002/art.40828/abstract>).

Safety profile of omalizumab in SLE. Omalizumab was well tolerated in patients with SLE. There were no localized or systemic allergic reactions in the double-blind or open-label phases. There were 52 AEs in 15 subjects during a period of 36 weeks. Most of these AEs (94.2%) were mild or moderate. In the first 16 weeks of treatment, subjects receiving omalizumab experienced 9 AEs, while those receiving placebo had 12 AEs (Table 1). No trend of involvement of a particular organ system was identified, and there was no significant difference between the treatment and placebo groups in terms of mild to moderate AEs.

Three AEs categorized as serious occurred during the study. One subject, while receiving placebo, developed chest pain secondary to bronchitis and cough and required overnight admission for observation to rule out acute coronary syndrome. Another subject randomized to receive omalizumab developed primary varicella infection at week 18 following exposure to chicken pox. This individual had emigrated from West Africa to the US, had no evidence of prior immunity against varicella, and was receiving azathioprine 2 mg/kg/day. One subject who was initially randomized to receive placebo developed pulmonary embolism after starting the open-label phase of the study at week 16. The subject was negative for antiphospholipid antibody-

Table 1. AEs experienced by SLE patients receiving omalizumab or placebo during the double-blind phase (day 0 to week 16)*

Body system	Omalizumab (n = 10)	Placebo (n = 5)	Total (n = 15)
Blood and lymphatic system disorders			
Mild	0 (0.0)	2 (16.7)	2 (9.5)
Moderate	0 (0.0)	2 (16.7)	2 (9.5)
Eye disorders			
Mild	0 (0.0)	0 (0.0)	0 (0.0)
Moderate	0 (0.0)	1 (8.3)	1 (4.7)
Gastrointestinal disorders			
Mild	0 (0.0)	0 (0.0)	0 (0.0)
Moderate	1 (11.1)	0 (0.0)	1 (4.7)
Infections and infestations			
Mild	0 (0.0)	0 (0.0)	0 (0.0)
Moderate	2 (22.2)	0 (0.0)	2 (9.5)
Investigations			
Mild	2 (22.2)	1 (8.3)	3 (14.3)
Moderate	0 (0.0)	0 (0.0)	0 (0.0)
Musculoskeletal disorders			
Mild	0 (0.0)	2 (16.7)	2 (9.5)
Moderate	0 (0.0)	0 (0.0)	0 (0.0)
Nervous system disorders			
Mild	1 (11.1)	0 (0.0)	1 (4.7)
Moderate	0 (0.0)	0 (0.0)	0 (0.0)
Renal and urinary disorders			
Mild	0 (0.0)	0 (0.0)	0 (0.0)
Moderate	1 (11.1)	1 (8.3)	2 (9.5)
Respiratory disorders			
Mild	1 (11.1)	2 (16.7)	3 (14.3)
Moderate	0 (0.0)	0 (0.0)	0 (0.0)
Skin disorders			
Mild	1 (11.1)	0 (0.0)	1 (4.7)
Moderate	0 (0.0)	0 (0.0)	0 (0.0)
Vascular disorders			
Mild	0 (0.0)	0 (0.0)	0 (0.0)
Moderate	0 (0.0)	1 (8.3)	1 (4.7)
Total			
Mild	5 (55.6)	7 (58.3)	12 (57.1)
Moderate	4 (44.4)	5 (41.7)	9 (42.9)

* Values are the number (%) of total adverse events (AEs) in each treatment group. AEs were graded according to the National Cancer Institute Common Toxicity Criteria Version 4.0. SLE = systemic lupus erythematosus.

ies and other genetic or acquired risk factors for thromboembolic events, raising the possibility of this event being related to omalizumab. One patient was withdrawn from the study by the investigators after randomization, since her underlying interstitial lung disease was considered an unacceptable risk for a phase I safety study. Another patient with a history of lupus nephritis was withdrawn at week 28 since she met the withdrawal criteria of >50% worsening of proteinuria (the protein-to-creatinine ratio increased from a baseline level of 0.6 mg/mg to 1.5 mg/mg).

Changes in SLE disease activity during the study.

At week 16, there was improvement in SLEDAI-2K scores in the omalizumab group compared to the placebo group ($P = 0.038$) (Figure 2). This improvement was maintained until the end of the treatment period (week 32), with a trend toward worsening SLEDAI-2K scores ($P = 0.54$) after 4 weeks off drug (Supplementary Figure 2, available on the *Arthritis & Rheumatology* web site at <http://onlinelibrary.wiley.com/doi/10.1002/art.40828/abstract>). In the group of 5 subjects assigned to receive placebo during the first 16 weeks of the trial, disease severity as measured by the SLEDAI-2K score improved after subjects subsequently received omalizumab for 16 weeks during the open-label phase ($P = 0.02$). While changes in the SLEDAI-2K score were statistically significant, the average reduction of 2 points may not be clinically meaningful (Supplementary Table 5, online at <http://onlinelibrary.wiley.com/doi/10.1002/art.40828/abstract>). The improvements in the SLEDAI-2K score were mainly in the arthritis, rash, and serologic domains.

The composite response criteria of the Systemic Lupus Erythematosus Responder Index 4 (SRI-4) (22) was achieved in 3 subjects. Two subjects randomized to receive omalizumab achieved SRI-4 at week 16 and maintained it at week 32, while 1 subject receiving placebo during the first 16 weeks met the SRI-4 criteria at week 32, after open-label treatment. No significant changes were observed in the patient-reported outcomes SF-36 and MAF. No new BILAG A scores or worsening of physician's global assessment were observed during the study. Disease activity as marked by subjects on a VAS remained stable in the omalizumab group (Supplementary Figure 3, online at <http://onlinelibrary.wiley.com/doi/10.1002/art.40828/abstract>). Steroid taper or withdrawal of immunosuppressive medications was not attempted during the study.

Laboratory findings indicating SLE disease activity (IgG anti-dsDNA and C3 and C4 levels) remained stable throughout the intervention and washout phases (Supplementary Figures 4–6, online at <http://onlinelibrary.wiley.com/doi/10.1002/art.40828/abstract>). As expected due to measurement of circulating drug IgE complexes, median total serum IgE levels increased after starting omalizumab both in subjects who were initially randomized to receive omalizumab and in subjects who were initially randomized to receive placebo and then started receiving omalizumab during the open-label phase (23).

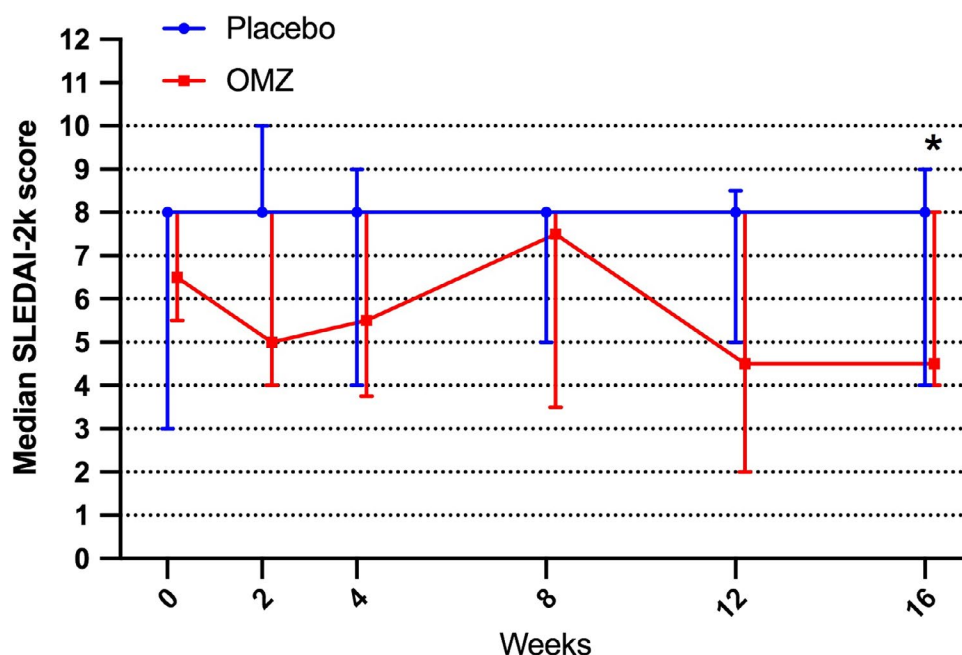


Figure 2. Systemic Lupus Erythematosus Disease Activity Index 2000 (SLEDAI-2K) scores for patients receiving placebo and patients receiving omalizumab (OMZ) during the double-blind phase (weeks 0–16). Values are the median and interquartile range. * = $P = 0.038$.

Effects of omalizumab on IFN gene signature. Subjects receiving omalizumab showed a trend toward improvement in IFN gene signature during the first 16 weeks of therapy ($P = 0.11$ versus week 0) (Supplementary Figure 7, online at <http://onlinelibrary.wiley.com/doi/10.1002/art.40828/abstract>). This difference was more pronounced in subjects who had a high IFN gene signature at baseline ($P = 0.052$ for week 16 versus week 0) (Supplementary Figure 8, online at <http://onlinelibrary.wiley.com/doi/10.1002/art.40828/abstract>). This suggests that omalizumab may modulate type I IFN pathways by blocking self-reactive IgE, and is consistent with previous reports of stimulation of type I IFN in pDCs by IgE ICs (6).

DISCUSSION

The identification of IgE autoantibodies and their role in basophil activation in animal models and in human SLE has revealed a new pathway potentially involved in SLE pathogenesis (2,5). In this proof-of-concept study, omalizumab, a humanized IgG1 monoclonal antibody against human IgE, was tested for the first time as an add-on therapy in SLE. Potential advantages of omalizumab in SLE include a side effect profile different from that of immunosuppressive drugs and a convenient once a month subcutaneous administration schedule. We have previously demonstrated the presence of IgE autoantibodies in >70% of SLE patients; hence, omalizumab as an add-on therapy to standard of care may be applicable to a large subset of SLE patients (5).

In this pilot clinical trial, omalizumab was well tolerated with no immediate or delayed allergic reactions. Statistically significant improvement in disease activity after 16 weeks or 32 weeks

of omalizumab treatment was indicated by the change from baseline in SLEDAI-2K score, but not by other measures of clinical activity. The proportion of SRI-4 responders was low when compared to what has been reported in other larger clinical trials. This is probably due to the small sample size in the present study and the overall mild disease activity at enrollment. In addition, the absolute change in the SLEDAI-2K score was ~2, which is below what is usually considered a clinically minimally important change (24,25). There was no worsening in patient-reported outcomes while subjects were receiving omalizumab.

A 5-year observational study of omalizumab in subjects with asthma has suggested a potential increased risk of serious cardiovascular and cerebrovascular events (23). In the present study, one subject developed pulmonary embolism after receiving the first dose of omalizumab. This raises the concern of whether the event was related to omalizumab or due to the increased background risk of thromboembolic events in patients with SLE. Given that cardiovascular risk is enhanced in SLE (26), future studies of omalizumab in SLE should include markers of vascular risk and assessments of vascular dysfunction.

This study is the first to show that omalizumab reduces the IFN gene signature, especially in SLE patients with a high IFN gene signature at baseline. This suggests that the mechanism of action of this drug in SLE may be at least in part through abrogation of dysregulated IFN pathways. In future studies, other biomarkers potentially involved in this pathway, such as CD62L and Th2 cytokines, should be measured.

Our study has several limitations. Importantly, we studied a small number of patients with mild clinical disease with no

organ-threatening manifestations. The safety data from this study need to be confirmed in a larger cohort with more active disease, by excluding subjects with an elevated risk of thromboembolic events. This exploratory study was not powered for efficacy, and a larger sample size will be needed to ascertain if omalizumab has potential to treat a selected subset of patients with SLE and high levels of anti-IgE antibodies. The mechanism of action of omalizumab in SLE also needs to be better defined through additional mechanistic studies controlling for intertest variability.

This is the first trial to test the safety and potential efficacy of blocking IgE autoantibodies as a novel nonimmunosuppressive treatment of SLE. The results from this exploratory study need to be confirmed in future larger studies adequately powered to measure efficacy.

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. Hasni 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.

Study conception and design. Hasni, Charles, Balow, Kaplan, Rivera.

Acquisition of data. Hasni, Gupta, Davis, Poncio, Temesgen-Oyelakin, Joyal, Fike, Manna, Carlucci, Biehl.

Analysis and interpretation of data. Hasni, Gupta, Temesgen-Oyelakin, Manna, Auh, Shi, Chan, Dema, Charles, Waldman, Siegel, Kaplan, Rivera.

ADDITIONAL DISCLOSURES

Author Siegel is an employee of Novartis Institutes for BioMedical Research.

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Supplementary Figure and Table Legends

Table S1: Reasons for screen failure

Table S2: SLE disease manifestations of all screened subjects with elevated IgE autoantibodies

Table S3: Demographics and Baseline characteristics of study subjects. All values are expressed as median(range)

Table S4: Immunosuppressive medications at baseline

Table S5: Individual SLEDAI 2K scores for each patient during the study

Figure S1: Clinical Trial Design: Subjects were randomized in blocks of 3 (2:1 Omalizumab vs Placebo) during the first double blind phase (weeks 0-16) to receive Omalizumab 600 mg loading dose followed by 300 mg Omalizumab or placebo every 4 weeks. All subjects received Omalizumab 300mg every 4 weeks during the open label phase (weeks 16-32). Subjects on placebo during weeks 0-16 were first given a 600 mg loading dose at week 16. All subjects were observed off medication for 4 weeks during phase 3.

Figure S2: Median SLEDAI 2K scores during open label (weeks 16-32) and off drug phase (weeks 32-36). Vertical bars represent the Interquartile ranges (IQRs) of the observed data. SLEDAI 2K: Systemic Lupus Erythematosus Disease Activity Index 2000. Week 32 * $p = 0.020$

Figure S3: Median Patient Global Assessment by Visual Analog Scale during the study. Vertical bars represent the interquartile ranges (IQRs) of the observed data.

Figure S4: Median IgG anti-dsDNA antibody level during the study. Vertical bars represent the interquartile ranges (IQRs) of the observed data.

Figure S5: Median C3 level during the study. Vertical bars represent the interquartile ranges (IQRs) of the observed data.

Figure S6: Median C4 level during the study. Vertical bars represent the interquartile ranges(IQRs) of the observed data.

Figure S7: Effect of Omalizumab on IFN-gene signature on all patients. IFN gene score based on four IFN-regulated genes (*IFI27*, *IFI44*, *IFI44L*, *RSAD2*) quantified in all subjects receiving Omalizumab. For those subjects who were on placebo during the double-blind phase, results are reported from weeks 16-32.

Figure S8. Effect of Omalizumab on type I Interferon (IFN) gene signature on patients with high IFN score at baseline visit. IFN gene score based on four IFN-regulated genes (*IFI27*, *IFI44*, *IFI44L*, *RSAD2*) of subjects with high IFN gene score at the start of trial before receiving Omalizumab.

Reasons for exclusion	Number Total =46
Declined to participate	12
SLEDAI 2K more than 14	3
SLEDAI 2k less than 4	17
History of Cancer	2
On disallowed medications	3
Medically unstable or history of asthma (CAD, ILD etc.)	7
Weight more than allowed by the protocol	2

Table S1

Manifestations of SLE	Subjects Included =16	Subjects Excluded =46
Lupus Nephritis	8 (50%)	35(76%)
Arthritis	14 (87%)	27(58%)
Serositis	2 (13%)	18(40%)
Malar Rash	12(75%)	27(58%)
Discoïd Rash	1(6%)	9(19%)
Immunological	16(100%)	46(100%)
ANA	16(100%)	46(100%)
Hematological	9(56%)	11(24%)
Mucositis	8(50%)	17(38%)
Photosensitivity	10(62%)	9(19%)
Alopecia	13(81%)	13(28%)
CNS	0	3(8%)

Table S2

Subject Demographics and Baseline Characteristics			
Variables	Omalizumab (n=10)	Placebo (n=5)	Total (n=15)
Age (years)	46.5(22-69)	44(26-58)	44(22-69)
Race/Ethnicity, N (%)			
African American	2 (20 %)	1 (20 %)	3 (20 %)
Asian	1 (10 %)	1 (20 %)	2 (13.3 %)
Caucasian	4 (40.0 %)	0 (0.0%)	4 (26.7 %)
Hispanic	3 (30.0 %)	3 (60.0 %)	6 (40.0 %)
Gender, N (%) Female	10 (100%)	5 (100%)	15 (100.0 %)
Disease Duration (years)	12(7-50)	6(1-16)	11(1-50)
SLEDAI 2K	6.5(3-10)	8(2-8)	7(2-10)
BMI (kg/m ²)	28.8(21.6-33.1)	26.39(21.3-35.6)	27.1(21.2-35.6)
IgA Level (mg/dL)	325(63-552)	303(140-430)	321(63-552)
IgE Level (IU/mL)	55.3(3.6-189)	102(5-628)	87.3(3.6-628)
IgG Level (mg/dL)	1148(790-3265)	1261(1107-1577)	1167(790-3265)
IgM Level (mg/dL)	66(27-237)	78(53-108)	66(27-237)
Complement C3 (mg/dL)	99.9(69.2-140.7)	91.2(46.9-127.3)	92.3(46.9-140.7)
Complement C4 (mg/dL)	14.05(4.3-34.1)	10.7(3.9-16.9)	12.5(3.9-34.1)
WBC (K/uL)	4.69(2.98-10.93)	5.18(4.4-6.06)	4.8(3-10.9)
Absolute Basophil Count (K/uL)	0.03(0.01 - 0.09)	0.02(0.01 - 0.05)	0.02(0.01-0.09)
Absolute Eosinophil Count (K/uL)	0.04(0.01 - 0.11)	0.06(0.01 - 0.11)	0.04(0.01 - 0.11)
Hemoglobin (g/dL)	12.25(9.8-15.3)	11.5(9.8-12.8)	12.1(9.8-15.3)
Hematocrit (%)	37.75(28.9-45)	34.3(30.7-39)	36.5(28.9-45)
Platelet (K/uL)	224(97-349)	270(200-309)	248(97-349)
ESR (mm/hr)	14.5(8-70)	16(13-46)	16(8-70)
Anti-dsDNA IgG (IU/mL)*	99.5(31-404)	77(38-156)	77(31-404)

Table S3

SLEDAI 2K: Systemic Lupus Erythematosus Disease Activity Index 2000

BMI: Body Mass Index

WBC: White Blood Cell count

ESR: Erythrocyte Sedimentation Rate

*Anti-dsDNA: measured using enzyme-labelled anti-isotope assay (ELiA)

Anti-dsDNA IgG values <= 30 = Negative

Immunosuppressive medications at baseline				
<i>Preferred Medication Term</i>		<i>Omalizumab</i>	<i>Placebo</i>	<i>Total</i>
PRED	n (Average dose)	7 (7.1 mg*/day)	5 (7.7 mg/day)	12 (7.4 mg/day)
HCQ	n (Average dose)	10 (390 mg/day)	5 (400 mg/day)	15 (393 mg/day)
AZA	n (Average dose)	2 (150 mg/day)	2 (150 mg/day)	4 (150 mg/day)
MMF	n (Average dose)	3 (2333 mg/day)	3 (2500 mg/day)	6 (2417 mg/day)
MTX	n (Average dose)	1 (10 mg/week)	0 (0 mg/week)	1 (10 mg/week)

Table S4

*mg/day=milligram per day

PRED=prednisone, HCQ = hydroxychloroquine, AZA= azathioprine, MMF= mycophenolate mofetil, MTX= methotrexate

SLEDAI 2K Scores of Individual Subjects															
Treatment group	OMZ*	PBO ^{&}	OMZ	OMZ	OMZ	OMZ	PBO	OMZ	PBO	OMZ	OMZ	PBO	OMZ	PBO	OMZ
Day 0	6	4	10	7	3	8	2	8	8	6	8	8	4	8	6
Week 16	8	8	4	5	4	4	2	8	6	4	8	8	2	10	6
Week 32	4	6	6	5	4	4	4	8	6	4	8	8	4	6	4
Week 36	4	4	8	7	4	8	2	8	6	4	10	8	4	7	4

*OMZ=Omalizumab

& PBO= Placebo

Table S5

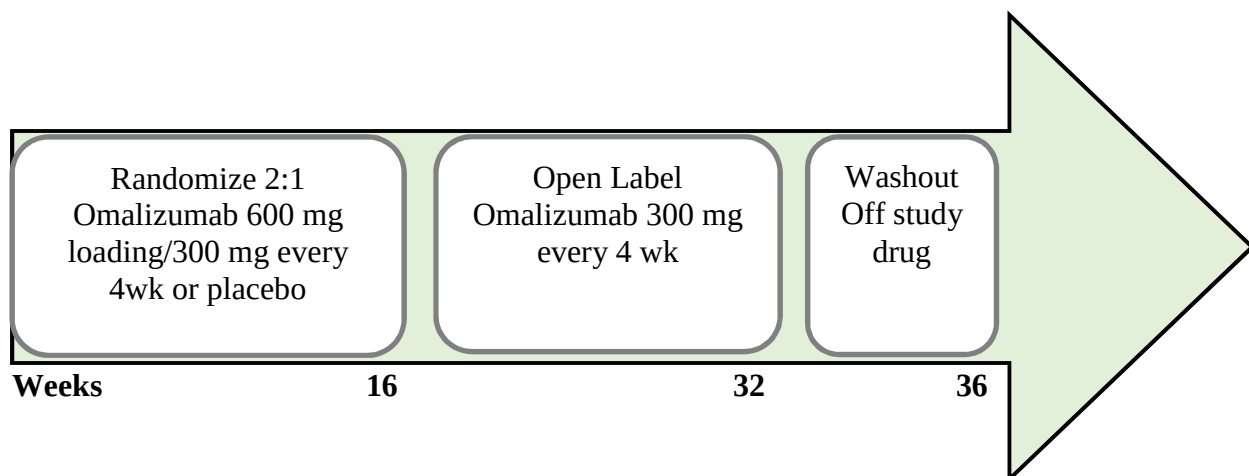


Figure S1

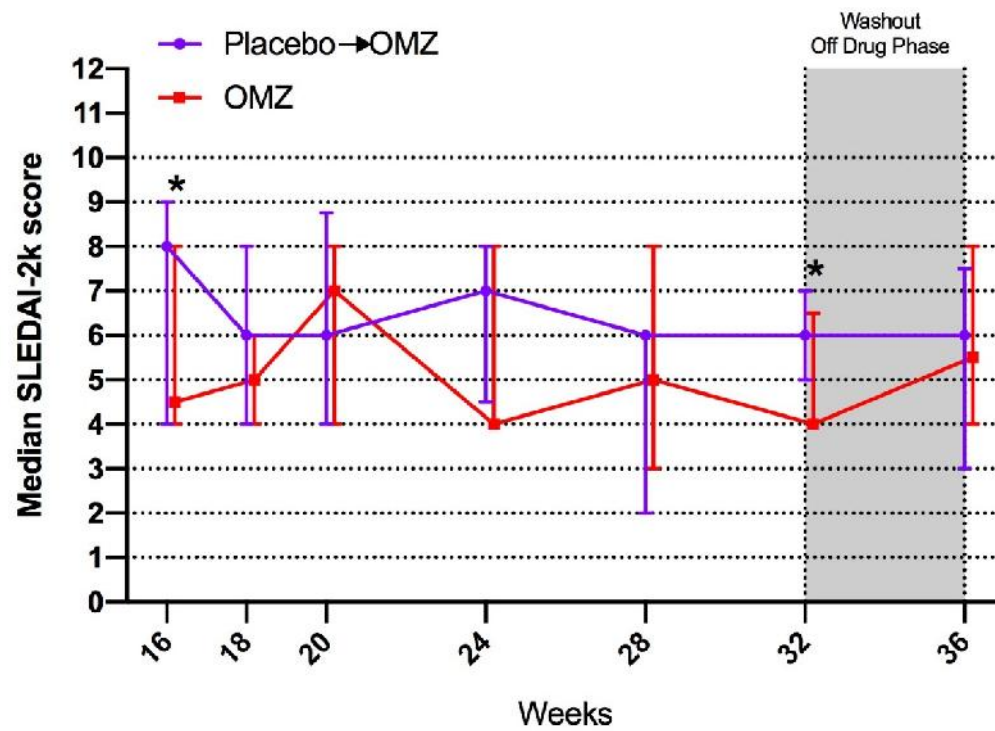


Figure S2

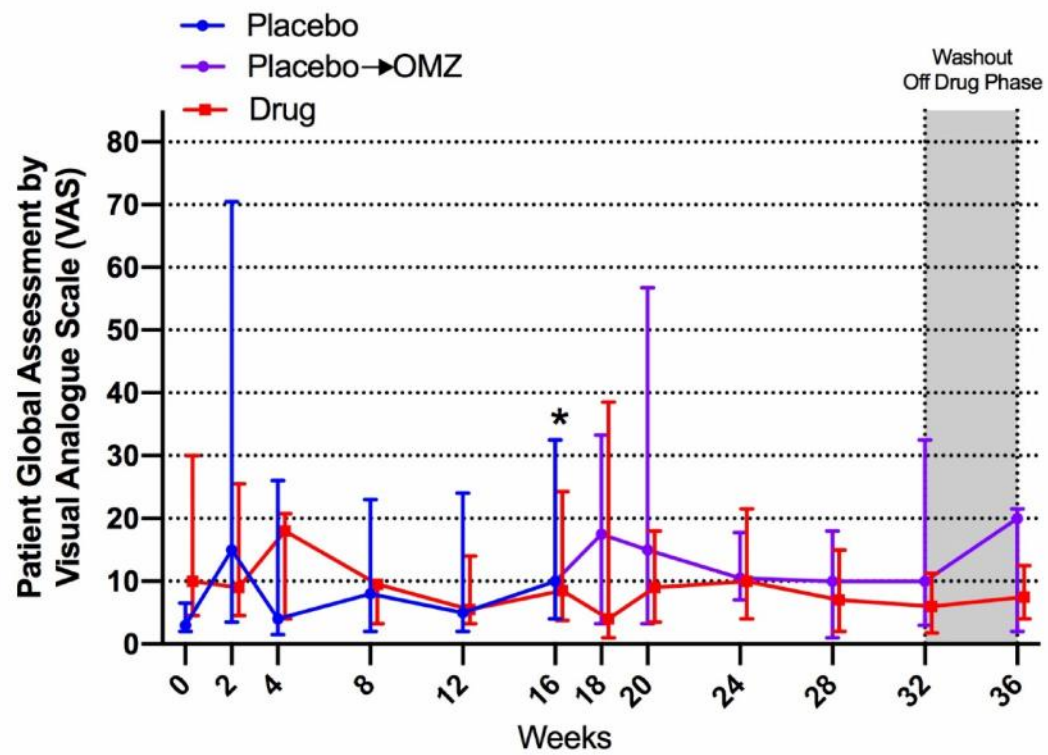


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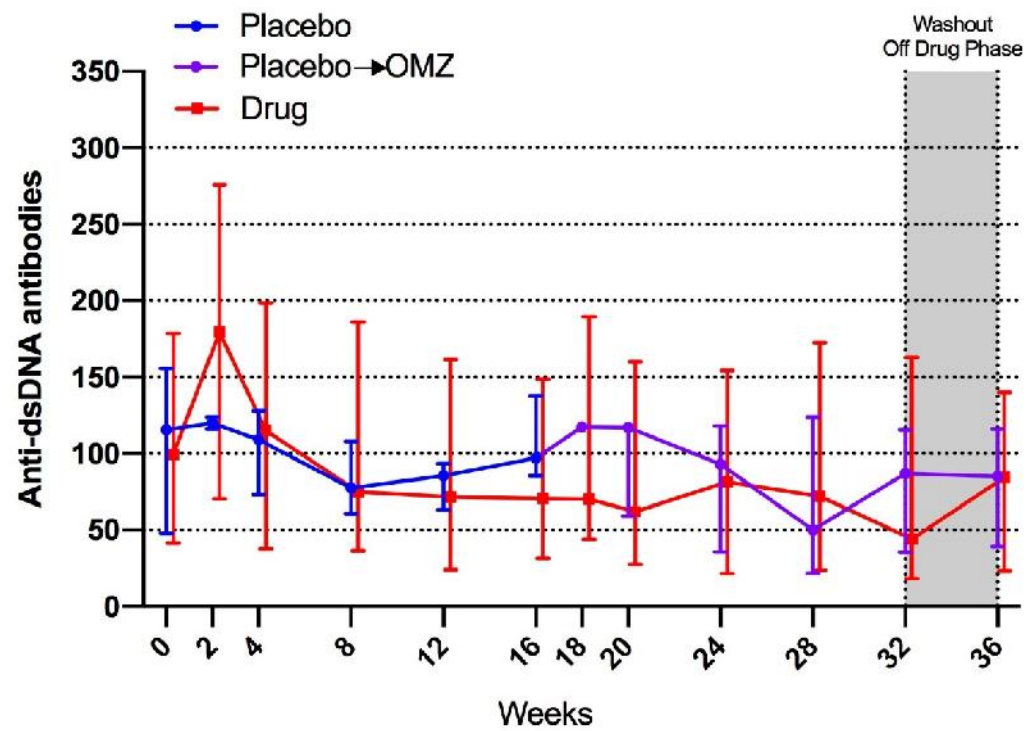


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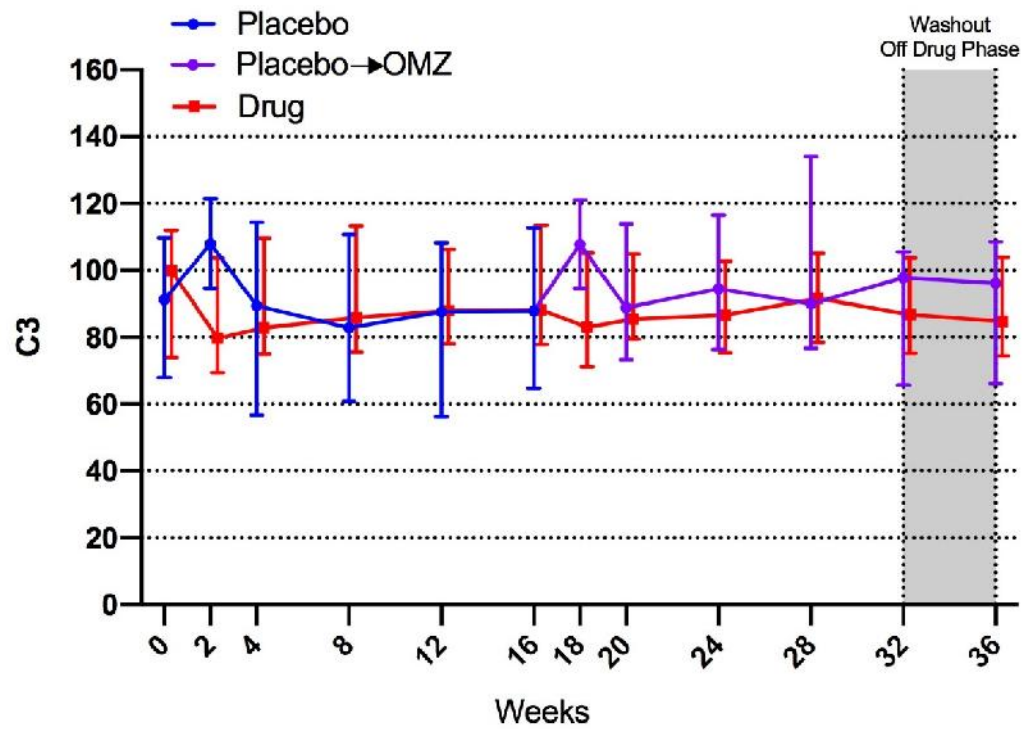


Figure S5

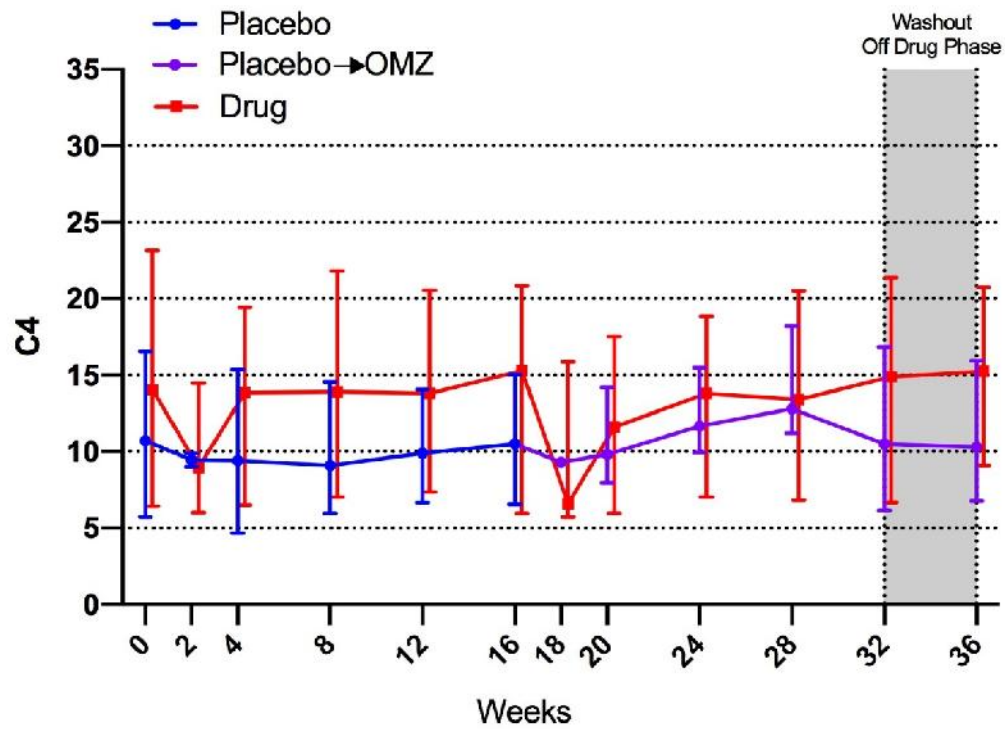
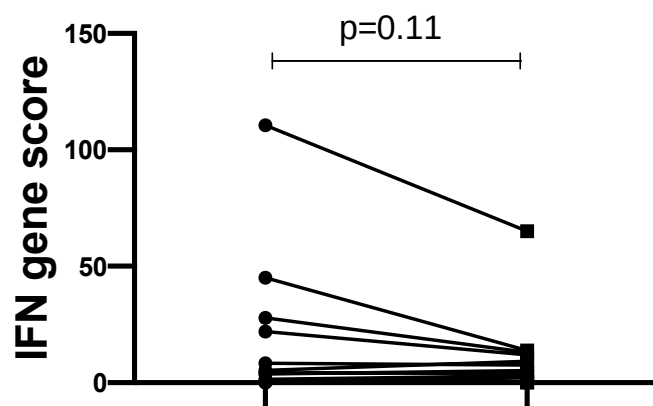


Figure S6



Week 0 Week 16

Figure S7

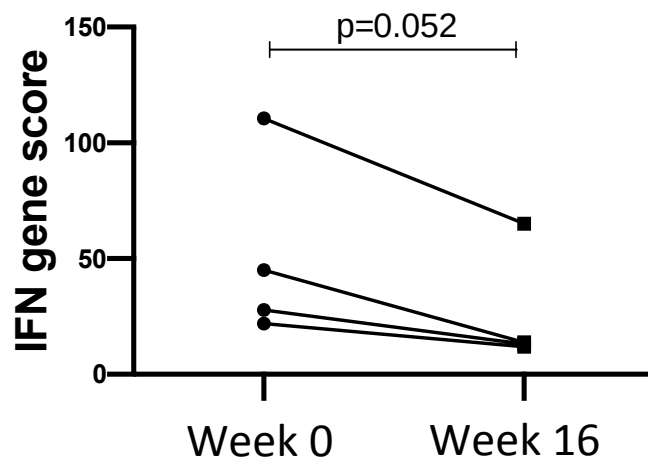


Figure S8

