Original paper/*Artykuł oryginalny*

Reumatologia 2013; 51, 2: 113-118
DOI: 10.5114/reum.2013.34819

Patients' preferences regarding biological treatment in doctors' and patients' opinions – the results of the RAISE* questionnaire survey

*Preferencje dotyczące stosowania leków biologicznych w opinii lekarzy i chorych – wyniki badania ankietowego RAISE**

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Key words: RAISE survey, biological treatment, doctor opinion, patients preferences.

Słowa kluczowe: ankieta RAISE, leczenie biologiczne, opinie lekarzy, preferencje chorych.

Summary

The purpose of the study was to assess the preferences of rheumatologists and patients with rheumatoid arthritis regarding the methods and frequency of biological drug administration. Patients were questioned about problems and difficulties associated with the use of biological medications (in particular, the perception of pain upon drug administration). Questions covered a range of issues including self-injection, help provided by relatives and friends or medical personnel, the preferred route of drug administration and dosing frequency, the degree of satisfaction with the effectiveness and safety of currently available therapies, unmet needs in relation to biological therapies, and what would be the ideal rheumatoid arthritis (RA) biological therapy product.

Material and methods: The survey, part of the international RAISE project, conducted in the form of a standardized personal interview by trained interviewers using a paper and pencil interview method, included 30 rheumatologists actively involved in the use of biological therapies and 120 patients receiving biological medications subcutaneously (52%) or intravenously (48%).

Results: Doctors rated performance of a subcutaneous injection by patients as easy or very easy; in their opinion patients rarely experience difficulty opening drug packaging (14%); however, problems do occur more frequently if using an injector (43%). The subcutaneous route of administration is preferred by 83% of patients, who rarely opt for intravenous therapy (3%). According to doctors, 85% of patients

Streszczenie

Cel pracy: Ocena preferencji metod i częstości podawania leków biologicznych w opinii lekarzy reumatologów i chorych na reumatoidalne zapalenie stawów (RZS). Chorych pytano o problemy i uciążliwości związane ze stosowaniem leków biologicznych (zwłaszcza percepcji bólu związanego z podaniem preparatu). Pytania dotyczyły m.in. samodzielnego wstrzykiwania leku, korzystania z pomocy osób bliskich czy personelu medycznego, preferowanej formy podania leku oraz częstotliwości przyjmowania kolejnych dawek, poziomu zadowolenia ze skuteczności i bezpieczeństwa obecnie dostępnych terapii, niespełnionych potrzeb związanych z terapiami biologicznymi, modelu preparatu idealnego do terapii biologicznej RZS.

Materiał i metody: Badaniem ankietowym metodą wywiadu bezpośredniego standaryzowanego (PAPI) przeprowadzonym przez przeszkolonych ankieterów, będącym częścią międzynarodowego projektu RAISE, objęto 30 lekarzy reumatologów prowadzących leczenie biologiczne i 120 chorych przyjmujących leki biologiczne podskórnie (52%) bądź dożylnie (48%).

Wyniki: Lekarze uważali, że wykonanie przez chorego zastrzyku podskórnego jest łatwe lub bardzo łatwe, problemy z otwarciem opakowania są rzadkie (u 14%), natomiast częstsze z użyciem wstrzykiwacza (u 43%). Podskórna droga podania leku jest preferowana przez 83% chorych, którzy rzadko decydują się na leczenie drogą dożylną (3%). Zdaniem lekarzy 85% chorych wykonuje iniekcje samodzielnie oraz preferuje częstość podawania leku raz w miesiącu. Trudności

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Submitted: 2.01.2013

self-inject their medication and their preferred frequency of drug administration is once per month. Twenty patients (17%) reported having difficulties opening drug packaging and 19 (16%) experienced problems handling the injector. Twenty-nine patients (24%) reported experiencing fear at the prospect of inserting a needle into their body. Adverse reactions following subcutaneous drug administration occurred in 29 patients and in 12 patients following intravenous drug administration (24% vs. 10%). The most frequently reported complaints were pain (20 patients, i.e. 17%) and allergic reactions at the site of injection (10 patients; 8%). For this reason someone other than the patient, usually a nurse, performed the injections for one in four patients. Subcutaneous drug administration was the preferred route for 46 patients (38%) while 47 preferred intravenous delivery (39%); for the remainder, the route of administration was immaterial. Patients preferred a dosing schedule of once a month or less.
Conclusions: The study revealed significant discrepancies in preferences between doctors and patients. Therefore it is the authors' opinion that patients should participate in the process of choosing the route of drug administration.

z otwarciem opakowania zgłosiło 20 chorych (17%), z obsługą wstrzykiwacza 19 chorych (16%). Strach przed wkłuciem igły zgłosiło 29 chorych (24%). Działania niepożądane po lekach podskórnych wystąpiły u 29 chorych, a po lekach dożylnych u 12 (24% *vs* 10%) Najczęściej zgłaszano ból (20 chorych, tj. 17%) i uczulenie w miejscu wkłucia (10 chorych, tj. 8%). Z tego powodu u co czwartego chorego zastrzyk wykonuje osoba druga, najczęściej pielęgniarka. Drogę podskórną podania leku preferowało 46 chorych (38%), a dożylną 47 (39%), dla pozostałych badanych było to bez znaczenia. Preferowana przez chorych częstość podania leku to raz w miesiącu lub rzadziej.
Wnioski: Uzyskane opinie znacznie się różnią, dlatego autorzy uważają, że w wyborze drogi podania leku powinien uczestniczyć chory.

Introduction

Rheumatoid arthritis (RA) is a chronic inflammatory disease of the joints that requires treatment over a period of many years [1]. A prompt diagnosis, possible thanks to the new ACR/EULAR criteria, is essential for the proper treatment of this debilitating disease because the probability of achieving remission is higher in the early phases of the disease than in its later stages [1–4]. With synthetic disease-modifying drugs, in particular methotrexate in therapeutic doses, achieving remission or low disease activity is possible in a vast majority of patients (82%) [5]. The remainder require combination therapy using biological drugs in accordance with guidelines specified in the EULAR recommendations [6]. A fundamental condition for the success of any form of therapy is patient compliance, which includes adherence to recommended doses. In many instances, everyday practice may differ from the controlled environment of clinical trials [7, 8], which can significantly impact therapy outcomes [9]. The level of doctor-patient cooperation is primarily an outcome of the combination of effectiveness and tolerance of the therapy; however, the patient's attitude towards the therapy, affected by a number of factors, should also not be overlooked [1].

The purpose of the study was:

1. To ascertain rheumatologists' opinions on the issue of the perceptions of RA patients treated using biological drugs regarding the convenience or inconvenience of using these products and patients' preferred route and frequency of biological drug administration.

2. To determine, based on the international RAISE patient study, problems and difficulties associated with the use of biological products (in particular, perception of pain upon drug administration); to estimate how many patients self-inject their medication and how many rely on help provided by relatives and friends or medical personnel; to ascertain the preferred route of drug administration and dosing frequency; to determine the degree of patient satisfaction with the effectiveness and safety of currently available therapies; to ascertain patients' unmet needs in relation to biological therapies for RA; and to establish a model of the ideal biological therapy product for RA.

Material and methods

The study was conducted in the period May–June 2010 in the form of a personal interview using a PAPI (paper and pencil interview) survey questionnaire, and consisted of a personal one-on-one conversation between a trained interviewer and the respondent, using a paper version of the standardized interview questionnaire. The study involved 30 physicians and 120 patients. All of the doctors were rheumatologists (21 women and 9 men), aged 31–60 and employed in centres providing biological drug treatment.

All of the patients fulfilled the criteria for diagnosing rheumatoid arthritis and had been receiving biological drug treatment for at least 3 months. Among the group of patients, 50 (42%) were being treated with etanercept (Enbrel; from Wyeth), 12 (10%) with adalimumab (Humira; from Abbott), 30 (25%) with infliximab (Remicade; from MSD) and 28 (23%) had received rituximab (MabThera; from Roche). The study group consisted of 92 females (77%) and 32 males (27%) with an average age of 52 years (20–75 years). Twenty-four patients had a higher education (20%), 57 (48%) had a secondary-level education, 8 (7%) had a post-secondary education, 26 (22%) had undergone vocational training and 5 (4%) had a primary level education. Twenty-seven patients were old-age pensioners (23%), 38 were on disability (32%), 35 had a job (29%),

10 (8%) were unfit to work as a result of RA and the remainder of the interviewed patients (6%) had never worked.

Results

As many as 25 doctors (85%) rated performance of a subcutaneous injection by a patient as very easy and 5 doctors (15%) considered the task to be easy. According to doctors, 85% of patients perform Enbrel injections themselves while 10% rely on a nurse to perform their injections, 3% rely on a caregiver and 1% on a doctor. According to the vast majority of doctors, patients do not have any difficulty in opening the outer packaging. Primarily, they require assistance in two instances: in opening the inner packaging and performing the injection (14% in each case); patients rarely request assistance in opening the outer packaging (7%). Fifty-seven percent of patients did not have any difficulty using the injector; 21% complained the injector lacked a feature showing that the full dose had been delivered; 18% had problems with holding the injector correctly; 7% felt the trigger was too small and 3.6% felt the inability to check how much medication had been delivered was a problem. Forty-three percent of patients have psychological difficulties with self-injection, but only 28% experience practical difficulties. For this reason, according to doctors, 83% of patients prefer subcutaneous injections and 3% prefer intravenous infusions, while for 14% the mode of delivery is immaterial (Fig. 1). Ninety-seven percent of patients would like to take the medication once a month; for 3% the dosing frequency is immaterial (Fig. 2). According to physicians, the incidence of adverse reactions in patients was similar, occurring in 7.5% of patients treated with rituximab, 6.8% treated with infliximab, 5.6% treated with adalimumab and in 8.1% treated with etanercept. Pain associated with drug administration was observed most frequently when using etanercept, in as many as 10.2% of patients, followed by adalimumab, in 5.5%, and least frequently when using infliximab and rituximab (in 3.9% of patients, for each drug respectively).

As for patients, 104 (87%) rated performing an injection as easy or very easy; only 15 (13%) reported difficulties. Eighty-nine patients (74%) self-injected and medical personnel performed injections for 24 patients (20%) while a caregiver or member of the family performed the injections for 4 (3%) and for 3 patients (2.5%), respectively. Problems with opening the outer packaging were reported by 20 patients (17%); 20 (17%) also reported problems with the inner packaging and 28 patients (23%) experienced problems with preparing injections while 34 (28%) had difficulties with self-injection. One patient in five reported practical and psychological difficulties connected with performing an injection. As many as 100 patients (84%) did not report any problems using the injector; 10 (8%) felt the absence of a feature showing the full dose had been delivered was an inconvenience; 7 (6%) had problems with holding the injector correctly; 3 (2.5%) reported that they were unable to ascertain the amount of medication delivered and 2 patients (2.3%) said that the trigger on the injector was not well placed; in addition, 2 patients (2.3%) stated that the trigger was too small.

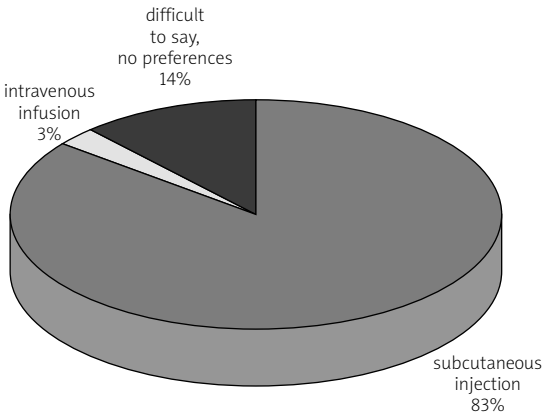

Fig. 1. Doctors' opinions about patients' preferences regarding the route of biological treatment administration.

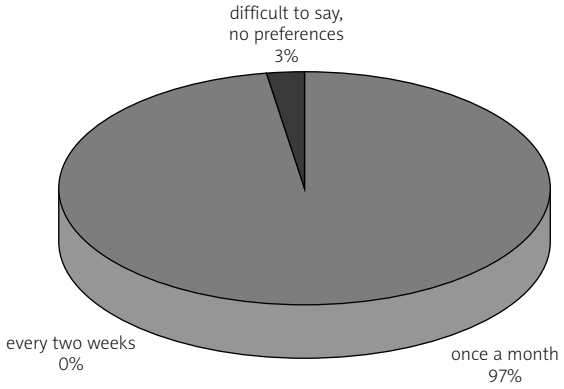

Fig. 2. Doctors' opinions about patients' preferences regarding frequency of biological treatment administration.

Two-thirds of the patients surveyed did not experience any significant anxiety in connection with injecting a biological drug (59 patients (49%) reported no anxiety, 25 (21%) felt some anxiety, 28 (23%) felt moderate anxiety and 8 (7%) experienced severe anxiety). One patient in four (24%) revealed that they had a fear of injections; one in five (17%) experienced pain at the site of the injection; 10 (8%) reported injection-site reactions; 8 patients (7%) worried about not receiving the correct dose and 5 (4%) about not operating the device correctly.

Patients' perceptions regarding medications delivered subcutaneously are that they lead to a greater number of

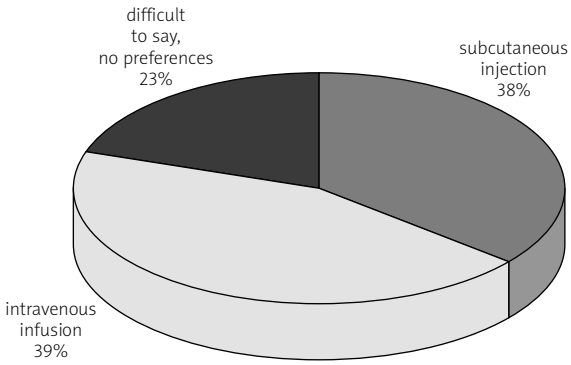

Fig. 3. Patients' preferences regarding the route of biological treatment administration.

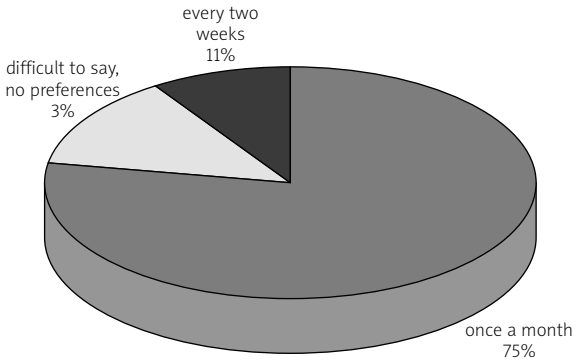

Fig. 4. Patients' preferences regarding frequency of biological treatment administration.

adverse reactions than drugs administered intravenously. Skin changes, in the form of allergic reactions or pain, occurred in 3 patients (2.5%) following intravenous therapy and in 10 patients (8.2%) following subcutaneous administration. Adverse skin reactions following over 10% of their drug doses were reported by 5 patients (4%) on intravenous therapy and 19 patients (16%) receiving subcutaneous therapy. Pain following 10% of delivered drug doses was reported by 29 patients (24%) receiving subcutaneous injections and 12 (10%) on intravenous therapy.

Patients receiving intravenous therapy tend to be more absorbed with the thought of their next scheduled dose than patients treated with injections. Among patients treated with subcutaneous injections, 43 (36%) give no thought to the subject at all, 55 (46%) think about it on the day of their injection and 22 (18%) think about it over a period of several days preceding their injection. Among patients receiving intravenous therapy, 39 (32%) give no thought to the subject at all, 35 (29%) think about it on the day they are scheduled to receive treatment, 39 (32%) think about it over a period of several days preceding their scheduled intravenous treatment, and 7 (6%) think about it all the time.

Concerning any changes in therapy, 65 patients (54%) did not see any need for introducing improvements to the therapy they were currently undergoing; 21 patients (18%) felt a moderate need and 34 (29%) felt a strong need for change. Patient preferences regarding the two routes of administration of biological drugs were almost evenly split, with 46 patients, i.e. 38%, preferring the subcutaneous route, 47 patients, i.e. 39%, preferring intravenous delivery, while for 27, i.e. 23%, the route of administration was immaterial (Fig. 3). The majority of patients – 90 (75%) – would prefer a once-monthly dosing schedule rather than every two weeks (13 patients, i.e. 11%); for 17 patients (14%), the dosing frequency was immaterial (Fig. 4). Expectations regarding any new drug focus primarily on maintaining a level of effectiveness similar to that of currently available medications, as stated by 118 patients (98%); on ensuring consistent effectiveness from one dose to the next – 119 (99%); and a once-monthly dosing schedule – 119 patients (99%).

Almost all of the patients, i.e. 119 (99%), also expressed the desire that any new drug should produce fewer drug reactions following subcutaneous administration and 115 patients (96%) additionally stated that packages containing the auto-injector should include simple instructions on how to use the device. Less essential – although still important for more than half of the patients – was the design of the auto-injector (disposable, with a side button and hidden needle). The most significant discrepancies between doctor and patient perceptions are presented in Table I.

Table I. Doctors' and patients' opinions regarding some aspects of biological treatment (data in %)

Aspect	Doctors' perception	Patients' perception
performing subcutaneous injections is easy/very easy	100	87
self-administration of injections	85	74
problems with opening the packaging	14	17
problems with the injector	43	16
adverse effects	5.6–8.1	10 *i.v.*; 24 s.c.
preferred route of drug delivery:		
subcutaneous	83	38
intravenous	3	38
no preferences	14	23
dosing once a month	97	75

Discussion

The effectiveness of any treatment depends to a great degree on regular dosing of prescribed medication and adherence to recommended doses. The problem increases in the case of long-term therapy, conducted over a number of years, where the effects are not immediately evident and oversights result in complications that develop late in the course of the disease, as is the case in chronic arthritis. A study by Fransen *et al*. [7] revealed that only 51% out of 411 interviewed doctors adhered to recommendations regarding the use of methotrexate in the treatment of rheumatoid arthritis. Non-adherence, resulting in reduced doses of methotrexate, was identified in 24% of treated patients while 25% received higher doses. The reduction in disease activity was statistically greater in the group whose treatment had been conducted in accordance with recommendations as compared to the group that received lower-than-recommended doses. Results obtained in the group treated with higher doses were no different from those achieved in the group treated in accordance with current recommendations. The rate of discontinuations due to adverse effects was similar in all of the groups. The authors concluded that adherence to recommendations is beneficial to the patient since it results in improved effectiveness without increasing drug toxicity. Data on patient compliance with treatment recommendations were unavailable since patients held their doctors responsible for changes in the dose of their medication. In a questionnaire survey conducted by Kulig *et al*. [9], patients placed the blame for the use of non-therapeutic doses of methotrexate on doctors; however, the authors of the study did not think this was a plausible explanation. Therefore, the only possible solution was to ascertain patients' needs and apprehensions, in order for doctors to modify their conduct accordingly, as far as possible, in the hope that this might prove an ideal solution. Patients treated with biological drugs appear to be best suited for this purpose, since one must assume they are among the best informed patients.

The methodology used in the international RAISE Study was for trained interviewers, who were not doctors, to conduct an interview using a questionnaire covering an extensive range of issues, which enabled standardization of the responses obtained from both patients and physicians. The current paper presents an analysis of a selected extract presenting patients' views on problems associated with the regular use of biological drugs, the rate of adverse effects and, primarily, their preferred route of drug administration, in order to compare patient responses with doctors' perceptions. The inclusion of a similar number of patients receiving subcutaneous and intravenous therapy (52% vs. 48%) was deliberate.

The presented data obtained indicate that the majority of patients perceived performing a subcutaneous injection as easy; however, in one out of four cases the medication was administered by an individual other than the patient, usually a nurse, which involved visiting a healthcare facility once a week. The cause was primarily psychological, connected with performing an injection (needle anxiety); difficulty opening the packaging posed a smaller problem and handling the injector device itself was not considered a problem. In the case of subcutaneous injections, pain and reactions at the injection site were a major issue, whereas in patients receiving their medication intravenously they were almost absent.

Doctors expressed a more optimistic outlook with regard to these issues. All of the doctors perceived performing a subcutaneous injection as easy, doubtless a natural consequence of dealing with this issue on a daily basis. In addition, in their opinion, a significantly greater number of patients performed the injections themselves, despite having overestimated the degree of difficulty involved in handling the injector.

According to patients, medications delivered subcutaneously produced a greater number of adverse effects than drugs delivered intravenously. One patient in four reported experiencing pain upon injection and skin changes in the form of allergic reactions. Such symptoms also occurred following the use of intravenous drugs, but their frequency was definitely lower.

Patients receiving intravenous therapy tend to be more absorbed with the prospect of their next scheduled dose than patients who self-inject, owing probably to the necessity of travelling to a hospital and staying there for several hours. Finally, patient preferences regarding the two routes of biological drug delivery were almost evenly split (38% preferred subcutaneous injections and 39% preferred the intravenous route). These results are clearly inconsistent with perceptions of doctors, in whose opinion almost all patients prefer to receive subcutaneous injections while only 3% prefer to receive their medication intravenously. However, patients did report a clear preference for dosing once a month, as opposed to once every two weeks, and doctors concurred on this issue.

Patients expressed satisfaction with their therapy since they did not expect a higher level of effectiveness from any new drugs; they did however draw attention to the fact that the dosing schedule should ensure a constant level of effectiveness. In the case of subcutaneously delivered drugs, patients would like to avoid experiencing allergic reactions and would like the auto-injector to be easier to handle (disposable, with a side button and hidden needle).

The results of the study do not differ significantly from reports published by McInnes *et al*. [10, 11], which sum up the outcomes of the RAISE study conducted in 8 European countries and Canada. These authors also determined that

some patients receiving biological drugs require emotional support and physical assistance in preparing subcutaneous injections and that their main problem was pain at the site of injection. Over half of the patients were satisfied with the injecting device they used and rated its handling as easy. However, 78 to 90% of patients expressed dissatisfaction with at least one aspect of this form of therapy, and usually complained of a burning sensation and pain at the site of injection. For 20%, pain upon injection was the most serious obstacle to performing self-injections while 10% admitted omitting at least one dose of medication due to this reason. Thirty-four to thirty-seven percent of patients were unsure of how to use the injector correctly and 2–16% of patients reported accidentally triggering the injector, which resulted in the loss of that dose of medication. Patients were more interested in a product that would ensure a constant level of effectiveness, simple to use and requiring less frequent dosing; these results were consistent with the findings of the Polish study.

The findings of a study by Tang *et al*. [1] may also be considered in the context of patient preference and compliance with regard to the use of biological drugs. In this retrospective study, which involved 1242 patients scheduled to receive treatment using a variety of anti-TNF drugs over a period of at least 24 months, the authors assessed continuity of treatment, which depended primarily on patients' compliance with a specific treatment. The mean period of treatment was 272.3 days. After one year, 74.6% of patients were still undergoing treatment; the proportion of patients receiving infliximab was higher than patients on subcutaneous therapy. The significant factor that determined continuity of therapy was the patient's attitude towards treatment.

A study by Harley *et al*. [12] involving 2662 Medicare-insured patients revealed that compliance was significantly higher in patients treated with infliximab combined with methotrexate than with etanercept or methotrexate in monotherapy. The authors were unable to explain the reason for these results and suggested that it may have been a combination of the dosing schedules of both therapies and the fact that patients treated with etanercept, similarly to patients treated with insulin, omitted doses as a result of apprehensions and anxiety connected with the process of self-injection.

In summary, it should be stated that patients are satisfied with treatment using biological drugs. Their preferences regarding the route of drug administration differ significantly from doctors' perceptions. Fear of complications following the use of drugs administered subcutaneously, difficulty using the injector, psychological aspects exacerbated by pain, and a natural aversion to self-injection pose significant problems. These issues should be considered when choosing a biological medicine.

Conclusions

1. Clearly, doctors and patients differ in their preferences regarding the route of administration of biological drugs.

2. The patient should participate in the decision-making process when choosing the route of drug administration.

The study was partly sponsored by MSD. The authors are lecturers for pharmaceutical companies.

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