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ORIGINAL RESEARCH

Patient Perceptions and Preferences of Two Etanercept Autoinjectors for Rheumatoid Arthritis: Findings from a Patient Survey in Europe

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ABSTRACT

Introduction: Benepali® was the first etanercept (Enbrel®) biosimilar to be approved in the European Union. Both Benepali and Enbrel are available as autoinjector devices. In a recent survey, nurses from France, Germany, Italy, Spain, and the United Kingdom (UK) reported that their patients with rheumatoid arthritis (RA) would prefer the Benepali autoinjector compared to the Enbrel MYCLIC autoinjector. To determine whether patients' perceptions were similar to those of the nurses, this survey evaluated patients' perceptions and preferences of the Benepali autoinjector versus the Enbrel MYCLIC autoinjector in the same five European countries.

Methods: Patients with RA using the Enbrel MYCLIC autoinjector participated in a 25-min, face-to-face questionnaire-interview. Patients were also shown an instructional video and device-handling leaflet, received a live demonstration on the Benepali autoinjector, and had access to both Benepali and Enbrel MYCLIC training autoinjectors. Patients rated the importance of ten autoinjector attributes on a seven-point scale (1 = not important at all; 7 = extremely important) and provided their autoinjector preferences based on specific attributes. Patients also gave their opinion on which autoinjector they would prefer to use for self-injection.

Results: Overall, 220 patients participated in the survey (France, $n = 30$; Germany, $n = 65$; Italy, $n = 67$; Spain, $n = 12$; UK, $n = 46$). 'Easy to operate the self-injection' was ranked as the most important attribute (mean score of 6.8), followed by 'easy to grip' (6.5), and 'intuitive/self-explaining usage' (6.3). Patients preferred the Benepali autoinjector, with the attribute of 'easier to operate' being a strong differentiator compared to the Enbrel MYCLIC autoinjector. Most patients (74%) reported that they would prefer to use the Benepali

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autoinjector over the Enbrel MYCLIC autoinjector. 'Easy to operate the self-injection' and 'button-free autoinjector' were key drivers when selecting an autoinjector.
Conclusions: Patients in Europe reported a preference for the Benepali autoinjector compared to the Enbrel MYCLIC autoinjector. This finding is consistent with results from a recently reported nurse survey.
Funding: Biogen.

Keywords: Autoinjector; Benepali; Biosimilar; Enbrel; Etanercept; Patients; Rheumatoid arthritis; Survey

INTRODUCTION

Conventional synthetic disease-modifying antirheumatic drugs (csDMARDs), such as methotrexate, hydroxychloroquine, and sulfasalazine, have long been the mainstay of treatment for RA, and their initiation in the early stages of disease can curb or halt the progressive synovitis and joint destruction, thereby limiting disability [1–3]. However, an improved understanding of the pathogenesis of RA over the past decade has led to the development of several biological DMARDs (bDMARDs) that directly target components of the RA inflammatory cascade, and have transformed the management of this disease [3]. The first targeted bDMARD for RA was the tumor necrosis factor (TNF)-antagonist, etanercept (Enbrel®), which was approved by the US Food and Drug Administration in 1998 [4]. Since then, a number of other bDMARDs have been approved and are now commercially available; many of these treatments are administered by subcutaneous (SC) injection, with a number of presentations and devices currently being available (prefilled syringes, vial and syringe, and autoinjector devices). A number of studies have reported that patients with RA prefer autoinjector devices over conventional methods of treatment administration, with patients citing such factors as these devices being easier to use, more convenient, more acceptable, less painful, and less time-consuming [5–7].

Although bDMARDs are effective in reducing RA symptoms, slowing disease progression, and improving physical function and quality of life [3, 8–10], they are costly [11]. Consequently, in many countries, not all patients who may be eligible for treatment with biological drugs according to guidelines are prescribed these drugs, with preference generally being given to those with more severe and aggressive disease [12]. Indeed, results from a cross-sectional study estimated that, in total, 320 million people in the European region (approximately 40%) have severely restricted access to bDMARDs in cases of RA, with barriers to access primarily being financial and administrative [11]. However, the patent expiry of some of these bDMARDs has enabled the introduction of therapeutically similar, and more affordable, alternatives—known as biosimilars [13].

Benepali® (manufactured by Biogen, Inc, Cambridge, MA, USA) was the first etanercept biosimilar to be approved in the European Union (EU) in 2016. Benepali, which underwent robust preclinical and clinical (phase I and phase III) testing in both healthy volunteers and patients with RA [14, 15], is approved for all the adult indications for which Enbrel is approved—namely, moderate-to-severe RA, psoriatic arthritis, axial spondyloarthritis (ankylosing spondylitis and non-radiographic axial spondyloarthritis), and plaque psoriasis [16]. Both Benepali and Enbrel are available as autoinjector devices. In a recent

European survey conducted in France, Germany, Italy, Spain, and the United Kingdom (UK), the majority of nurses (86%) reported that their patients would prefer the Benepali autoinjector compared to the Enbrel MYCLIC autoinjector [17]. To determine whether patients were in agreement with nurses, this survey evaluated patients' perceptions and preferences of the Benepali autoinjector versus the Enbrel MYCLIC autoinjector in the same five European countries.

METHODS

This survey, which consisted of a 25-min, face-to-face, structured, questionnaire-interview, was designed to assess patient perceptions and preferences for the Benepali autoinjector compared to the Enbrel MYCLIC autoinjector. The survey was conducted between December 2015 and April 2016 in France, Germany, Italy, Spain, and the UK. The survey, including the pilot survey, was conducted by Kantar Health, an independent global market research and consulting firm, based in Munich, Germany. Kantar Health performed the survey in accordance with market research guidelines, data protection laws, and data privacy legislation, ensuring the implementation of an effective quality assurance system. Kantar Health operates in compliance with ISO 20252:2012, the International Standard for Market, Opinion and Social Research and, as a member of numerous market research associations, including Arbeitskreis Deutscher Markt und Sozialforschungsinstitute e.V. (ADM), the European Pharmaceutical Marketing Research Association (EphMRA), the Council for American Survey Research Organizations (CASRO), and the European Society for Opinion and Market Research (ESOMAR), strictly adheres to the latest industry codes of conduct and guidelines in market research.

Patient Population

Patient recruitment was outsourced by Kantar Health to another agency, Schmiedl Marktforschung GmbH, who enrolled patients from a number of sources, including patient panels and patient-support groups, as well as recommendations from nurses and physicians. To be eligible to participate in the survey, patients had to have been diagnosed with moderate or severe RA by a physician and had to be using the Enbrel MYCLIC autoinjector for at least 1 month at the time of recruitment into the survey. There were no specific exclusion criteria for this survey. Patients provided written consent before participating in the survey and were compensated for their time with an honorarium.

Questionnaire Design

The survey was developed in a two-stage process, with the guidance on the interview questions and process taken from a recent survey in patients with relapsing–remitting multiple sclerosis, which investigated patients' perceptions of the importance of different general attributes of autoinjectors [18]. Initially, an English structured quantitative master questionnaire was created, which was then tested and validated in pilot interviews ($n = 4$) to ensure appropriate content, flow, and clarity of the survey. During these pilot interviews, respondents were asked to provide those autoinjector attributes that they considered to be the most important for

inclusion in the main quantitative survey. These interviews were also used to determine whether respondents fully understood the instructions provided with the questionnaire. The final version of the English questionnaire was then translated into four languages (German, Italian, French, and Spanish). All interviews were conducted in the relevant local language and were performed by experienced interviewers working on behalf of the recruitment agency (Schmiedl Marktforschung GmbH). Interviewer training was conducted by Kantar Health via video conference prior to commencement of the survey, with scheduled weekly feedback calls to check on the progress of the interviews and to ensure that they were being performed correctly.

During a 25-min face-to-face interview, each patient was asked a series of questions in sequence by the interviewer and all responses were documented. In addition, patients were shown an instructional video and device-handling leaflet for the Benepali autoinjector, received a live demonstration on the Benepali training autoinjector, and were given access to both the Benepali and Enbrel MYCLIC training autoinjectors.

The questionnaire was broadly divided into four sections. In the first section (Q1), patients were asked to rate the importance of ten attributes, when using an autoinjector device in general for self-injection of their RA treatment, on a seven-point scale (1 = not important at all; 7 = extremely important). The following attributes were assessed: (1) size of the autoinjector, (2) attractive design of the autoinjector, (3) easy to grip the autoinjector, (4) easy to operate the self-injection with the autoinjector, (5) audible feedback after treatment has been successfully injected, (6) visual feedback after treatment has been successfully injected, (7) concealing the injection needle in the injector body, (8) intuitive/self-explaining usage, (9) button-free autoinjector, and (10) weight of the autoinjector. In the second section of the questionnaire (Q2–Q11), patients were asked for their preference of autoinjector (Benepali, Enbrel MYCLIC, or both the same) based on nine of the ten attributes assessed in section 1 (button-free device was excluded from this section as this attribute related only to the Benepali autoinjector). In the third section of the questionnaire (Q12–Q13), patients were asked which autoinjector they would prefer to use for self-injection of their RA treatment (Benepali, Enbrel MYCLIC, or no preference), taking into consideration the information that they had received from the instructional video and device-handling leaflet, their own previous experience of handling the Enbrel MYCLIC autoinjector and their first experience of handling the Benepali autoinjector. Patients were then asked to select the top three attributes that drove their preference for one autoinjector over the other, based on the attributes assessed in section 1 of the questionnaire. The final section of the questionnaire included questions on patient demographics, including country of origin, gender, and age (see supplementary material for full details on the questionnaire).

Data Analysis

The analysis population included all patients who completed the survey. During the face-to-face interviews, patient responses were recorded by the interviewer and data input from all interviews was collected by the recruitment agency (Schmiedl Marktforschung GmbH). All analyses were performed by Kantar Health. Based on the results of previous quantitative

primary market research surveys, a minimum of 30 respondents per country is a validated and robust sample size and an eligible base for significant testing [19]. Statistical significance was estimated using Student's *t* test (Microsoft Excel, Ver. 2013, Microsoft Corp. Redmond, WA, USA).

RESULTS

Patient Characteristics

A total of 220 patients from France ($n = 30$), Germany ($n = 65$), Italy ($n = 67$), Spain ($n = 12$), and the UK ($n = 46$) participated in this survey. The lower number from Spain was due to the lower availability of patients with the required experience in using the Enbrel MYCLIC autoinjector. The majority of patients were female (72%) and aged 51–60 years (36%) (Table 1). All patients participating in the survey were using the Enbrel MYCLIC autoinjector.

Table 1 Demographic and baseline characteristics of patients participating in the survey ($n = 220$)

Characteristic	Description	Number of patients, *n* (%)
Country	Germany	65 (30%)
	France	30 (14%)
	Italy	67 (30%)
	UK	46 (21%)
	Spain	12 (5%)
Gender	Male	62 (28%)
	Female	158 (72%)
Age	≤30 years old	4 (2%)
	31–40 years old	27 (12%)
	41–50 years old	66 (30%)
	51–60 years old	78 (36%)
	≥61 years old	45 (20%)

Importance of Attributes when Using an Autoinjector Device for Self-injection

Patients were asked to evaluate the importance of ten attributes, when using an autoinjector device in general for self-injection of their RA medication, on a seven-point scale (1 = not important at all; 7 = extremely important). Overall, 'easy to operate the self-injection' was ranked as the most important attribute by patients (mean score of 6.8), followed by 'easy to grip' (6.5), 'intuitive/self-explaining usage' (6.3), 'visual feedback after treatment has been successfully injected' (6.0), 'concealing the injection needle in the injector body' (5.9), and 'audible feedback after treatment has been successfully injected' (5.8). The attributes of 'button-free device', 'weight of the autoinjector', and 'size of the autoinjector' were considered by patients to be of less importance, with mean scores of 5.3, 5.3, and 5.1, respectively (Fig. 1).

Patient Preferences for Autoinjector Based on Attributes Assessed

Patients were asked for their preference of autoinjector based on nine of the ten attributes previously assessed ('button-free device' was not included in this section). Overall, the attribute of 'easier to operate' was a strong differentiator for the Benepali autoinjector compared to the Enbrel MYCLIC autoinjector, with 78% of patients reporting that the Benepali autoinjector was 'easier to operate' than the Enbrel MYCLIC autoinjector (Fig. 2). Furthermore, country-specific data showed that patients from all five EU countries preferred the Benepali autoinjector

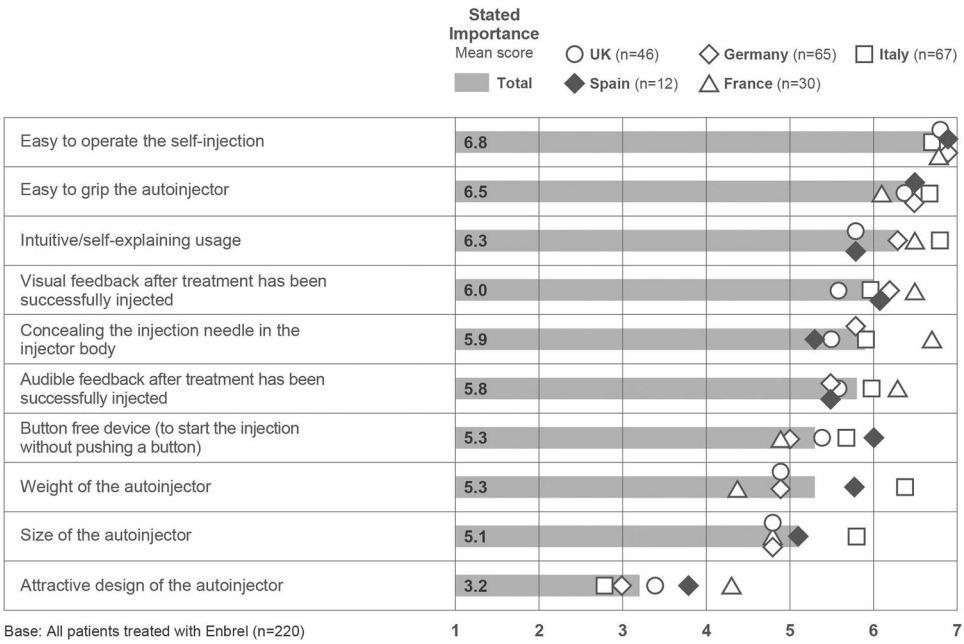

Fig. 1 Importance of attributes when using an autoinjector device for self-injection, as assessed by patients (mean scores on a scale of 1–7; 1 = not important at all; 7 = extremely important)

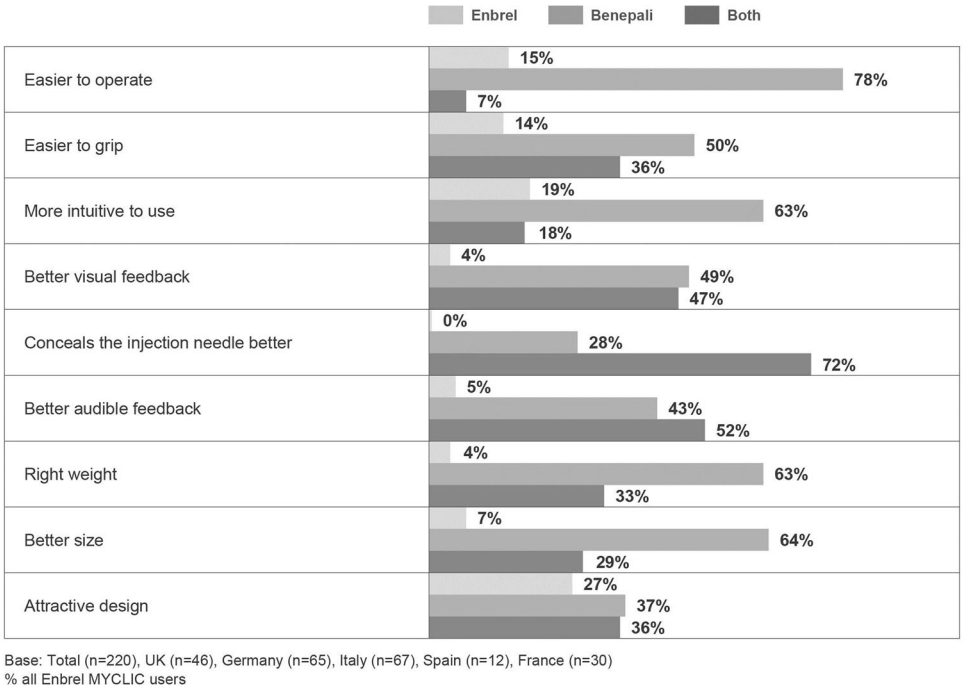

Fig. 2 Patient preference for the Benepali versus Enbrel autoinjectors based on attributes assessed

compared to the Enbrel MYCLIC autoinjector based on the attribute of 'easier to operate' (Fig. 3).

Overall, patients preferred the Benepali autoinjector compared to the Enbrel MYCLIC autoinjector for attributes of 'easier to grip',

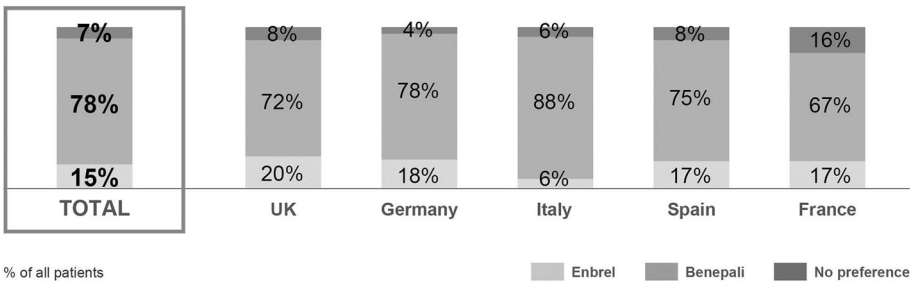

Fig. 3 Patient preferences for autoinjector based on the attribute of 'easier to operate the self-injection': Country-specific data

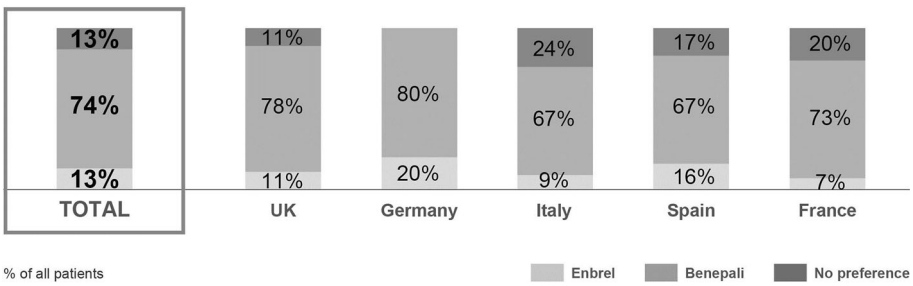

Fig. 4 Patient opinions as to which autoinjector they would prefer to use for self-injection

'more intuitive to use', 'better visual feedback', 'right weight', 'better size', and 'attractive design' (Fig. 2). The attribute of 'conceals the injection needle better' was rated as being the same for both autoinjectors by 72% of patients.

Patient Preference for Autoinjector and Attributes that Drive Patient Choice of Autoinjector

Patients were asked their opinion as to which autoinjector they would prefer to use for self-injection of their RA treatment. The majority of patients ($n = 163/220$ [74%]) reported that they would prefer to use the Benepali autoinjector, with only a small number of patients ($n = 28/220$ [13%]) reporting a preference for the Enbrel MYCLIC autoinjector. In addition, 29 patients (13%) stated that they had no preference for either device. A preference for the Benepali autoinjector was also reported across all five EU countries (Fig. 4).

Patients were also asked to select the top three attributes that drove their preference for one autoinjector over the other. Of the 163 patients who preferred the Benepali autoinjector, the reasons most commonly given were 'easy to operate the self-injection' ($n = 117$), followed by 'button-free autoinjector' ($n = 110$). Of the 29 patients who preferred the Enbrel MYCLIC autoinjector, the most common reasons given were 'easy to operate' ($n = 26$), and 'intuitive/self-explaining usage' ($n = 17$) (Fig. 5).

DISCUSSION

Results from this patient survey ($n = 220$) conducted in five countries in the EU reported that the majority of patients (74%) who were using the Enbrel MYCLIC autoinjector preferred the Benepali autoinjector to the Enbrel MYCLIC autoinjector for self-injection of their RA medication. These results were closely aligned with those of the recently reported nurse survey

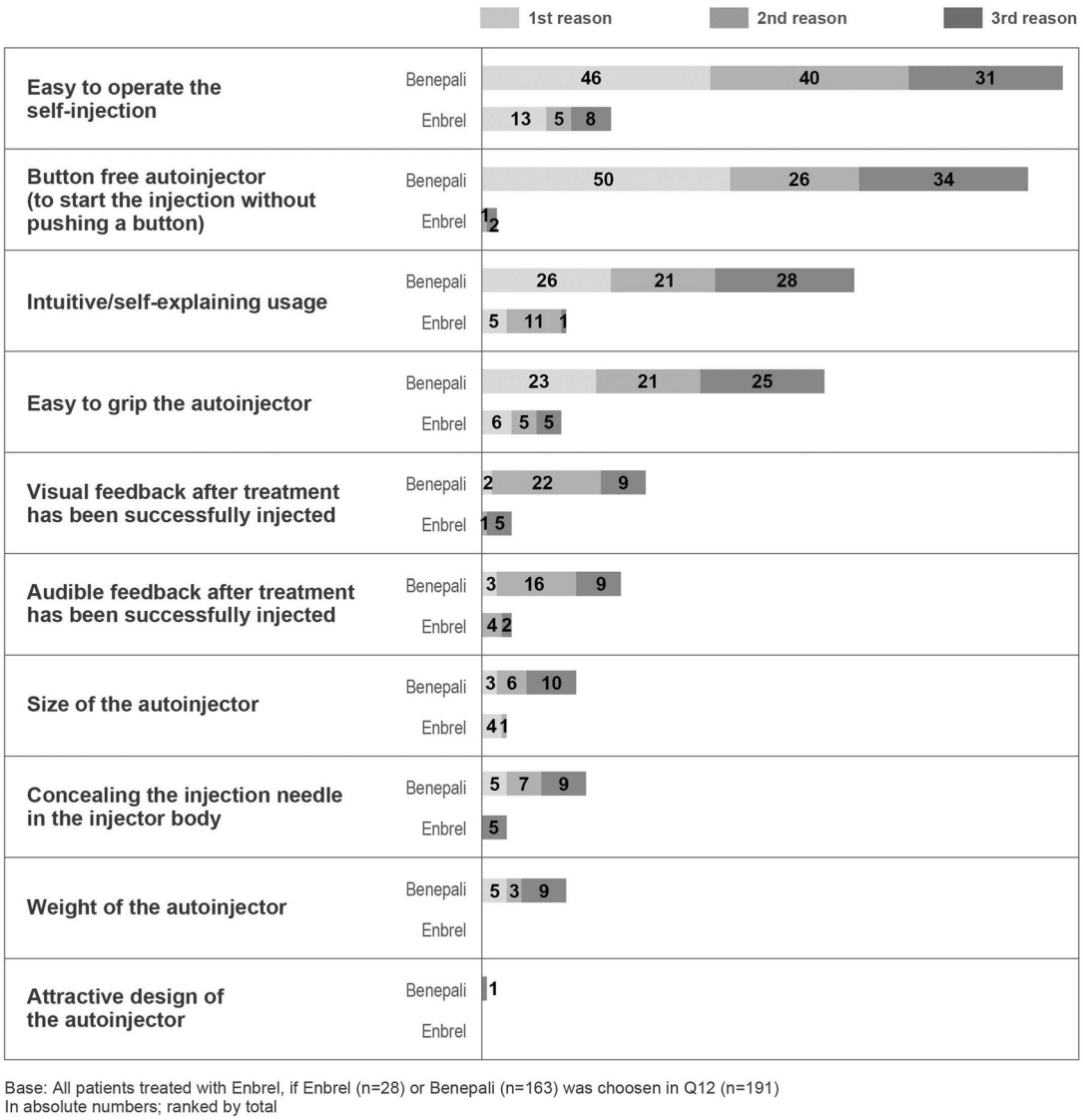

Fig. 5 Top three attributes driving patient selection

($n = 149$), which was based on the same protocol, and reported that 86% of nurses felt that their patients would prefer the Benepali autoinjector [17].

Overall, attributes of 'easy to operate the self-injection', 'easy to grip', and 'intuitive/self-explaining usage' were considered by patients as being the most important attributes when using an autoinjector to manage their RA. This was consistent with the results from the nurse survey, in which these three attributes were also considered by nurses as being the most important attributes when selecting an autoinjector for their patients with RA [17]. In line with the nurse survey, patients rated the attribute of 'easy to operate the self-injection' as a strong differentiator for the Benepali autoinjector compared to the Enbrel MYCLIC autoinjector in this survey. However, the attribute of 'intuitive/self-explaining usage', which nurses reported as a strong

differentiator for the Benepali autoinjector [17], was considered by patients in this survey as being a moderate differentiator. Finally, attributes of 'easy to operate the self-injection' and 'button-free autoinjector' were reported as key drivers impacting patients' choice of autoinjector. Once again, these results were identical to those reported from the nurse survey, in which these two attributes were also reported as being key drivers impacting nurses' choice of autoinjector [17]. Altogether, the attributes of the Benepali autoinjector that patients most preferred, which were in alignment with results from the nurse survey [17], can be described as those that make the handling process easier for the patient, suggesting that both patients and nurses in Europe consider the Benepali autoinjector to be easier to handle than the Enbrel MYCLIC autoinjector. This is of paramount importance, as many patients with RA suffer from compromised dexterity, which can affect the ability to perform the steps required [20].

Adherence to biological therapy is essential for sustaining long-term efficacy and optimizing therapeutic outcomes in patients with RA. However, adherence to the therapeutic regimen has been reported as low (varying from 30 to 80%), with the route of administration being an important factor in treatment adherence [21, 22]. Delivery of Benepali with the autoinjector, which appears to be easily performed by patients with RA, may increase patient tolerance of self-administration, possibly improving adherence, which in turn could significantly improve the effectiveness of drug therapy.

As with all market research, there are some limitations to this survey that need to be acknowledged. The survey results are based on patient perception of the Benepali autoinjector rather than actual clinical experience and do not represent a global perspective, as all patients came from Europe. In addition, the low patient numbers from Spain mean that results cannot be extrapolated to Spain. Furthermore, as patients volunteered to participate in the survey, an inherent self-selection bias may have been present, along with interviewer bias. However, to minimize selection bias, screening criteria were developed and rigorously adhered to, ensuring that only patients representative of the target population were recruited into the survey. Similarly, to reduce interviewer bias, comprehensive briefings were conducted with all interviewers across the five EU countries to ensure that all interviews were conducted in an identical manner. Finally, results from this survey are based on patients' perceptions of the Enbrel MYCLIC autoinjector following usage of at least 1 month at the time of recruitment compared to a demonstration of the Benepali autoinjector only. As such, a further survey is warranted to determine if results of this survey are replicated after exposure to both autoinjectors for the same time period. Despite these limitations, the fact that findings from this patient survey mirrored those of the nurse survey, which was based on the same protocol [17], and demonstrated a large patient preference for the Benepali autoinjector, provides further credence to these results.

Although the biosimilars market is relatively new in Europe, a preliminary analysis of pricing behavior indicates that biosimilars in some therapeutic areas are priced below reference biologics, often with discounts of 10–35% [23]. Due to the lower cost of biosimilars versus reference products, there has been considerable interest in determining whether patients who have already been treated on a reference product treatment can be switched to its

biosimilar without adverse consequences. To date, a number of switching studies in patients with RA and ankylosing spondylitis have shown that biosimilars can be used in place of reference products while maintaining efficacy and safety [24–27], although, as yet, no independent randomized controlled trials have reported switching from original to biosimilar drugs. The availability of Benepali, the first etanercept biosimilar available in Europe, may help to reduce costs, thereby relieving the burden on healthcare budgets and improving patient access to treatment [13]. Moreover, the fact that patients reported a preference for the Benepali autoinjector over the Enbrel MYCLIC autoinjector may provide an additional consideration point for clinicians when considering a patient's therapy. In addition, lower costs may also assist in the overall earlier introduction of biological therapy [26, 28], thereby providing a unique opportunity to change the course of RA, after the start of symptoms but before the onset of radiographic damage [29].

CONCLUSIONS

Benepali, the first etanercept biosimilar, has now been approved in the EU for the treatment of RA. Results from this patient survey in five EU countries reported that, overall, patients preferred the Benepali autoinjector compared to the Enbrel MYCLIC autoinjector for the majority of attributes assessed, a finding that was in alignment with results from a recently reported nurse survey [22]. Notably, patients preferred the Benepali autoinjector for attributes of 'easy to operate the self-injection' and 'easy to grip', suggesting that patients found the Benepali autoinjector easier to handle than the Enbrel MYCLIC autoinjector.

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Disclosures. Kunal Thakur is an employee of Biogen International GmbH. Alexandra Handrich is an employee of Biogen International GmbH. Mourad Farouk Rezk is an employee of Biogen International GmbH. Anna Biberger is an employee of Kantar Health, the company that designed and analyzed the survey.

Compliance with Ethics Guidelines. Patients provided written consent before participating in the study.

Data Availability. Datasets generated during the current study are available from the corresponding author on reasonable request.

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