Smoking reduces the efficacy of belimumab in mucocutaneous lupus.

Ioannis Parodis, Alvaro Gomez, Martina Frodlund, Andreas Jönsen, Agneta Zickert, Christopher Sjöwall, Anders A Bengtsson and Iva Gunnarsson

The self-archived postprint version of this journal article is available at Linköping University Institutional Repository (DiVA):

<http://urn.kb.se/resolve?urn=urn:nbn:se:liu:diva-149494>

N.B.: When citing this work, cite the original publication.

This is an electronic version of an article published in:

Parodis, I., Gomez, A., Frodlund, M., Jönsen, A., Zickert, A., Sjöwall, C., Bengtsson, A. A., Gunnarsson, I., (2018), Smoking reduces the efficacy of belimumab in mucocutaneous lupus., *Expert Opinion on Biological Therapy*. <https://doi.org/10.1080/14712598.2018.1494719>

Original publication available at:

<https://doi.org/10.1080/14712598.2018.1494719>

Copyright: Taylor & Francis (STM, Behavioural Science and Public Health Titles - No Open Select)

<http://www.tandf.co.uk/journals/default.asp>

ORIGINAL RESEARCH

Smoking reduces the efficacy of belimumab in mucocutaneous lupus

Ioannis Parodis^{1,2}, Alvaro Gomez^{1,2}, Martina Frodlund³, Andreas Jönsen⁴, Agneta Zickert^{1,2}, Christopher Sjöwall³, Anders A Bengtsson⁴, Iva Gunnarsson^{1,2}

¹ Division of Rheumatology, Department of Medicine, Karolinska Institutet, Stockholm, Sweden

² Rheumatology, Karolinska University Hospital, Stockholm, Sweden

³ Rheumatology/Division of Neuro and Inflammation Sciences, Department of Clinical and Experimental Medicine, Linköping University, Linköping, Sweden

⁴ Rheumatology, Department of Clinical Sciences Lund, Lund University, Lund, Sweden

Correspondence to: Ioannis Parodis | MD PhD

Address: Rheumatology, Karolinska University Hospital, SE-171 76 Stockholm, Sweden

E-mail: ioannis.parodis@ki.se

Phone: +46722321322

Abstract

Objectives: Recently, we demonstrated a negative impact of smoking in belimumab efficacy in patients with systemic lupus erythematosus (SLE). Here, we particularly investigated clinical effects of belimumab and a potential impact of smoking in mucocutaneous and articular SLE.

Methods: We surveyed 62 SLE patients treated between 2011 and 2017. Evaluation included the mucocutaneous descriptors of SLEDAI-2K (rash, alopecia, mucosal ulcers; mcSLEDAI-2K), CLASI, the arthritis SLEDAI-2K descriptor (arSLEDAI-2K) and the 28-joint count.

Results: mcSLEDAI-2K and CLASI activity decreased from baseline to month 6 and 12 ($P<0.001$ for all). No worsening in CLASI damage was observed. Current or previous smokers displayed a higher probability of unchanged/worsened mcSLEDAI-2K compared to never smokers (OR: 6.4; 95% CI: 1.5–27.4; $P=0.012$), also after adjustment for antimalarial agents. arSLEDAI-2K scores had decreased at month 6 ($P<0.001$) and 12 ($P<0.001$). Likewise, tender and swollen 28-joint counts had improved at month 6 ($P=0.010$ and $P<0.001$, respectively) and 12 ($P=0.001$ for both). We observed no impact of smoking on belimumab efficacy in articular SLE.

Conclusion: We observed a negative impact of smoking on the efficacy of belimumab in mucocutaneous SLE. In contrast, no impact of smoking on belimumab efficacy was seen in patients with articular manifestations.

Keywords: belimumab, biological agents, drug efficacy, rheumatology, systemic lupus erythematosus

1. Introduction

Belimumab, a monoclonal antibody against soluble B lymphocyte stimulator (BLyS, also known as BAFF), has been shown to reduce disease activity in patients with systemic lupus erythematosus (SLE), but the need for defining patient subsets in which belimumab may be most beneficial still remains. Towards this goal, a deeper understanding of the interplay between immunity and environmental factors in disease severity and drug efficacy is essential.

Tobacco smoking is a major environmental risk factor that has been identified for inflammatory rheumatic diseases, with convincing data in SLE [1-8] and rheumatoid arthritis (RA) [7-11]. In RA, smoking has been shown to decrease the efficacy of methotrexate and TNF inhibitors [12, 13]. In SLE, smoking has been found to contribute to the development of the disease, as well as to disease severity and organ damage [14, 15]. Furthermore, smoking has been associated with the occurrence of antibodies to double-stranded (ds)DNA [3] and phospholipids [16]. In cutaneous SLE in particular, smoking has been shown to not only contribute to disease activity and damage [17, 18], but also to decreasing the efficacy of antimalarial agents [19, 20].

Post-hoc analyses of data from clinical trials of belimumab have suggested beneficial effects of belimumab in serologically active SLE patients [21], as well as particularly beneficial effects in patients with mucocutaneous and articular SLE [22]. Real-life experiences have contributed to further evaluation of the efficacy of belimumab [23-26]. We recently documented decreasing disease activity during treatment with belimumab in

SLE patients from three Swedish tertiary referral centers, and a negative impact of smoking on the efficacy of the treatment [26]. In order to better understand this interaction, we expanded our survey to include investigation of the efficacy of belimumab in distinct organ domains, mucocutaneous and articular SLE in particular, and a potential impact of tobacco smoking on treatment outcomes in these specific organ domains.

2. Patients and methods

2.1 Patients

Sixty-two patients with active SLE despite standard of care treatment from the Karolinska (n=34), Skåne (n=19) and Linköping (n=9) University Hospitals treated with belimumab between 2011 and 2017 were enrolled in this prospective observational study. All patients fulfilled the 1982 revised criteria [27] and/or the Systemic Lupus International Collaborating Clinics criteria [28] for classification of SLE.

Belimumab was administered according to clinical routines, *i.e.* intravenously at a dose of 10 mg/kg at weeks 0, 2, 4, and every fourth week thereafter, unless individual adjustments were clinically indicated. The decision for treatment with belimumab was steered by the treating physician; no therapeutic intervention was applied for the purpose of the study.

For inclusion in this analysis, a minimum of six months of follow-up was required, with the exception of withdrawals due to adverse events and/or inadequate effect. Evaluation of the clinical effects of belimumab treatment was conducted at month 6 and month 12 from treatment initiation.

Written informed consent was obtained from all patients prior to recruitment. The study protocol was reviewed and approved by the regional ethics review boards in Stockholm, Lund and Linköping.

2.2 Evaluation of mucocutaneous and musculoskeletal manifestations

Global SLE disease activity was assessed using the SLE disease activity index 2000 (SLEDAI-2K) [29]. We evaluated the mucocutaneous activity using the sum of the mucocutaneous descriptors of the SLEDAI-2K, *i.e.* rash, alopecia, and mucosal ulcers (herein termed mcSLEDAI-2K). In patients from the Karolinska University Hospital, mucocutaneous activity and damage were additionally assessed using the cutaneous lupus erythematosus disease area and severity index (CLASI) [30]. For the purpose of adjustment in logistic regression models, we also used the mucocutaneous descriptors of the Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index (SDI) [31], *i.e.* scarring alopecia, extensive scarring of panniculus other than scalp and pulp space, and skin ulceration (SDI skin domain), since SDI assessments were available in the entire patient cohort. Musculoskeletal activity was evaluated using the arthritis descriptor of SLEDAI-2K, and in patients from the Karolinska University Hospital, the 28-joint count was additionally used [32].

2.3 Definitions

Improvement in the mcSLEDAI-2K was defined as a negative score shift in at least one of the mucocutaneous descriptors and no new onset in the other ones, *i.e.* a reduction of at least two points, representing a greater change than the suggested minimal clinically meaningful SLEDAI-2K improvement (≥ 1 points) [33]. The CLASI activity score was used to stratify the patients into groups of none or mild (CLASI activity score 0–9), moderate (score 10–20) and severe (score 21–70) mucocutaneous disease, and CLASI activity improvement was defined as a ≥ 4 -point and/or $\geq 20\%$ decrease in the CLASI activity score [34]. Improvement in the arthritis descriptor of SLEDAI-2K was defined as a negative

descriptor score shift (from 4 to 0). Severe joint involvement was defined as ≥ 8 tender and ≥ 8 swollen joints in the 28-joint count, simultaneously manifest [35].

2.4 Statistics

For comparisons between baseline and subsequent time points, the non-parametric Wilcoxon signed-rank test was used. The Pearson's chi-square or Fisher's exact tests were used to investigate contingent associations between binominal samples, and logistic regression was applied when adjustment for possible confounding factors was indicated and applicable. *P*-values < 0.05 were considered statistically significant. Statistical analysis was performed using the IBM SPSS Statistics 24 software. The GraphPad Prism 7 software was used for the construction of graphs.

3. Results

Baseline characteristics of the patients are presented in Table 1. The median age of the patients at treatment initiation was 42.7 years (interquartile range, IQR: 31.6–52.4), 91.9% were women, and 95.2% were Caucasian. The median disease duration from the SLE diagnosis until treatment initiation was 7.7 years (IQR: 4.3 – 14.2), and the median baseline SLEDAI-2K score was 8.0 (IQR: 4.0–14.0).

The most common indications for initiation of belimumab treatment were arthritis (n=29; 46.8%), mucocutaneous involvement (n=29; 46.8%), hematological abnormalities (n=10; 16.1%) and nephritis (n=8; 12.9%).

Results are presented in detail in Table 2. Due to the limited number of patients, both mean (range) and median (interquartile range) values are reported. The changes reported derived from analysis based on completers only rather than intention-to-treat. In five patients, belimumab was discontinued earlier than six months of follow-up due to adverse events (n=4) or inadequate effect (n=1); these patients were excluded from analyses requiring follow-up data. Numbers of observations are displayed in Table 2.

3.1 Mucocutaneous domain

At baseline, the mean mcSLEDAI-2K score was 2.3 (range 0–6; n=62), and 44/62 (71.0%) patients had a mcSLEDAI-2K score >0 (Table 2). CLASI assessments were available in 33 patients (mean baseline CLASI activity score: 8.4; range: 0–39); of these 33 patients, 21 patients had none or mild, 8 patients moderate, and 4 patients severe mucocutaneous

disease (Figure 1). Patients with no mucocutaneous activity at baseline were also considered in the comparative analyses between baseline and month 6 or 12 to ensure that contingent new onset of mucocutaneous symptoms was not omitted from the results.

Of the 44 patients with baseline mcSLEDAI-2K score >0 , five patients had withdrawn at month 6; among patients remaining on treatment ($n=39$), 24 patients (61.5%) met the definition of mcSLEDAI-2K improvement. At month 12, 24/34 patients (70.6%) had improved while nine patients had withdrawn either due to allergic reactions ($n=2$), inadequate effect ($n=6$), or pregnancy plans ($n=1$); one patient had not reached the 12-month follow-up visit at the end of the observation. Nineteen patients (43.2%) had attained a mcSLEDAI-2K score of 0 at month 12. Twenty-seven patients had a CLASI activity score ≥ 1 at baseline; 20/26 patients (76.9%) met the definition of CLASI improvement at month 6, and 19/23 patients (82.6%) at month 12. None of these patients had a severe mucocutaneous disease (CLASI activity score ≥ 20) at month 12.

We observed decreased mcSLEDAI-2K scores from baseline to month 6 (mean: 1.1; range: 0–4; $P<0.001$) and month 12 (mean: 0.9; range: 0–6; $P<0.001$). We found decreased CLASI activity scores at month 6 (mean: 5.1; range: 0–25; $P<0.001$) and month 12 (mean: 3.3; range: 0–19; $P<0.001$) compared to baseline. Mucocutaneous activity was also found to decrease between month 6 and month 12 according to CLASI ($P=0.011$), but not according to mcSLEDAI-2K ($P=0.302$) (Figure 1). The percentages of patients presenting with each one of the individual descriptors of the mcSLEDAI-2K at the different follow-up time points are displayed in Figure 1.

In Figure 2, we display representative images to illustrate the treatment outcome with regard to cutaneous activity in three of the study participants.

3.2 Mucocutaneous damage

At baseline, the mean CLASI damage score was 1.1 (range: 0–6; n=33), and the mean SDI skin domain score was 0.24 (range: 0–2). We investigated potential change in mucocutaneous damage using the CLASI component for damage. We observed no significant worsening in the CLASI damage score through month 6 (mean score: 1.2; range: 0–6; P=0.655) or month 12 (mean score: 1.6; range: 0–10; P=0.102).

3.3 Analysis in relation to smoking status

Since mcSLEDAI-2K was available for all study participants, as opposed to CLASI which only was used at one of the centers, we based the investigation of the effects of smoking on mcSLEDAI-2K data only.

In total, 25/44 patients (56.8%) with mcSLEDAI-2K >0 at baseline had improved by month 12. Among current (n=4) and former smokers (n=13), seven patients improved in the mucocutaneous domain while 10 patients did not. In contrast, among patients who had never smoked (n=22), 18 patients improved and four patients did not (P=0.009; Pearson's chi-square test). In order to adjust for possible confounding factors, we conducted logistic regression analysis with mucocutaneous improvement as the dependent variable. The probability of poor response to belimumab was found to be more than six times higher in patients who had been exposed to tobacco smoking (odds ratio, OR: 6.4; 95% confidence interval, CI: 1.5–27.4; P=0.012), which remained unchanged and significant after

adjustment for antimalarial agents (OR: 6.6; 95% CI: 1.5–28.3; P=0.012). Accordingly, this interaction was still significant after separate adjustments for the SLE disease duration until baseline, as well as sex, age, number of disease-modifying antirheumatic drugs (DMARDs), use of glucocorticoids, prednisone equivalent dose (mg/day), and mucocutaneous SDI damage at baseline (Table 3). In a multivariate model, higher number of DMARDs tested until baseline (OR: 2.1; 95% CI: 1.1–4.0; P=0.017) and current or previous exposure to tobacco (OR: 5.3; 95% CI: 1.1–27.2; P=0.044) were independently associated with reduced treatment efficacy (Table 3). The corresponding forest plot is shown in Figure 3.

The low number of current smokers with baseline mcSLEDAI-2K >0 (n=4) limited us from conducting the same analysis for current versus former and never smokers. However, all four patients who currently smoked still had active mucocutaneous disease (SLEDAI-2K >0) at month 12.

3.4 Arthritis

At baseline, 29/62 (46.8%) patients had arthritis according to SLEDAI-2K. We observed an improvement (negative score shift) in 21/28 (75%) of these patients at month 6, and in 19/25 patients (76%) at month 12. When considering all patients, we observed decreased SLEDAI-2K scores for the arthritis domain both at month 6 (9/57 patients; 15.8%; P<0.001) and month 12 (6/49 patients; 12.2%; P<0.001) (Figure 1).

According to the 28-joint count, the mean tender joint count at baseline was 5.7 (range: 0–26; n=34) and the mean swollen joint count was 3.6 (range: 0–26; n=34), with five patients

having a severe joint involvement (≥ 8 tender and ≥ 8 swollen joints). At month 6, the respective counts had decreased to a mean of 2.7 (range: 0–15; n=32) for tender joints ($P=0.010$) and a mean of 0.7 (range: 0–8; n=32) for swollen joints ($P<0.001$). The observed decreases were sustained at month 12, with the mean tender joint count being 1.0 (range: 0–9; $P=0.001$; n=28) and the mean swollen joint count being 0.1 (range: 0–1; $P=0.001$; n=28) (Figure 1) (Table 2). Between month 6 and month 12, no further significant improvement was seen for either tender ($P=0.083$) or swollen ($P=0.141$) joints (Table 2). In one of the five patients with severe joint involvement at baseline, belimumab was discontinued earlier than 6 months of follow-up due to adverse events; two of the other four patients had improved by $\geq 50\%$ at month 6, and three at month 12.

In total, 20 patients displayed an articular improvement by month 12, defined as a negative SLEDAI-2K score shift for the arthritis descriptor; this was found to be irrespective of whether the patients had been exposed to tobacco smoking ($P=1.0$; Fisher's exact test).

4. Discussion

In the present study, we demonstrated that belimumab combined with standard of care therapy was an effective treatment strategy for limiting mucocutaneous and articular symptoms in a real-life clinical setting of SLE patients. Importantly, an association between tobacco smoking and poor clinical responses in mucocutaneous SLE was observed. Our findings provide important information with respect to previous reports of a negative impact of smoking on SLE disease activity and damage [14, 15], as well as on drug efficacy [19].

We recently reported decreasing disease activity and no significant organ damage progression during treatment with belimumab in the same clinical setting of SLE patients [26]. In the present subanalysis, we investigated the effects of belimumab on distinct organ domains, mucocutaneous manifestations and arthritis in particular. In conformity with previous findings of belimumab treatment preventing SLE damage accrual [26, 36, 37], we confirmed a preventive effect on mucocutaneous damage progression.

We observed improvements in the mucocutaneous domain at month 6 and month 12 from treatment initiation, assessed using the mucocutaneous descriptors of SLEDAI-2K (rash, alopecia, mucosal ulcers), as well as the skin-specific and SLE-specific measure CLASI. It is worth noting that assessments with CLASI displayed a greater sensitivity in detecting improvements in cutaneous disease compared to the mcSLEDAI-2K, capturing improvements even between month 6 and month 12, despite the fact that CLASI assessments were available in fewer patients. The superiority of CLASI over mcSLEDAI-

2K has been documented previously [35]; a reasonable explanation for this discrepancy might be that CLASI is a quantitative index using a continuous scale as opposed to SLEDAI-2K which demands total absence of symptoms for a negative score shift and no grading within the weight of a specific descriptor. From a clinical point of view, this points to the importance of the use of appropriate instruments for the evaluation of disease activity and treatment response in trials, as well as in clinical practice.

Another interesting finding was an association between current or previous exposure to tobacco smoking and reduced efficacy of belimumab in the mucocutaneous organ domain. Recently, we reported an association between smoking and a reduced and/or delayed efficacy of belimumab in relation to global SLE activity. In the present subanalysis, we found a direct effect of smoking on mucocutaneous outcomes while no impact on the arthritis domain was observed. These implications are in line with previous reports of tobacco smoking reducing the efficacy of antimalarial agents in cutaneous SLE [19, 20], but the underlying mechanism is poorly understood.

It is worth noting that the patients of the current study received belimumab as an add-on treatment to standard of care therapy, including antimalarial agents in the vast majority of the patients. Consequently, a concern that could be raised is whether our observations reflect an effect of smoking on the efficacy of the background therapy, antimalarial agents in particular, or a more specific effect on belimumab. However, no major changes were made in the background therapy during the observation period other than an intentional reduction of the glucocorticoid dosages, which supports the notion of a specific effect of smoking on the belimumab treatment. More importantly, our result was consistent after

adjustment for the use of antimalarial agents, where smoking still was found to reduce the probability of a beneficial mucocutaneous outcome with a factor 6.6. Furthermore, the association between smoking and mucocutaneous outcomes was not affected by the SLE disease duration, sex, age, number of DMARDs, use of glucocorticoids, prednisone equivalent dose, or skin damage at baseline. The mechanistic explanation of this phenomenon remains to be clarified. The hypothesis that smoking mediates the production of neutralizing anti-drug antibodies, as seen in multiple sclerosis [38, 39], might provide an explanation and warrants investigation. It is worth noting that higher numbers of DMARDs tested until baseline, reasonably reflecting a more severe disease course, were also associated with reduced treatment efficacy in mucocutaneous symptoms.

Belimumab treatment was also found to be effective in the arthritis domain. We observed improvements both in the arthritis descriptor of SLEDAI-2K and the 28-joint count, which were irrespective of smoking status. This contrasts with previous reports of tobacco exposed RA patients showing impeded responses to TNF inhibitors [13] and rituximab [40], and implies that the impact of smoking might differ depending on the underlying disease, possibly due to different immunologic milieus.

It has been hypothesized that smoking induces the development of anti-dsDNA antibodies [3] through increased apoptosis [7], a known effect of smoking [41], or immunogenicity to smoking-induced DNA adducts [3, 42, 43]. The obvious site where the tobacco smoke encounters the immune defense is the lungs, where a tobacco-induced influx of apoptosis-prone neutrophils may exist [41], providing self-antigens and triggering the production of autoantibodies. Although it remains unclear for how long after cessation this effect of

smoking may be sustained, an effect of tobacco on disease severity and therapy resistance might provide an explanation to the reduced efficacy of belimumab. However, the discrepancy in the impact of smoking on the efficacy of belimumab in cutaneous versus articular SLE has yet to be elucidated.

The documentation of efficacy of belimumab in mucocutaneous and articular manifestations in patients with SLE is not novel. Post-hoc analyses from randomized clinical trials of belimumab have shown that patients with these manifestations are more likely to respond to belimumab treatment [22], and consistent real-life experiences have also been reported [37, 44]. In the present study, we corroborated previous findings, and also showed that tobacco smoking may negatively impact the efficacy of belimumab on mucocutaneous manifestations. We also confirmed a previously documented superiority of the CLASI over mcSLEDAI-2K in detecting change [35]. Interestingly, continuous improvements after six months of treatment were documented for mucocutaneous but not articular manifestations, implying that early treatment evaluation by month 6 could be adequate for the arthritis domain, but might underestimate delayed skin improvements.

The observational design of the study, the low number of patients and the lack of a placebo arm constituted several of the limitations. Major strengths included the prospective assessment of the patients and the consistency of the surveillance tools used at the contributing centers. The real-life nature of our clinical setting might have limitations, but it eliminates the selection bias, and provides information that cannot be derived from clinical trials.

5. Conclusion and future perspective

In this prospective study, belimumab treatment combined with background therapy was efficacious in limiting mucocutaneous and articular symptoms in patients with SLE. Exposure to tobacco smoking was associated with reduced efficacy of belimumab on mucocutaneous SLE, but unlike RA treated with biologics no impact of smoking on the arthritis domain was documented. Further survey of the impact of smoking on the efficacy of belimumab at a mechanistic level is merited.

Authors' contributions

Study conception, design and coordination: IP, AG, IG

Acquisition of serum samples and clinical assessment: IP, CS, AJ, AZ, MF, AB, IG

Statistics and interpretation of the results: IP, AG, IG

Manuscript draft: IP, AG, CS, AJ, AZ, MF, AB, IG

All authors read and critically revised the manuscript for intellectual content, approved its final version prior to submission, and agree to be accountable for all aspects of the work.

Competing interests

The authors declare that they have no competing interests.

Availability of data and materials

The datasets used and analyzed during the current study are available from the corresponding author upon reasonable request.

Bibliography

Papers of special note have been highlighted as either of interest (•) or of considerable interest (••) to readers.

1. Ghaussy NO, Sibbitt WL, Jr., Qualls CR. Cigarette smoking, alcohol consumption, and the risk of systemic lupus erythematosus: a case-control study. *J Rheumatol.* 2001;28(11): 2449-53.
2. Costenbader KH, Kim DJ, Peerzada J, Lockman S, Nobles-Knight D, Petri M, et al. Cigarette smoking and the risk of systemic lupus erythematosus: a meta-analysis. *Arthritis Rheum.* 2004;50(3): 849-57. doi: 10.1002/art.20049
3. Freemer MM, King TE, Jr., Criswell LA. Association of smoking with dsDNA autoantibody production in systemic lupus erythematosus. *Ann Rheum Dis.* 2006;65(5): 581-4. doi: 10.1136/ard.2005.039438
4. Ekblom-Kullberg S, Kautiainen H, Alha P, Leirisalo-Repo M, Julkunen H. Smoking and the risk of systemic lupus erythematosus. *Clin Rheumatol.* 2013;32(8): 1219-22. doi: 10.1007/s10067-013-2224-4
5. Jiang F, Li S, Jia C. Smoking and the risk of systemic lupus erythematosus: an updated systematic review and cumulative meta-analysis. *Clin Rheumatol.* 2015;34(11): 1885-92. doi: 10.1007/s10067-015-3008-9
6. Versini M, Tiosano S, Comaneshter D, Shoenfeld Y, Cohen AD, Amital H. Smoking and obesity in systemic lupus erythematosus: a cross-sectional study. *Eur J Clin Invest.* 2017;47(6): 422-7. doi: 10.1111/eci.12757

7. Majka DS, Holers VM. Cigarette smoking and the risk of systemic lupus erythematosus and rheumatoid arthritis. *Ann Rheum Dis*. 2006;65(5): 561-3. doi: 10.1136/ard.2005.046052
8. Klareskog L, Padyukov L, Alfredsson L. Smoking as a trigger for inflammatory rheumatic diseases. *Curr Opin Rheumatol*. 2007;19(1): 49-54. doi: 10.1097/BOR.0b013e32801127c8
9. Karlson EW, Lee IM, Cook NR, Manson JE, Buring JE, Hennekens CH. A retrospective cohort study of cigarette smoking and risk of rheumatoid arthritis in female health professionals. *Arthritis Rheum*. 1999;42(5): 910-7. doi: 10.1002/1529-0131(199905)42:5<910::AID-ANR9>3.0.CO;2-D
10. Uhlig T, Hagen KB, Kvien TK. Current tobacco smoking, formal education, and the risk of rheumatoid arthritis. *J Rheumatol*. 1999;26(1): 47-54.
11. Stolt P, Bengtsson C, Nordmark B, Lindblad S, Lundberg I, Klareskog L, et al. Quantification of the influence of cigarette smoking on rheumatoid arthritis: results from a population based case-control study, using incident cases. *Ann Rheum Dis*. 2003;62(9): 835-41.
12. Saevarsdottir S, Wallin H, Seddighzadeh M, Ernestam S, Geborek P, Petersson IF, et al. Predictors of response to methotrexate in early DMARD naive rheumatoid arthritis: results from the initial open-label phase of the SWEFOT trial. *Ann Rheum Dis*. 2011;70(3): 469-75. doi: 10.1136/ard.2010.139212
13. Saevarsdottir S, Wedren S, Seddighzadeh M, Bengtsson C, Wesley A, Lindblad S, et al. Patients with early rheumatoid arthritis who smoke are less likely to respond to treatment with methotrexate and tumor necrosis factor inhibitors: observations from

the Epidemiological Investigation of Rheumatoid Arthritis and the Swedish Rheumatology Register cohorts. *Arthritis Rheum.* 2011;63(1): 26-36. doi: 10.1002/art.27758

14. Ghaussy NO, Sibbitt W, Jr., Bankhurst AD, Qualls CR. Cigarette smoking and disease activity in systemic lupus erythematosus. *J Rheumatol.* 2003;30(6): 1215-21.

15. Montes RA, Mocarzel LO, Lanzieri PG, Lopes LM, Carvalho A, Almeida JR. Smoking and Its Association With Morbidity in Systemic Lupus Erythematosus Evaluated by the Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index: Preliminary Data and Systematic Review. *Arthritis Rheumatol.* 2016;68(2): 441-8. doi: 10.1002/art.39427

16. Gustafsson JT, Gunnarsson I, Kallberg H, Pettersson S, Zickert A, Vikerfors A, et al. Cigarette smoking, antiphospholipid antibodies and vascular events in Systemic Lupus Erythematosus. *Ann Rheum Dis.* 2015;74(8): 1537-43. doi: 10.1136/annrheumdis-2013-205159

17. Turchin I, Bernatsky S, Clarke AE, St-Pierre Y, Pineau CA. Cigarette smoking and cutaneous damage in systemic lupus erythematosus. *J Rheumatol.* 2009;36(12): 2691-3. doi: 10.3899/jrheum.090403

18. Bourre-Tessier J, Peschken CA, Bernatsky S, Joseph L, Clarke AE, Fortin PR, et al. Association of smoking with cutaneous manifestations in systemic lupus erythematosus. *Arthritis Care Res (Hoboken).* 2013;65(8): 1275-80. doi: 10.1002/acr.21966

19. Chasset F, Frances C, Barete S, Amoura Z, Arnaud L. Influence of smoking on the efficacy of antimalarials in cutaneous lupus: a meta-analysis of the literature. *J Am Acad Dermatol*. 2015;72(4): 634-9. doi: 10.1016/j.jaad.2014.12.025

•• **A study addressing the impact of smoking on drug efficacy (antimalarial agents) in cutaneous SLE.**

20. Dutz J, Werth VP. Cigarette smoking and response to antimalarials in cutaneous lupus erythematosus patients: evolution of a dogma. *J Invest Dermatol*. 2011;131(10): 1968-70. doi: 10.1038/jid.2011.237

•• **An article about the impact of smoking on disease severity and drug efficacy (antimalarial agents) in cutaneous SLE.**

21. van Vollenhoven RF, Petri MA, Cervera R, Roth DA, Ji BN, Kleoudis CS, et al. Belimumab in the treatment of systemic lupus erythematosus: high disease activity predictors of response. *Ann Rheum Dis*. 2012;71(8): 1343-9. doi: 10.1136/annrheumdis-2011-200937

22. Manzi S, Sanchez-Guerrero J, Merrill JT, Furie R, Gladman D, Navarra SV, et al. Effects of belimumab, a B lymphocyte stimulator-specific inhibitor, on disease activity across multiple organ domains in patients with systemic lupus erythematosus: combined results from two phase III trials. *Ann Rheum Dis*. 2012;71(11): 1833-8. doi: 10.1136/annrheumdis-2011-200831

•• **A post-hoc analysis of data from two phase III trials of belimumab, demonstrating clinical efficacy across organ domains.**

23. Collins CE, Dall'Era M, Kan H, Macahilig C, Molta C, Koscielny V, et al. Response to belimumab among patients with systemic lupus erythematosus in clinical practice settings: 24-month results from the OBServe study in the USA. *Lupus Sci Med.* 2016;3(1): e000118. doi: 10.1136/lupus-2015-000118

24. Scheinberg M, de Melo FF, Bueno AN, Costa CM, de Azevedo Bahr ML, Reis ER. Belimumab for the treatment of corticosteroid-dependent systemic lupus erythematosus: from clinical trials to real-life experience after 1 year of use in 48 Brazilian patients. *Clin Rheumatol.* 2016;35(7): 1719-23. doi: 10.1007/s10067-016-3268-z

25. Schwarting A, Schroeder JO, Alexander T, Schmalzing M, Fiehn C, Specker C, et al. First Real-World Insights into Belimumab Use and Outcomes in Routine Clinical Care of Systemic Lupus Erythematosus in Germany: Results from the OBServe Germany Study. *Rheumatol Ther.* 2016. doi: 10.1007/s40744-016-0047-x

26. Parodis I, Sjowall C, Jonsen A, Ramskold D, Zickert A, Frodlund M, et al. Smoking and pre-existing organ damage reduce the efficacy of belimumab in systemic lupus erythematosus. *Autoimmun Rev.* 2017;16(4): 343-51. doi: 10.1016/j.autrev.2017.02.005

•• A real-life observational study of belimumab demonstrating a negative impact of smoking on belimumab efficacy.

27. Tan EM, Cohen AS, Fries JF, Masi AT, McShane DJ, Rothfield NF, et al. The 1982 revised criteria for the classification of systemic lupus erythematosus. *Arthritis Rheum.* 1982;25(11): 1271-7.
28. Petri M, Orbai AM, Alarcon GS, Gordon C, Merrill JT, Fortin PR, et al. Derivation and validation of the Systemic Lupus International Collaborating Clinics classification criteria for systemic lupus erythematosus. *Arthritis Rheum.* 2012;64(8): 2677-86. doi: 10.1002/art.34473
29. Gladman DD, Ibanez D, Urowitz MB. Systemic lupus erythematosus disease activity index 2000. *J Rheumatol.* 2002;29(2): 288-91.
30. Albrecht J, Taylor L, Berlin JA, Dulay S, Ang G, Fakharzadeh S, et al. The CLASI (Cutaneous Lupus Erythematosus Disease Area and Severity Index): an outcome instrument for cutaneous lupus erythematosus. *J Invest Dermatol.* 2005;125(5): 889-94. doi: 10.1111/j.0022-202X.2005.23889.x
31. Gladman D, Ginzler E, Goldsmith C, Fortin P, Liang M, Urowitz M, et al. The development and initial validation of the Systemic Lupus International Collaborating Clinics/American College of Rheumatology damage index for systemic lupus erythematosus. *Arthritis Rheum.* 1996;39(3): 363-9.
32. Fuchs HA, Brooks RH, Callahan LF, Pincus T. A simplified twenty-eight-joint quantitative articular index in rheumatoid arthritis. *Arthritis Rheum.* 1989;32(5): 531-7.

33. Choi CB, Liang MH, Bae SC. Progress in defining clinically meaningful changes for clinical trials in nonrenal manifestations of SLE disease activity. *Arthritis Res Ther*. 2016;18: 1. doi: 10.1186/s13075-015-0906-9
34. Klein R, Moghadam-Kia S, LoMonico J, Okawa J, Coley C, Taylor L, et al. Development of the CLASI as a tool to measure disease severity and responsiveness to therapy in cutaneous lupus erythematosus. *Arch Dermatol*. 2011;147(2): 203-8. doi: 10.1001/archdermatol.2010.435
35. Khamashta M, Merrill JT, Werth VP, Furie R, Kalunian K, Illei GG, et al. Sifalimumab, an anti-interferon-alpha monoclonal antibody, in moderate to severe systemic lupus erythematosus: a randomised, double-blind, placebo-controlled study. *Ann Rheum Dis*. 2016;75(11): 1909-16. doi: 10.1136/annrheumdis-2015-208562

• **This study has also documented a superiority of CLASI to SLEDAI-2K in terms of sensitivity in detecting change in mucocutaneous activity.**

36. Bruce IN, Urowitz M, van Vollenhoven R, Aranow C, Fettiplace J, Oldham M, et al. Long-term organ damage accrual and safety in patients with SLE treated with belimumab plus standard of care. *Lupus*. 2016;25(7): 699-709. doi: 10.1177/0961203315625119
37. Iaccarino L, Bettio S, Reggia R, Zen M, Frassi M, Andreoli L, et al. Effects of Belimumab on Flare Rate and Expected Damage Progression in Patients With Active Systemic Lupus Erythematosus. *Arthritis Care Res (Hoboken)*. 2017;69(1): 115-23. doi: 10.1002/acr.22971

38. Hedstrom AK, Alfredsson L, Lundkvist Ryner M, Fogdell-Hahn A, Hillert J, Olsson T. Smokers run increased risk of developing anti-natalizumab antibodies. Mult Scler. 2014;20(8): 1081-5. doi: 10.1177/1352458513515086

• **A study investigating effects of smoking on anti-drug development in another autoimmune disease (multiple sclerosis).**

39. Hedstrom AK, Ryner M, Fink K, Fogdell-Hahn A, Alfredsson L, Olsson T, et al. Smoking and risk of treatment-induced neutralizing antibodies to interferon beta-1a. Mult Scler. 2014;20(4): 445-50. doi: 10.1177/1352458513498635

• **A study investigating effects of smoking on anti-drug development in another autoimmune disease (multiple sclerosis).**

40. Khan A, Scott DL, Batley M. Smoking, rheumatoid factor status and responses to rituximab. Ann Rheum Dis. 2012;71(9): 1587-8. doi: 10.1136/annrheumdis-2012-201758

• **A study investigating potential associations between smoking and the efficacy of rituximab in patients with rheumatoid arthritis.**

41. Kirkham PA, Spooner G, Rahman I, Rossi AG. Macrophage phagocytosis of apoptotic neutrophils is compromised by matrix proteins modified by cigarette smoke

and lipid peroxidation products. *Biochem Biophys Res Commun*. 2004;318(1): 32-7. doi: 10.1016/j.bbrc.2004.04.003

42. Hung RJ, Boffetta P, Brennan P, Malaveille C, Gelatti U, Placidi D, et al. Genetic polymorphisms of MPO, COMT, MnSOD, NQO1, interactions with environmental exposures and bladder cancer risk. *Carcinogenesis*. 2004;25(6): 973-8. doi: 10.1093/carcin/bgh080

43. Wu X, Zhao H, Suk R, Christiani DC. Genetic susceptibility to tobacco-related cancer. *Oncogene*. 2004;23(38): 6500-23. doi: 10.1038/sj.onc.1207811

44. Vashisht P, Borghoff K, O'Dell JR, Heath-Holmes M. Belimumab for the treatment of recalcitrant cutaneous lupus. *Lupus*. 2017;26(8): 857-64. doi: 10.1177/0961203316682097

Figure legends

Figure 1. Response of the cutaneous and articular disease activity.

The figure depicts graphs of (A) cutaneous disease severity according to CLASI at baseline, month 6, and month 12, (B) response of the mucocutaneous domain according to the mcSLEDAI-2K (sum of mucocutaneous descriptors of SLEDAI-2K) and CLASI, (C) percentages of patients with individual SLEDAI-2K mucocutaneous and articular descriptors, and (D) response of the articular domain according to the 28-joint count. Data are presented as percentages, or means and error bars corresponding to 95% confidence intervals.

* $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$

LE: lupus erythematosus; SLEDAI-2K: systemic lupus erythematosus disease activity index 2000; CLASI: cutaneous lupus erythematosus disease area and severity index.

Figure 2. Response of the cutaneous disease activity in three patients.

The figure delineates representative images illustrating the response of subacute cutaneous lupus erythematosus activity during treatment with belimumab in three study participants.

mcSLEDAI-2K: sum of mucocutaneous descriptors of systemic lupus erythematosus disease activity index 2000; CLASI: cutaneous lupus erythematosus disease area and severity index.

Figure 3. Baseline predictors of poor response in the mucocutaneous domain.

Forest plot illustrating results from logistic regression analysis (Table 3). Vertical lines group variables analyzed together in multivariate models.

*P<0.05; **P<0.01

SLEDAI-2K: systemic lupus erythematosus disease activity index 2000; SDI: systemic lupus international collaborating clinics (SLICC)/American college of rheumatology (ACR) damage index; DMARDs: disease-modifying antirheumatic drugs.

Table 1. Baseline characteristics	
Sex; n=62	
<i>Female; N (%)</i>	57 (91.9)
Ethnicity; n=62	
<i>Caucasian; n (%)</i>	59 (95.2)
<i>African/African American; N (%)</i>	3 (4.8)
Age (years); M (IQR); n=62	42.7 (31.6–52.4)
SLE duration (years); M (IQR); n=62	7.73 (4.28–14.2)
SLEDAI-2K; M (IQR); n=60	8.0 (4.0–14.0)
Number of DMARDs tested until baseline*; M (IQR); n=62	3 (1–4)
Number of DMARDs at baseline*; M (IQR); n=62	1 (0–1)
<i>Azathioprine; N (%)</i>	20 (32.3)
<i>Mycophenolate; N (%)</i>	10 (16.1)
<i>Methotrexate; N (%)</i>	9 (14.5)
<i>Cyclosporine; N (%)</i>	2 (3.2)
Use of antimalarial agents at baseline; N (%); n=62	47 (75.8)
Use of glucocorticoids at baseline; N (%); n=62	58 (93.5)
Prednisone equivalent dose at baseline (mg/day); M (IQR); n=60	10.0 (7.5–15.0)
Mucocutaneous manifestations ever; n=62	60 (96.8)
Mucocutaneous manifestations at baseline; n=62	49 (79.0)
Arthritis ever; n=62	58 (93.5)
Arthritis at baseline; n=62	39 (62.9)
Smoking status at baseline; n=61	
<i>Current smokers; N (%)</i>	8 (13.1)
<i>Former smokers; N (%)</i>	21 (34.4)
<i>Never smokers; N (%)</i>	32 (52.5)
* Excluding antimalarial agents.	
SLE: systemic lupus erythematosus; SLEDAI-2K: SLE disease activity index 2000; DMARDs: disease-modifying antirheumatic drugs; M: median; IQR: interquartile range.	

Table 2. Results

Endpoint		N	Mean	Median	IQR	Range	P-value		
							0–6 months	0–12 months	6–12 months
mcSLEDAI-2K	Baseline	62	2.3	2.0	0.0–4.0	0–6	<0.001	<0.001	0.302
	Month 6	57	1.1	0.0	0.0–2.0	0–4			
	Month 12	49	0.9	0.0	0.0–2.0	0–6			
CLASI activity score	Baseline	33	8.4	7.0	1.5–12.5	0–39	<0.001	<0.001	0.011
	Month 6	32	5.1	2.0	0.0–7.0	0–25			
	Month 12	28	3.3	1.0	0.0–5.0	0–19			
CLASI damage score	Baseline	33	1.1	0.0	0.0–2.0	0–6	0.655	0.102	0.102
	Month 6	32	1.2	0.0	0.0–2.0	0–6			
	Month 12	28	1.6	0.0	0.0–2.8	0–10			
Tender joints count	Baseline	34	5.7	2.5	0.0–8.0	0–26	0.010	0.001	0.083
	Month 6	32	2.7	0.0	0.0–1.8	0–15			
	Month 12	28	1.0	0.0	0.0–1.5	0–9			
Swollen joints count	Baseline	34	3.6	1.0	0.0–5.0	0–26	<0.001	0.001	0.141
	Month 6	32	0.7	0.0	0.0–0.0	0–8			
	Month 12	28	0.1	0.0	0.0–0.0	0–1			

mcSLEDAI-2K: sum of the mucocutaneous descriptors of the systemic lupus erythematosus disease activity index 2000; CLASI: cutaneous lupus erythematous disease area and severity index; N: number of observations; IQR: interquartile range

Table 3. Baseline predictors of poor response in the mucocutaneous domain

	Coefficient	OR	95% CI		P-value
			Lower	Upper	
Univariate analyses					
Sex	1.879	6.545	0.610	70.231	0.121
Age at baseline (years)	0.023	1.023	0.969	1.080	0.410
Disease duration until baseline (years)	-0.001	0.999	0.903	1.105	0.986
Baseline SLEDAI-2K score	-0.058	0.944	0.829	1.074	0.379
Baseline mucocutaneous SDI score	0.878	2.406	0.650	8.910	0.189
Use of antimalarial agents at baseline	-0.087	0.917	0.183	4.583	0.916
Use of glucocorticoids at baseline	-0.201	0.818	0.120	5.595	0.838
Baseline prednisone equivalent dose (mg/day)	-0.025	0.976	0.905	1.052	0.521
Number of DMARDs* at baseline	0.275	1.317	0.341	5.076	0.690
Number of DMARDs* until baseline	0.781	2.183	1.252	3.806	0.006
Current or former versus never smokers	1.861	6.429	1.506	27.445	0.012
Multivariate models					
Sex	2.160	8.672	0.628	119.720	0.107
Current or former versus never smokers	1.986	7.285	1.538	34.498	0.012
Age at baseline (years)	0.006	1.006	0.946	1.069	0.851
Current or former versus never smokers	1.827	6.212	1.399	27.589	0.016
Disease duration until baseline (years)	-0.028	0.972	0.865	1.093	0.635
Current or former versus never smokers	1.931	6.897	1.549	30.713	0.011
Baseline SLEDAI-2K score	-0.032	0.968	0.846	1.108	0.639
Current or former versus never smokers	1.810	6.110	1.411	26.459	0.016
Baseline mucocutaneous SDI score	0.398	1.488	0.353	6.284	0.588
Current or former versus never smokers	1.740	5.696	1.260	25.755	0.024
Use of antimalarial agents at baseline	-0.275	0.760	0.127	4.550	0.764
Current or former versus never smokers	1.880	6.554	1.519	28.280	0.012
Use of glucocorticoids at baseline	0.615	1.850	0.220	15.583	0.571
Current or former versus never smokers	1.987	7.292	1.581	33.640	0.011
Baseline prednisone equivalent dose (mg/day)	-0.046	0.955	0.883	1.034	0.259
Current or former versus never smokers	2.073	7.948	1.734	36.427	0.008
Number of DMARDs* at baseline	1.039	2.826	0.565	14.134	0.206
Current or former versus never smokers	2.234	9.335	1.812	48.086	0.008
Number of DMARDs* until baseline	0.760	2.139	1.149	3.984	0.017
Current or former versus never smokers	1.676	5.344	1.050	27.208	0.044

Results from logistic regression analysis.

*Excluding antimalarial agents.

SLEDAI-2K: systemic lupus erythematosus disease activity index 2000; SDI: systemic lupus international collaborating clinics (SLICC)/American college of rheumatology (ACR) damage index; DMARDs: disease-modifying antirheumatic drugs; OR: odds ratio; CI: confidence interval.

Patient 1

Baseline

CLASI activity: 21
mcSLEDAI-2K: 4

Month 6

CLASI activity: 18
mcSLEDAI-2K: 4

Month 12

CLASI activity: 6
mcSLEDAI-2K: 4

Month 24

CLASI activity: 3
mcSLEDAI-2K: 2

Patient 2

Baseline

CLASI activity: 25
mcSLEDAI-2K: 4

Month 18

CLASI activity: 11
mcSLEDAI-2K: 2

Patient 3

Baseline

CLASI activity: 39
mcSLEDAI-2K: 6

Month 12

CLASI activity: 7
mcSLEDAI-2K: 2