


# Preference for Subcutaneous Injection or Intravenous Infusion of Biological Therapy Among Italian Patients With SLE

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## Abstract

This article focuses on the patients' acceptance of a subcutaneous injection device for patients with systemic lupus erythematosus, which in the upcoming years could be introduced beside the intravenous infusion of biological therapy. An online questionnaire was completed by 548 patients from different Italian regions. The preference for subcutaneous injection was 41.2%, for intravenous infusion was 36.9%, and 21.9% were uncertain. Patients with previous experience of biological therapies were less uncertain ( $P = .001$ ). The reported motivations for the preference were analyzed through a lexicometric approach with the software T-LAB. Results revealed that respondents who preferred subcutaneous injections reported motivations that were more related to convenience, avoiding the discomfort of reaching the hospital. Patients who preferred intravenous infusion emphasized the importance of safety feelings related to the presence of qualified assistance during the therapy administration. In conclusion, patients appreciated the convenience that characterizes subcutaneous injections but also emphasized the importance of feeling safe during the administration. The study suggests that the choice of prescribing subcutaneous injections or intravenous infusions should be shared with patients, discussing possible resistances and avoiding preconceptions about patients' preferences.

## Keywords

injection, infusion, preference, patients' experience, lupus

## Introduction

Systemic lupus erythematosus (SLE) is a chronic progressive autoimmune disease that can affect any organ, including the skin, kidneys, lungs, brain, heart, and joints. SLE exhibits considerable variation in its manifestations between individuals, generally alternating periods of intense flares and periods of remission, and it normally requires long-term therapies (1,2).

The pathogenesis of SLE involves multiple components of the immune system including B cells, T cells, cytokines, and growth factors. In recent years, new therapeutic agents targeting these mediators selectively have been tested for the treatment of SLE. However, despite the enthusiasm in the field of biologic therapies, only few of them met their primary outcome in phase 3 trials (3). The treatment of belimumab plus standard therapy in patients with SLE has been studied extensively in recent years (4). The results suggest that treatment with belimumab plus standard therapy is more effective than placebo plus standard therapy in patients with SLE, which represents major progress in the treatment of

SLE (4,5). Also rituximab has been shown to be effective in the treatment of nonrenal SLE, especially in terms of disease activity, immunologic parameters, and steroid-sparing effect. However, it can only be recommended for organ-specific manifestations such as arthritis and thrombocytopenia and an open debate exists about the role of rituximab in the treatment of lupus nephritis (5).

The long-term efficacy of any therapy, particularly a biological therapy, is significantly influenced by the degree of adherence to the therapeutic regimen (6). At this regard, patients' preference of a specific medication administration route should be carefully considered by clinicians, because

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patient preference will ensure optimal treatment adherence and ultimately improve patient experience or satisfaction (7).

In patients with SLE, the abovementioned biologic therapies have been delivered through intravenous infusion, which usually takes place in a day hospital regime. This article focuses on the patients' intention to opt for a subcutaneous injection route, which in the upcoming years will be probably introduced beside the intravenous infusion. The subcutaneous injection would allow patients to self-administer the therapy at home. At least for belimumab in lupus, the evidences about the efficacy of a subcutaneous injecting device are very promising (8,9). At this regard, initial trials of a single dose of subcutaneous belimumab in healthy volunteers, self-administered using the autoinjector or prefilled syringe, demonstrated acceptable pharmacokinetic, tolerability, reliability, usability, and safety profiles (10). Moreover, a subsequent phase II, open-label, single-arm, multidose study of subcutaneous belimumab in patients with SLE in real-life conditions demonstrated that the autoinjector was reliable and well tolerated for home administration (11). A recent study with a group of patients with SLE ( $n = 42$ ) showed also that, among the 42 patients who switched from intravenous belimumab to the autoinjector, 76% expressed a preference for the autoinjector over intravenous administration (12).

The specific aim of this large-scale survey study was to explore the preference for the adoption of a subcutaneous injection device (vs the intravenous infusion) and the reported motivations behind this choice. The reported preferences were considered in relation to participants' age, time from diagnosis, and past experience of biologic therapy.

## Methods

### Procedure

This survey, which consisted of a 15-minute, online questionnaire, was designed to assess patient perceptions and preferences for the subcutaneous injections compared with the intravenous infusion of biologics. The survey was conducted between May and June 2017 in Italy. The link to the survey was published on the website of the organization "Lupus Italy" and in its official newsletter. The questionnaire was anonymous, and no identifying information was collected. The eligible criteria were having diagnosis of SLE and being able to complete a short online questionnaire in Italian. The survey was approved by the board of the national patients' organization and was performed in accordance with international ethical standards, data protection laws, and data privacy legislation.

### The Questionnaire

The first draft of the questionnaire was developed by the authors and was then subject to 2 rounds of piloting with 5 patients each. The revisions to the questionnaire were made both in terms of clarity and presentation. The following areas were assessed.

*Demographic* information was collected including gender, age (years), years from diagnosis (YFD), and Italian region of residence.

*Past experience* was assessed asking if, in their past, the doctor has ever prescribed a biological therapy, such as rituximab and/or belimumab (possible answers: 0 = no; 1 = yes).

*Preference* for subcutaneous injection or intravenous therapy was assessed with the following question: "In case you were asked to express your preference for the way of receiving a biological therapy, what of the following would you prefer?". Possible answers were "A weekly subcutaneous self-administered, at home," "A monthly intravenous infusion, in clinic," "I don't know".

Finally, *motivations* for the reported preference were assessed through an open question, leaving the respondents to freely express their views.

## Data Analysis

The first group of analyses focused on patients' preference and it considered if the preference for a specific delivery was associated with gender, age-group, YFD, and past experience of biological therapy. For univariate analyses,  $\chi^2$  was used, while for multivariate analysis, we used logistical regression. Analyses were performed through the software SPSS 21.

The second group of analyses focused on the reported motivations for the preference and was conducted with the software T-LAB (version 9.1). This software represents a set of linguistic and statistical tools for content analysis and text mining (13,14). The textual corpus under analysis was made of all the open answers that were provided as motivation for the expressed preference. Through the tool "specificity analysis," it was possible to identify the "typical" keywords (ie, statistically overused words, through the use of  $\chi^2$  test) in a corpus subset defined by a categorical variable. In the specific context of our study, we identified keywords that were typical of the respondents who preferred infusions and keywords that were typical of the respondents who preferred subcutaneous injections.

## Results

A total of 562 questionnaires were collected. After a preliminary check of the data, 14 cases were excluded because they were incomplete or did not meet the eligible criteria. The final sample thus consisted of 548 patients. The regions of the respondents covered the different country areas: 30.9% northwest, 11.7% northeast, 22.4% Center, and 35.0% south and islands.

Females were 95.6% of the sample. The mean age of the respondents was 43.09 ( $\pm 11.57$ ) years. The lower limit was 18 and the upper was 74. For the following analyses, the sample was divided into 2 numerically homogeneous age

**Table 1.** Preference for Biological Therapy in Specific Subgroups.

| Variable             | Preference for Biological Therapy |                      |              | $\chi^2$ | P Value |
|----------------------|-----------------------------------|----------------------|--------------|----------|---------|
|                      | Subcutaneous Injection            | Intravenous Infusion | I Don't Know |          |         |
| Gender               |                                   |                      |              |          |         |
| Male                 | 45.8%                             | 25.0%                | 29.2%        | 1.69     | .429    |
| Female               | 41.0%                             | 37.4%                | 21.6%        |          |         |
| Age-group            |                                   |                      |              |          |         |
| 18-42 years          | 44.8%                             | 36.2%                | 19.0%        | 4.00     | .135    |
| 43-74 years          | 37.5%                             | 37.5%                | 24.9%        |          |         |
| Years from diagnosis |                                   |                      |              |          |         |
| 1-12 years           | 40.0%                             | 37.1%                | 22.9%        | 0.47     | .790    |
| 13-50 years          | 42.5%                             | 36.6%                | 20.9%        |          |         |
| Past experience      |                                   |                      |              |          |         |
| No                   | 40.2%                             | 33.8%                | 26.0%        | 14.24    | .001    |
| Yes                  | 43.9%                             | 44.5%                | 11.6%        |          |         |

groups: 18 to 42 (50.9% of cases) and 43 to 74 years old (49.1% of cases).

Years from diagnosis were, on average, 13.85 ( $\pm 9.60$ ) ranging from around 1 to 50. For the following analyses, participants were divided into 2 groups: 1 to 12 YFD (50.2%) and 13 to 50 YFD (49.8%). As regards past experience, 28.3% of respondents reported that, during their life with the illness, they received the proposal of a biological therapy.

### Preference for Subcutaneous Injection Versus Intravenous Infusion

The preference for a subcutaneous injection device was 41.2%. The preference for an intravenous delivery was 36.9%. Finally, 21.9% of respondents “didn’t know.” Table 1 presents the distribution of preferences according to gender, age-group, YFD, and past experience of biological therapies. Patients who had at least some experience with biological treatment showed less uncertainty in the preference for injections or infusions (ie, a lower percentage of “I don’t know” answers).

In a second analysis, we performed a logistic regression to assess the specific contribution of each of the variables in Table 1, on the preference for subcutaneous injection or intravenous infusion. None of the variables showed a significant effect in the final model (data not shown).

### Motivations for Preferring Subcutaneous Injection or Intravenous Infusion

Participants who clearly expressed a preference (for intravenous infusion or subcutaneous injection) had the opportunity to motivate their choice in an open-ended question. The answers provided by these participants were analyzed

**Table 2.** The 10 Most Overused Words by the Respondents Who Prefer Intravenous Infusions.<sup>a</sup>

| Word              | Total Occurrences | Occurrences in the Sample of Patients Who Prefer Infusions | $\chi^2$ | P Value |
|-------------------|-------------------|--|----------|---------|
| sentire/To feel   | 54                | 47 (87.04%)  | 33.89    | <.001   |
| controllo/control | 22                | 21 (95.45%)  | 19.93    | <.001   |
| personale/staff   | 19                | 18 (94.74%)  | 16.65    | <.001   |
| tranquillo/quiet  | 19                | 18 (94.74%)  | 16.65    | <.001   |
| medico/doctor     | 24                | 21 (87.50%)  | 15.05    | <.001   |
| effetto/effect    | 19                | 15 (78.95%)  | 7.25     | .007    |
| paura/fear        | 9                 | 8 (88.89%)   | 5.98     | .014    |
| puntura/puncture  | 22                | 16 (72.73%)  | 5.34     | .021    |
| infermiere/nurses | 10                | 8 (80.00%)   | 4.05     | .044    |

<sup>a</sup>Both the English translation and the original Italian words are reported.

through a lexicometric approach. In the following paragraphs, we describe the content of the motivations that were reported by respondents who preferred intravenous infusions and by respondents who preferred subcutaneous injections.

**Motivations for preferring intravenous infusions.** Table 2 presents the words that were statistically overused by the patients who reported their preference for the intravenous infusion. These words emphasize some of the perceived main advantages of receiving the medication through intravenous infusion, such as feeling safe and quite during the infusion, thanks to the assistance of qualified staff (doctors and nurses) who are responsible of the procedure and can intervene in case of unexpected side effects. The following 3 quotes are examples of typical answers provided by patients who reported their preference for intravenous infusion.

I would *feel* more *quiet*, because I would be *assisted* by a qualified *staff*. (Female, 53 years)

I would *feel* more *safe* against possible *side effects*. (Female, 58 years)

The *presence* of *nurses* and *medical* equip would give me more *safety*. (Female, 36 years)

**Motivations for preferring subcutaneous injections.** Table 3 presents the words that were statistically overused by the patients who reported their preference for subcutaneous injections. These words emphasize some of the reported main advantages of receiving the medication through subcutaneous injections, which resides in the higher comfort and convenience of managing the medication at home (avoiding the hospital), having more time for a possible job. The

**Table 3.** The 10 Most Overused Words by the Respondents Who Prefer Subcutaneous Injections.

| Word                      | Total Occurrences | Occurrences in the Sample of Patients Who Prefer Subcutaneous Injections | $\chi^2$ | P Value |
|---------------------------|-------------------|--|----------|---------|
| comodo/<br>comfortable    | 26                | 25 (96.15%)  | 21.03    | <.001   |
| comodità/<br>comfort      | 23                | 22 (95.65%)  | 18.14    | <.001   |
| ospedale/<br>hospital     | 95                | 69 (72.63%)  | 18.07    | <.001   |
| casa/house                | 36                | 30 (83.33%)  | 14.87    | <.001   |
| lavoro/job                | 13                | 12 (92.31%)  | 8.68     | <.001   |
| tempo/time                | 30                | 23 (76.67%)  | 7.68     | .007    |
| gestire/to<br>manage      | 14                | 12 (85.71%)  | 6.57     | .014    |
| evitare/to avoid          | 19                | 15 (78.95%)  | 5.74     | .021    |
| praticità/<br>convenience | 11                | 9 (81.82%)   | 4.04     | .044    |
| cura/cure                 | 11                | 9 (81.82%)   | 4.04     | .044    |

following 3 quotes are examples of typical answers provided by patients who reported their preference for subcutaneous injections.

To avoid losing a working day to go to the hospital. (Female, 32 years).

I think it is easier for the patient, without going to the hospital which is quite far. (Female, 51 years)

Because I believe that managing autonomously the therapy, rather than at hospital is more comfortable. (Female, 31 years)

## Discussion

The present study focused on a largely unexplored issue, that is, the SLE patients' point of view on the possibility to use subcutaneous intravenous injections for new biological therapies. Our study showed that the subcutaneous injection is the most preferred choice, followed by intravenous infusions. This pattern is confirmed with marginal differences in different subgroups, defined by the other variables (gender, age, YFD). Among patients who are older than 43 years and patients who had past experience of biological treatments, the percentages of preferences for infusions and subcutaneous injections are very similar, suggesting that older patients are more resistant to experiment the new form of delivery (subcutaneous injections).

These results partially confirm the results of previous studies, which tested patients' preference for subcutaneous injections versus intravenous infusions in other diseases and for other medications (15). With specific regard to patients with SLE, a previous study with a small group of patients showed even a higher percentage of preference for the autoinjector over intravenous administration. However,

differently from the previous study (in which patients shifted from intravenous infusion to the autoinjector), in our study patients were asked to express their hypothetical preference, without direct experience of subcutaneous injection of biological therapies (12).

Moreover, in this study, a specific attention was paid to the reported motivations, which were analyzed also through a lexicometric approach. In our study, a consistent percentage of patients expressed their preference for intravenous infusions. Even if many patients reported several reasons for preferring the subcutaneous injection, many other patients emphasized the importance of safety feelings that derive from the presence of qualified assistance during the therapy administration. In conclusion, we believe that patients' preferences and motivations should be carefully considered by clinicians, discussing patients' beliefs and possible resistances.

A limitation of this study is that diagnosis was self-reported, in the absence of a specific rheumatological assessment. Moreover, through our sampling procedure, even if we reached a large number of patients from different Italian regions, we did not obtain a statistically representative sample of the Italian SLE population. For this reason, generalizability of the findings should be considered with caution. Finally, considering that many patients reported that the use of subcutaneous injections would help them in managing their work commitments, in future research it would be interesting to consider the role played by different indicators of occupational status.

## Authors' Note

The data sets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. Online informed consent was obtained from all individual participants included in the study. Gruppo Italiano LES is a nonprofit organization and none of the authors received personal funding for this research.

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