Diagnostic pathway and treatment preferences for systemic lupus erythematosus: a physician-based discrete choice experiment

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Abstract

Objective

To assess physicians' preferences on diagnostic pathways and treatment priorities for systemic lupus erythematosus (SLE) using a discrete choice experiment (DCE).

Methods

A board of 11 SLE experts and a DCE expert statistician defined informative profiles of diagnostic pathways, pharmacological therapies, and two distinct profiles of mild-moderate and severe SLE. An independent panel of 115 clinicians involved in SLE management was invited to participate. Parameter estimates from the model were interpreted as relative preference weights (PWs). The mean PWs were used to calculate each attribute's relative importance (RI).

Results

95 clinicians (57% females, 71% rheumatologists) completed the DCEs. The DCEs could not identify a hierarchy of importance among diagnostic pathway attributes. Nevertheless, "referral time to a rheumatologist" was considered more important for mild-moderate (RI=25%) and severe (RI=20%) SLE. Among the therapeutic attributes, the effect on organ damage progression after 12 months showed the highest preference for mild-moderate (RI=35%) and severe (RI=41%) SLE patients, followed by reduction in disease activity levels (max RI=19%) and glucocorticoid dose (max RI=13%) after six months. Reducing prednisone dose below 5 mg/day scored higher utility levels for mild-moderate (PW=66.1) than severe (PW=14.2) SLE. Administration route, action rapidity, patient-global assessment, and serious infection risk showed lesser relevance (RI 7–8%). No distinctions were found among subgroups categorised by the clinicians' areas of expertise.

Conclusion

These DCEs highlight a high degree of awareness among lupus-treating physicians, with no differences across medical specialties, of the unmet need for early diagnosis and prevention of damage accrual in SLE management.

Key words

systemic lupus erythematosus, qualitative research, quality indicators, health care

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Received on March 7, 2024; accepted in revised form on July 5, 2024.

Funding: this work was supported with an unconditional grant by AstraZeneca Italy.

Competing interests: M. Piga has received consultancy fees from AstraZeneca, GSK and Otsuka, and speaker fees from AstraZeneca, GSK, Otsuka and Roche. M. Mosca has received honoraria and research support from Abbvie, AstraZeneca, BMS, GSK, Janssen, Lilly, Novartis, Otsuka and UCB. F. Conti has received speaker fees from Abbvie, BMS, Galapagos, Lilly, Pfizer and UCB. M. Govoni has received fees for sponsorised lectures from AstraZeneca and GSK, and research/grant support from Abbvie, Eli Lilly and GSK. The other authors have declared no competing interests.

Introduction

Systemic lupus erythematosus (SLE) is a complex, multisystem chronic autoimmune disease with heterogeneous clinical and serological features, characterised by a relapsing-remitting course, and it poses significant challenges in diagnosis and treatment (1). According to different lupus cohorts worldwide, half or more SLE patients fail to maintain the treatment targets of remission or low disease activity (2-4), reflecting some barriers in implementing the treat-to-target strategy, such as diagnostic delay and low response rate to conventional drugs (5). The current study uses a discrete choice experiment (DCE) to assess physicians' priorities for the diagnostic pathway and treatment in SLE.

Materials and methods

Study design

DCE is a consensus process based on scientific evidence and clinical experience guided by solid methodology, allowing the identification of prioritised attributes (6). This study was planned, conducted, analysed, and reported following specific recommendations (7). The study was placed in the Italian context, where the National Health Service provides free and equal access for all citizens to all healthcare services, including primary, hospital, and emergency care, visits, diagnostic procedures, and therapies, including biologics and other innovative drugs.

DCE attributes identification and levels definition

A board of 11 experts in SLE was constituted, and a methodologist/statistician instructed them on DCE. A focus group proposed and finally defined all the phases of possible diagnostic-therapeutic pathways (Table I). Regarding pharmacological therapy, features were listed considering the following categories: efficacy, clinical management, and patient-reported outcome (Table II). Two clinical scenarios were defined, one referring to severe SLE (*i.e.* woman between 20 and 30 years old, with joint pain, fever, and proteinuria) and one to mild-moderate SLE (*i.e.* woman between 20 and 40 years old, with joint pain and skin rash), and for each attribute, three representative and plausible levels were chosen: satisfactory, unsatisfactory, and intermediate. Four DCEs were finalised: therapies for severe SLE, therapies for mild-moderate SLE, diagnostic-therapeutic pathways for severe cases, and diagnostic-therapeutic pathways for mild-moderate cases. The DCE experimental design and sample size calculation are in the Supplementary file.

Besides answers to DCE tasks, clinicians were asked to provide information about their birth year, degree year, specialty (rheumatology, nephrology, dermatology, internal medicine, other), number of SLE patients visited per year (less than 25, 25-50, more than 50), and their informed consent for the collection and analysis of data for the study.

The project can be considered an opinion poll, and according to Italian law, it does not require approval by an Ethical Committee or Institutional Review Board.

Statistical analysis

To measure preference weights (PWs), we used the Choice-Based-Conjoint analysis Hierarchical Bayes procedure, recommended and provided by Sawtooth Software (CBC/HB algorithm). According to the Bayesian approach, the *a posteriori* probability combines the probability that a respondent will select a specific concept in a choice task given a particular set of utilities (likelihood) as well as the probability that the respondent's utilities are consistent with the pattern of utilities observed in the rest of the respondents (sample density acting as *a priori* probability). The parameter estimates from the model can be interpreted as relative PWs. These weights indicate the average preference for one attribute level over others. They also reflect the relative utility strength for each attribute level, where more positive numbers indicate higher utility and negative numbers indicate disutility. The mean PWs have been used to calculate each attribute's relative importance (RI).

Results

The study was conducted as a survey from November 2022 to February

Table I. Attributes and levels selected for the discrete choice experiment about diagnostic pathway.

Attribute	Levels for severe SLE	Levels for mild-moderate SLE
Request for ANA at first visit to GP	50% 70% 90%	50% 70% 90%
ANA positive patients sent to rheumatologist	65% 80% 95%	65% 80% 95%
Referral time to rheumatologist (days)	10 20 30	10 20 30
Time to clinical diagnosis or prescription of biopsy (days)	7 14 21	7 14 21
Time to referral [Time since the (eventual) prescription of biopsy to the complete diagnostic report] (days)	14 21 30	
Frequency of visits	1st month - 2nd month 45 days - 3rd month 3rd month -6th month	1st month - 2nd month 45 days - 3rd month 3rd month -6th month

ANA: anti-nuclear antibody. GP: general practitioners.

Table II. Attributes and levels selected for the discrete choice experiment about therapy features.

Attribute	Levels for severe SLE	Levels for mild-moderate SLE
Efficacy		
Disease activity (6 months after the start of treatment vs. baseline)	-80 -60 -40	-80 -60 -40
Glucocorticoid dose at 6 months after the start of treatment	2.5 mg/day 5 mg/day 7.5 mg/day	0 mg/day 2.5 mg/day 5 mg/day
Risk of serious infections at 12 months	1% 2% 5%	0.5% 1% 2.5%
Probability of organ damage progression at 12 months	5% 10% 20%	2.5% 5% 10%
Clinical management		
Route of administration	oral subcutaneous IV	oral subcutaneous IV
Onset of action	12 weeks 16 weeks 24 weeks	12 weeks 16 weeks 24 weeks
Patient-reported outcome		
Patient Global Assessment	30 40 50	10 20 40

2023, including 95 clinicians (29% non-rheumatologists) who dealt with SLE (clinicians' characteristics are reported in Supplementary Table S1).

DCE about the diagnostic pathways

Concerning diagnostic pathways, DCE failed to identify a hierarchy of importance among the different phases, as no strong departures from the null hypothesis emerged (Suppl. Fig. S1-S2). However, "Referral time to a rheumatologist" was considered important for both mild-moderate (RI=25%) and severe (RI=20%) SLE, while "Frequency of visits" was relevant for severe (RI=22%) and not relevant for mild-moderate (RI=14%) SLE.

No differences emerged between subgroups defined according to the specialisation of the clinicians (Suppl. Fig. S3-S4).

DCE about therapy features

The first attribute in order of importance in orienting preferences for treatment choice in severe SLE was the "Probability of organ damage progression at 12 months after the start of the treatment" (RI=41%), followed by the attribute "Disease activity (6 months vs. baseline)" (RI=19%) and "GC dose at six months" (RI=11%) (Fig. 1A). The remaining attributes were similarly little relevant (RI between 7 and 8%). The relative distribution of the importance of attributes for mild-moderate SLE ranked similarly to severe SLE (Fig. 1B). Worthy of note is the higher importance of organ damage progression (RI=41%) and the lower importance of "Patient Global Assessment" (RI=7%) for severe SLE.

Limiting to 5% the probability of organ damage progression for severe SLE (Fig. 2A) represents the first target of clinicians (PW=128.9), who consider it significantly more helpful than an 80% decrease in disease activity (PW=72.2), which in turn was the second clinical target. Still referring to these two attributes, a 10% probability of organ damage progression falls in the "utility" area (PW=21.8; lower bound of 95% CI >0) while a 60% decrease of disease activity slightly but significantly in the "disutility" area (PW= -11.9). With regards to GC dose after six months from the start of the therapy, only a PDN dose of 7.5 mg/day is considered a disutility (PW=-36.2), and a small, even if significant, difference is observed between 2.5 (PW=25.2) and 5 mg/day (PW=11.0), both in the "utility" area. The differences across levels of the other attributes are smaller. Sim-

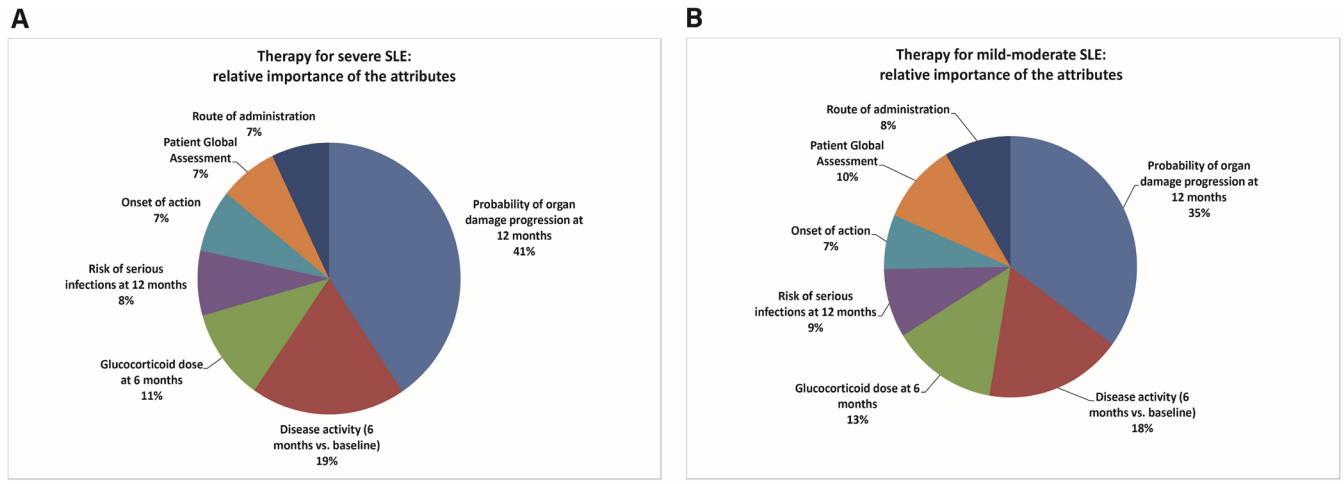

Fig. 1. Therapy for severe (**A**) and mild-moderate (**B**) SLE: relative importance of the attributes.

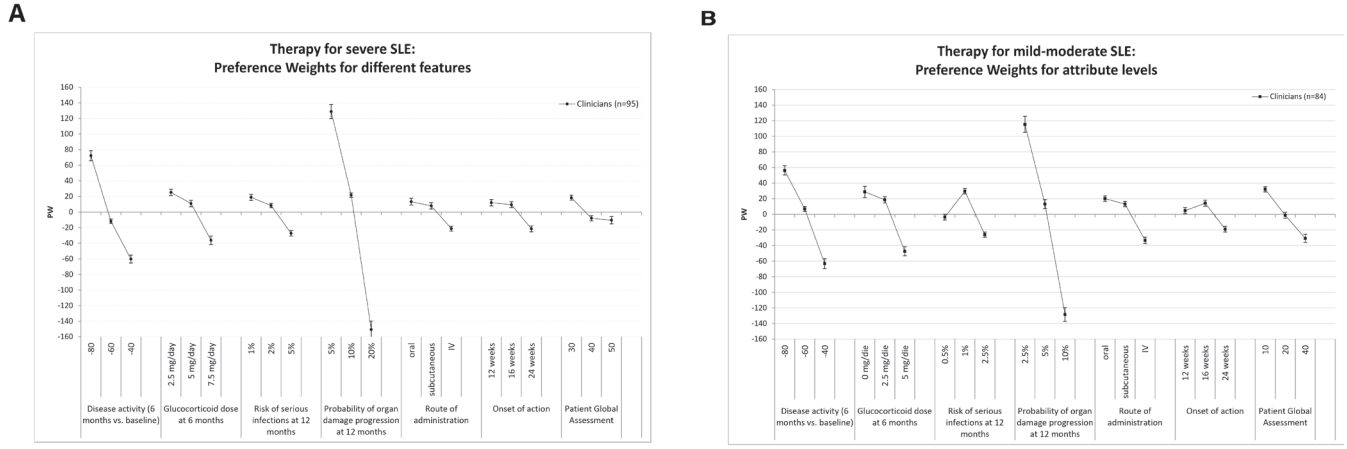

Fig. 2. Therapy for severe (**A**) and mild-moderate (**B**) SLE: preference for attribute levels. The values of these weights indicate the average preference for one attribute level over other attribute levels, also reflecting the relative strength of utility for each attribute level, where more positive numbers indicate higher utility and more negative numbers indicate higher disutility.

ilar patterns appeared when clinicians were presented with a mild-moderate SLE (Fig. 2B), with some noticeable differences from severe SLE: a 60% decrease in disease activity is slightly more acceptable (PW=6.9), and 10, 20, and 40 levels of PGA (PW=32.1, -1.2, 30.8, respectively) are more able to modulate clinicians' preferences. Finally, we should also report an unexpected finding since a 1% risk of serious infections (PW=29.6) appears preferable to 0.5% (PW= -3.5), pointing out the limitation of the threshold of this specific attribute.

Looking at both categories of patients, the utility increase in reducing the dose of GCs from 5 to 2.5 mg/day is 14.2 points (from PW=11.0 to PW=25.2) for severe SLE and 66.1 (from PW=-47.5 to PW=18.6) for mild-moderate SLE.

No statistically significant differences emerged for severe or mild-moderate SLE, according to clinical specialisation (rheumatology *vs*. other) (Suppl. Fig. S5-S6).

Discussion

The major findings emerging from this study are that clinicians prioritised the referral time to the rheumatologist to obtain an earlier diagnosis and the efficacy of treatment in inhibiting the progression of organ damage, followed by disease activity control and GC dose reduction, both for mild-moderate and severe SLE. Moreover, the physicians' preferred attributes for diagnostic pathways and therapeutic features in SLE did not differ across medical specialties. Although these points are reinforced by numerous recommendations, including the latest from EULAR (8), the awareness of these unmet needs among physicians has not yet been documented and measured with scientific techniques.

The SLE diagnostic delay is still too long and is mainly driven by the delay between the first visit to a doctor and the assessment by a rheumatologist (9), which supports the DCE findings about reducing as much as possible the time between the onset of symptoms and referral to the rheumatologist. After the diagnosis has been made and treatment initiated, patients should be treated to target remission and prevent organ damage accrual (10). On the one hand, the DCE results confirm the physician's awareness of the need to prevent organ damage as a surrogate marker of increased risk of further damage, impaired quality of life, and death. On the other hand, it claims the physician's preferences for treatment choices based

on more robust evidence for drugs' effectiveness in preventing damage development and accrual by suppressing disease activity, preventing flare, and sparing GCs in SLE patients. The available evidence on the efficacy and safety of belimumab and anifrolumab led to a recent update of the EULAR recommendations on SLE treatment, which support their early use as an add-on to or in combination with standard-of-care to achieve and maintain remission or LDA with the lowest possible dose of GC (8). Exposure to low-dose glucocorticoids (GCs) has been shown to have harmful effects (11,12), while biologics have been proven to reduce the need for GCs while lowering disease activity and preventing flares (13-15). As a result, the new recommended maintenance dose threshold for prednisone (PDN) is now set at ≤5 mg/day, stricter than the previous ≤7.5 (8).

This study has some limitations. First, although the treatment choice in SLE must be based on a shared patient-physician decision, patients were not involved in the present study. Future projects should compare physicians' preferences worldwide as the perspective is not the same across Europe and can be even more different in other regions.

In conclusion, the results of these DCEs confirm the widespread awareness among physicians in various medical specialties regarding the unmet need for early diagnosis and prevention of damage accrual in SLE management.

Acknowledgements

This work was supported with an unconditional grant by AstraZeneca Italy.

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