

Patient Satisfaction And Disease Control In Patients With Systemic Lupus Erythematosus Is Not Affected By Switching From Intravenous Belimumab To Subcutaneous Injections

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Purpose: Since the launch of belimumab in 2011, the BLYS antibody has been increasingly used in the therapy of systemic Lupus erythematosus (SLE). Comparative studies showed that the intravenous (i.v.) and subcutaneous (s.c.) administration forms do not differ in their efficacy. Since the approval of the s.c. therapy, many patients have been switched from i.v. to s.c. administration. The clinical course of these patients and their satisfaction regarding the drug have not yet been investigated.

Methods: A total of 9 patients with SLE were switched from i.v. to s.c. belimumab between 12/2017 and 03/2018. We assessed a self-developed questionnaire on drug satisfaction, disease activity (SLEDAI-2k), serological activity (leukocytes, DNA antibodies, complement), disease damage (SLICC/ACR damage index) and functional status (health-assessment questionnaire) at switching (T0) and after 6 months (T1). Association of the questionnaires with the form of administration (i.v. vs s.c.) was analyzed for each variable separately by linear regression analyses, adjusted for age, gender and disease duration.

Results: At switching, disease activity of all patients was well controlled (median SLEDAI-2k = 2 [Interquartile range 0–4]) and the patients were mainly satisfied with their therapy. No evidence for any difference in disease activity, disease damage or patient satisfaction 6 months after switching was found. In tendency, patients were more satisfied with the s.c. administration.

Conclusion: The switch from i.v. to s.c. belimumab was successful in all cases and had no effect on disease activity or patient satisfaction. Despite the small sample size, s.c. belimumab seems to offer a good alternative to i.v. application.

Keywords: SLE, patient satisfaction, b-cell therapy, BLYS-antibody

Introduction

Belimumab, the fully human monoclonal inhibitor of the B-lymphocyte stimulator (BlyS) has been approved in 2011 for the treatment of adult patients with active, autoantibody-positive systemic lupus erythematosus (SLE) as an add-on to standard-of-care therapy. The first approved biological drug for SLE has been shown to positively affect disease activity, especially mucocutaneous, musculoskeletal and immunological manifestations, damage accrual and serological activity.^{1–3} In addition, there is evidence, that health-related quality of life and other patient-reported outcomes significantly improve with belimumab treatment.⁴ Until 2017 belimumab was only

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available as an intravenous (i.v.) medication, administered monthly at a dosage of 10 mg/kg. Intravenous administration requires a significant amount of time for the predominantly young and working patients, which can, among other things, burden the relationship between employer and employee. In addition to an increased workload for the attending physicians, monitored infusion units must be provided.

In 2017, subcutaneous (s.c.) belimumab was approved by FDA (07/2017) and EMA (11/2017) at a dosage of 200 mg weekly, based on the placebo-controlled BLISS-SC study.⁵ Since then many patients have been switched to s.c. administration. Indirect comparisons showed a similar efficacy of i.v. and s.c. administration.⁶ Nonetheless, the clinical course of patients switched from i.v. to s.c. and their satisfaction with the drug has not yet been investigated. In this research, we aimed at monitoring patients in our clinic switched from i.v. to s.c. belimumab over a period of 6 months with regard to disease activity, damage, functional status and satisfaction with the drug.

Methods

The study was approved by the local ethics committee of the Medical Faculty at Heinrich-Heine-University Duesseldorf (#2019-410) and conformed to the provisions of the Declaration of Helsinki. Inclusion criteria were a diagnosed SLE as defined by the 1997 ACR criteria and a switch from i.v. belimumab treatment to s.c. application between 12/2017 and 03/2018. S.c. belimumab was first administered 4 weeks after the last belimumab infusion. We analyzed disease activity using the SLEDAI-2k, disease damage via the SLICC/ACR damage index (SDI), as well as functional status (health assessment questionnaire, HAQ) and a self-designed questionnaire about patient satisfaction assessed at switching (T0) and 6 months after (T1) as part of our clinical routine diagnostics. Medication adherence was indirectly assessed by prescription renewal rates which were due every 3 months. No separate written informed consent was necessary.

Questionnaire About Patient Satisfaction

The questionnaire comprised 5 questions at T0 and T1, with an additional, sixth question at T1. The first 5 questions addressed symptom improvement, practicability of the administration route, improvement in coping with the daily routine, happiness with the drug and general satisfaction with all lupus-related drugs. The additional question at T1 asked if the patient was planning to continue s.c. belimumab treatment in the future. All questions were

answered on a 5-point Likert Scale from 0 to 4 (0= no agreement, 4 = to a great extend) and were evaluated separately. The questionnaire was newly developed for this study and has not been validated before.

Statistical Analysis

Data management and analyses were performed using R Version 3.5.0 (The R Foundation for Statistical Computing) with a significance level of $\alpha=0.05$. Descriptive data are presented either as median and 1st quartile – 3rd quartile (Interquartile range IQR= Q_1-Q_3) for skewed variables or mean and standard deviation (SD) for symmetric variables. Linear regression analyses were performed for each variable (HAQ, SLEDAI, SDI, complements, ds-DNA) separately to identify an association with the type of administration, adjusted for age, gender and disease duration.

Results

Clinical And Demographic Baseline Data

From December 2017 to March 2018, a total of 9 patients in our clinic were receiving monthly belimumab infusions. All 9 patients (8 females, 1 male) had anticipated the approval of s.c. belimumab and were switched to s.c. treatment as a result of shared-decision making. In no case, either physician or patient refused the treatment change. The patients had a median age of 45 years (IQR 38–51) with a median disease duration of 19 years (IQR 18–26). Median duration on i.v. belimumab at T0 was 4 years (IQR 2.3–4.4). At T0, disease activity of all patients was well controlled with a median SLEDAI-2k of 2 (IQR 0–4) and damage was low with a median SDI of 1 (IQR 0–2) (Table 1). At T0, patients were highly satisfied with their i.v. belimumab therapy (Figure 1).

Clinical Course And Satisfaction From T0 To T1

Six months after switching, disease activity was similar with a median SLEDAI-2k of 2 (IQR 2–4). There was no damage accrual over the course of 6 months (median SDI = 1, IQR 0–2) and functionality remained stable with a mean HAQ score of 0.6 (SD 0.3). No flares were recorded during the observation period. One female patient was very satisfied with the i.v. application form, whereas she considered the s.c. application route not at all convenient. Reason for this was a general discomfort and aversion to self-injections in this patient. Furthermore, in her assessment, the patients confirmed that the advantages of subcutaneous therapy (flexibility, no days absent from work due to infusions) outweighed her discomfort.

Table 1 Patient Characteristics At T0

Age in years, median (IQR)	45 (38–51)
Disease duration in years, median (IQR)	19 (18–26)
Duration of i.v. belimumab-therapy in years, median (IQR)	4.0 (2.3–4.4)
HAQ, mean (SD)	0.71 (0.4)
SLEDAI-2k, median (IQR)	2 (0–4)
SDI, median (IQR)	1 (0–2)
ds DNA-antibody (ELISA), mean (SD)	354.9 (255.9)
C3c in mg/dL, mean (SD)	91.38 (18.2)
C4 in mg/dL, mean (SD)	16 (7.9)
WBC in 1000/ μ L, mean (SD)	5.9 (1.7)

Abbreviations: IQR, interquartile range; SD, standard deviation; SDI, SLICC ACR damage index; SLEDAI-2k, systemic lupus erythematosus disease activity index 2000I; WBC, white blood cells.

Despite this patient’s anxiety of self-injections, all patients stated the strong intention to continue their subcutaneous belimumab treatment in the future.

Drug prescriptions were renewed as required (every 12 weeks) by all patients, which indicates a good adherence.

Linear Regression Analyses

Linear regression analysis revealed no evidence for any difference in disease activity (SLEDAI-2k) ($p=0.4$), disease

damage (SDI, $p=1.0$) or patient satisfaction 6 months after switching ($p=0.2-0.6$, for each question). Satisfaction seemed to be higher with the s.c. administration form although not statistically significant.

Regarding serological activity, there was evidence of an improvement of complement levels (C3c and C4) as well as ds-DNA-antibody levels over time ($p<0.005$ for C3c and C4, $p<0.05$ for ds-DNA-antibodies) (Table 2). After the exclusion of cases with normal levels at both time-points, no association was seen (data not shown).

Discussion

Since its approval, belimumab, as the only biological drug for SLE, has been a safe option for patients with active, antibody-positive SLE refractory to standard treatment. With the market authorization for the s.c. application, treatment with belimumab has become much more convenient. Prior studies reported a good efficacy and similar safety compared to placebo for both intravenous and subcutaneous application.^{1,5,7} The clinical course in patients who were switched from i.v. to the s.c. application of belimumab has not been systematically looked at. This

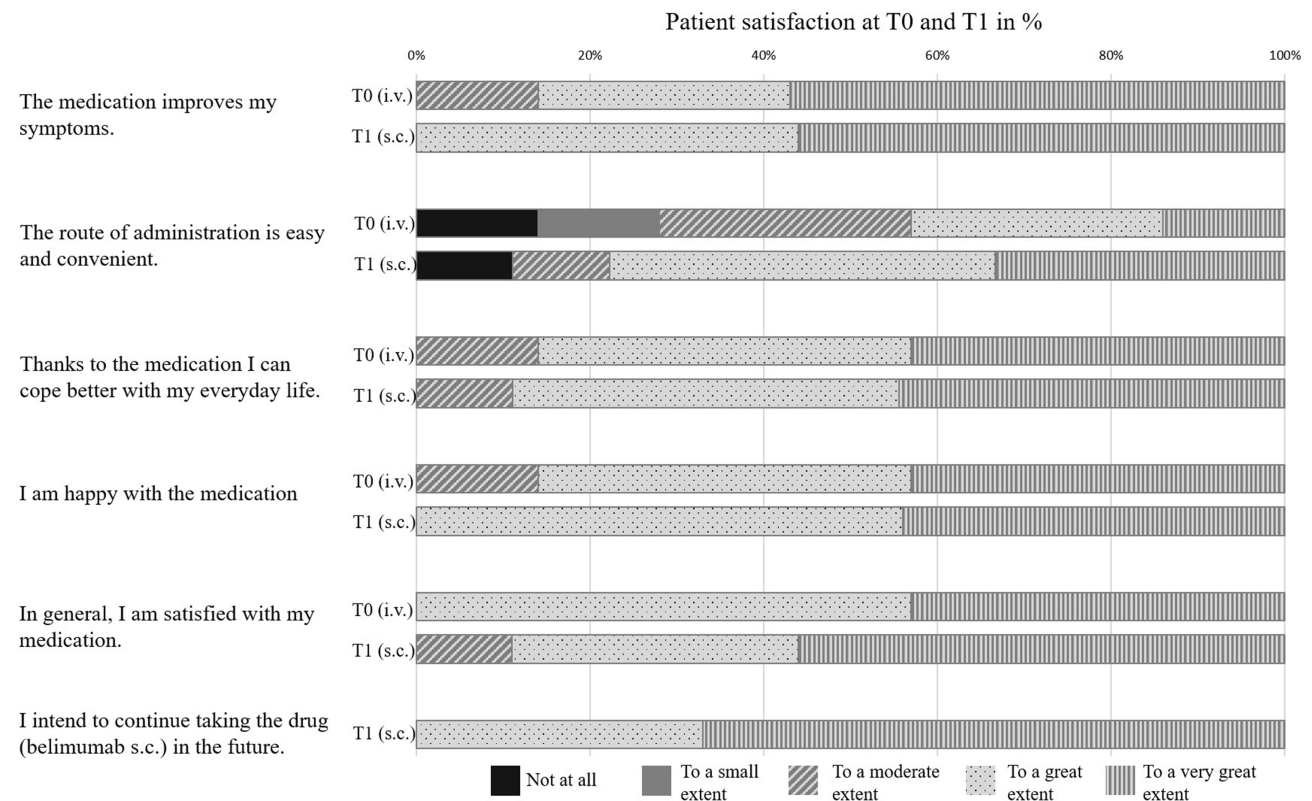


Figure 1 Drug satisfaction at T0 and T1 in percent.

Table 2 Clinical Parameters And Functional Status At T0 (i.v. belimumab) And T1 (S.c. belimumab). Linear Regression Analysis Was Applied To Identify An Association Of Parameters With The Route Of Administration (i.v. vs. s.c.)

	i.v. (T0)	s.c. (T1)	p-value
HAQ, mean (SD)	0.71 (0.4)	0.62 (0.3)	p = 0.3
SLEDAI-2k, median (IQR)	2 (0–4)	2 (2–4)	p = 0.4
SDI, median (IQR)	1 (0–2)	1 (0–2)	p = 1.0
ds DNA-antibody (ELISA), mean (SD)	354.9 (255.9)	284.3 (261.0)	p = 0.014
C3c in mg/dL, mean (SD)	91.4 (18.2)	93.3 (18.1)	p < 0.0001
C4 in mg/dL, mean (SD)	16.0 (7.9)	16.9 (8.4)	p = 0.004

Note: p-values in bold indicate an impact of the administration route on the tested parameters, $p < 0.05$.

Abbreviations: HAQ, health assessment questionnaire; IQR, interquartile range; SD, standard deviation; SDI, SLICC ACR damage index; SLEDAI-2k, systemic lupus erythematosus disease activity index 2000; WBC, white blood cells.

research gives a first impression of the course of patients regarding their clinical parameters, functional status and satisfaction 6 months after switching.

All nine patients had anticipated the approval of s.c. belimumab and agreed on switching the treatment, which was supported by their treating physicians. In all patients, disease activity and functional status remained stable over the course of 6 months and no damage accrual was recorded. Interestingly, the serological parameters C3c, C4 and ds-DNA-antibody improved with the treatment switch. However, this finding could not be replicated after the exclusion of patients with normal C3c, C4 and dsDNA-antibody levels both at T0 (with i.v. administration) and T1 (s.c. application) and hence non-relevant changes of serological parameters over time. As shown before, belimumab treatment does reduce antibody-levels and sustainably normalizes serological activity.³ Nonetheless, the effect on serological markers has never been investigated systematically in i.v. compared to s.c. belimumab. Based on previous indirect comparisons, we do not expect one application form to perform better than the other neither in improving clinical nor serological activity.⁶ Accordingly, we did not find evidence for a stronger effect of s.c. belimumab on serological markers. Extended analyses should focus on changes in B-cell levels and total IgG levels in these patients.

Regarding patient satisfaction, no significant changes were recorded with s.c. belimumab. This is somewhat surprising since s.c. application is usually considered to be more convenient, less time-consuming and better to integrate into patients' daily routine than i.v. infusions. In

contrast, i.v. administration is sometimes preferred due to the reassuring effect of the doctors presence and the safety and convenience of hospital administration.⁸ A recent study, assessing the satisfaction with the belimumab auto-injector in 43 patients who were switched from either i.v. or s.c. prefilled syringes over a course of 8 weeks reported that 96% preferred the auto-injector over i.v. infusion due to convenience.⁹ Nonetheless, 62% reported disadvantages of the s.c. application, that was mainly discomfort at the injection site and pain. Main reason for the preference of i.v. infusions was the perception of a better feeling using intravenous application, which again suggests a reassuring effect of the administration route.⁹ However, studies assessing patient's preferences and satisfaction with TNF- α -inhibitor treatment in rheumatoid arthritis (RA) found a discrepancy in patients already on treatment compared to treatment naïve patients. The latter preferred s.c. treatment over i.v. infusions (47% vs 27%), whereas 27% had no preference.¹⁰ In contrast, patients already on treatment preferred their current treatment administration over an alternative route given that effectiveness, adverse effects and financial costs were the same (85% for i.v., 71% for s.c.).¹¹ In addition and as a contrast to our study, the change from i.v. TNF- α inhibition to s.c. applications always involves a change in substance. The RIVIERA study revealed a similar distribution of RA patients' preference of i.v. and s.c. drug administration.⁸ When offered a switch from i.v. to s.c. on the same drug, 45% of RA patients with either tocilizumab or abatacept favored to stay on the i.v. treatment.¹² To the best of our knowledge, patient satisfaction before and after a switched from i.v. to s.c. administration of the same drug has not yet been looked at.

In our cohort overall satisfaction with the long-term i.v. treatment was already high, so that the achievement of higher satisfaction levels was hampered. Importantly, satisfaction did not decrease over time and all patients intended to continue their s.c. treatment in the future.

Regarding disease activity, Dashiell-Aje et al found some evidence for symptom amelioration in patients using the auto-injector with 40% reporting disease improvement and 21% deterioration. In 33% no change was noticed.⁹ However, we could not find any evidence for an association of disease activity and short-time damage accrual with the type of administration. In contrast to our series, the above-mentioned study assessed only the subjective change in symptoms, which might differ from objective outcome measures. Also, patients were assessed

after 8 weeks of treatment, a rather short-time period. Three approval studies BLISS-52, BLISS-76 and BLISS-SC showed a similar efficacy of i.v. and s.c. treatment, thus a switch should not affect outcome parameters.^{1,5,13} Nonetheless, systematic studies with greater number of patients are needed to investigate this subject.

This research has some limitations. The small sample size and the short follow-up period of 6 months allow for assumptions rather than definite statements. However, we did not see distinct variations in our sample characteristics regarding disease activity, damage or functional status, indicating a homogeneous patient cohort. All patients included had a longstanding, well-controlled disease and already several years of i.v. belimumab treatment. Therefore, our results do not permit any conclusions for active and/or newly diagnosed patients and clinical improvement was practically impossible in our patients. Furthermore, we can only indirectly deduce good adherence from prescription data. All patients renewed their prescriptions after 12 weeks, which is the amount of time covered by one prescription. Consequently, no patient was without prescription and the option to obtain the drug at any time. However, we cannot use this method to identify patients who do not redeem their prescriptions or do not take their medication. In the personal conversations, there were no additional hints for non-adherence. Unfortunately, the measurement of blood levels as the most reliable adherence measure is not commercially available for belimumab.

Conclusion

In summary, the switch from i.v. belimumab to s.c. application was successful in all 9 cases and had no effect on patient satisfaction or disease activity. Despite the small sample size, belimumab seems to offer a good alternative to i.v. application, especially in cases with longstanding and well-controlled disease.

Author Contributions

JM, GC, RB and MS conceptualized the study; JM, RFB, JGR, OS and GC did data acquisition; JM, RB, GC and MS analyzed the data; JM, GC and RB drafted the manuscript and RFB, OS, JGR and MS critically analyzed and revised the manuscript. All authors gave their final approval for the manuscript being published and agreed to be accountable for all aspects of the work.

Disclosure

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