Concise report

Patient preferences in the choice of anti-TNF therapies in rheumatoid arthritis. Results from a questionnaire survey (RIVIERA study)

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Abstract

Objective. To identify the determinants of anti-TNF-naive patients’ preferences for the route of administration of anti-TNF agents.

Methods. The study was carried out in 50 Italian rheumatology centres (802 patients). All patients completed a 31-item questionnaire addressing their perceptions of current treatment and the preferences for treatment with anti-TNF agents. Statistical methods included analysis of variance (ANOVA), t-test and chi-square test.

Results. The response rate to the questionnaire was 97.6%. At the time of the survey, 310 (39.9%) patients were dissatisfied with current treatments, owing to inefficacy, side effects and inconvenience of administration. The i.v. and s.c. routes of administration were preferred by 50.2 and 49.8%, respectively. No significant difference was found in patients by gender, age, RA duration or number of drugs used. Reasons for the choice of i.v. administration were the safety of treatment at the hospital and the reassuring effect of physician presence. The s.c. administration was chosen for the convenience of treatment and in particular for home treatment. Patients dissatisfied with current therapy due to side effects preferred s.c. administration ($P=0.029$), whereas patients choosing the i.v. route had slightly higher scores on ‘today pain’ ($P=0.047$) and ‘articular pain’ ($P=0.023$) of the Rheumatoid Arthritis Disease Activity Index (RADAI).

Conclusions. Both i.v. and s.c. treatments were well accepted by patients. However, treatment choice has to be discussed with patients, as individual preference seems to be determined by personal attitudes towards safety and convenience, by past experience and by the perception of current disease status.

Key words: Rheumatoid arthritis, Anti-TNF therapy, Decision making, Patient empowerment.

Introduction

RA is a chronic inflammatory disease leading to joint erosion and disability. Anti-TNF-α blockade controls RA disease activity and progression significantly improving a patient’s quality of life. This kind of treatment is usually well accepted by RA patients; nevertheless, the adherence to treatment is sometimes poor [1]. Although current anti-TNF agents differ in several aspects, both controlled trials and population-based studies demonstrate similar efficacy in RA [2–4]. Therefore, it has been suggested that priority should be given to a patient’s choice of the agent to use [5], in agreement with the guidelines...
recommending the involvement of patients in decision-making processes [6], and in outcome assessment [7], because patient drug choice sometimes may diverge from the physician choice [8–10].

Moreover, it has been suggested that the route of administration might affect the outcome of anti-TNF-α drugs, regarding the degree of adherence to the therapeutic regimen [11]: the aim of the RIVIERA (suRvey on IntraVenous Infusion and SC injection Expectations in Rheumatoid Arthritis) study was to evaluate RA patients’ preferences for treatment (i.v. or s.c.), based on the route and frequency of administration of different anti-TNF drugs. The study was specifically designed to evaluate treatment options and determination of the choice from the patient’s perspective.

Patients and methods

Eight hundred and twenty-two patients affected by RA from 50 Italian rheumatology centres were consecutively enrolled in the study. Patients were invited to fill a 31-item questionnaire addressing their perceptions of current treatment, and their preferences for treatment with anti-TNF drugs. This study was not consequent on other clinical studies. Ethical approval was obtained for this study from the Ethics Committee of the University of Firenze—Ospedale Careggi, Florence.

All patients were aged >18 years, and were able to sign the written informed consent and to complete the questionnaire. Inclusion criteria were diagnosis of RA according to the 1987 ACR criteria and eligibility for an anti-TNF-α drug. Exclusion criteria included previous therapies with an anti-TNF-α drug and administration of any other s.c. or i.v. drugs at regular intervals (for instance, insulin, desensitization therapies and hepatic).

The primary endpoints were the assessment of the preferences and the determinants of patients’ choice for i.v. or s.c. administration.

Questionnaire

The questionnaire was self-administered. Areas covered included:

(i) personal data (age and sex) and RA duration;
(ii) previous and concomitant treatments for RA;
(iii) relationship between the current therapies and the physical conditions;
(iv) patient compliance;
(v) previous adopted therapies;
(vi) time and number of kilometres and means of transportation used by the patient to reach the hospital; and
(vii) family status and assistance to patients.

At the end of the questionnaire, after reading information given about the different routes of administration for anti-TNF-α drugs, patients had to give a preference between s.c. and i.v. drug administration and explain the reason for their choice.

The questionnaire also assessed the favourite site of drug administration and, referring to the preferred venue for drug administration, the person chosen for the administration of the drug (family member, physician and nurse) and the feasibility of self-administration. The questionnaire used does not include leading questions.

Patients’ satisfaction with current treatment was assessed by a 5-point Likert scale; disease activity was assessed by the RADAI questionnaire.

Data analysis

The analysis of variance (ANOVA), two-tailed t-test and chi-square test were used for normally distributed data, whereas Pearson’s correlation coefficient and binomial regressions were used for non-parametric data. The trial was supported by Schering Plough according to good clinical practice rules, and the elaboration and analysis of the data was performed independently.

Results

Patient characteristics

A total of 802 out of 822 RA patients consulted, agreed to participate in the study and completed the questionnaire. The response rate was 97.59%.

The subject population included 617 (76.9%) women and 185 (23.1%) men; patients were distributed nationwide (33% from northern Italy, 36% from central Italy and 31% from southern Italy). The mean (s.d.) age was 55.62 (13.08) (median 57, range 18–85) years; the mean disease duration was 8.82 (8.34) (median 6, range 0–47) years.

In Italy, all the prescribing centres are situated in hospitals. The distribution of the share of patients in each region did not permit a statistically significant evaluation.

Current treatments

At the time of the survey, almost all patients (98%) stated that they were strictly following the treatment based on DMARDs. The vast majority of patients (n = 768, 95.8%) were on DMARDs—either monotherapy (43.9%) or combination (51.9%). The most prescribed DMARDs were MTX (82.3%), HCQ (36.8%) and LEF (27.4%). Most patients were also concomitantly treated with NSAIDs (69.4%), COX-2 inhibitors (38%) or corticosteroids (70.8%).

Patient satisfaction

Sixty-six per cent of the patients (n = 535) responded that they received the best therapy for RA. When asked about the reasons for their statement, these patients said that they were strictly following the treatment based on DMARDs, that they trusted their physician independently of treatment efficacy (n = 313, 58.5%) or both (n = 95, 17.8%). However, 486 (60.6%) patients were completely satisfied with current treatments, whereas other patients (n = 309, 38.6%) were not satisfied because of inefficacy (83.2%, n = 257), side effects (22.8%, n = 70), inconvenience of administration (2.3%, n = 7) or other (2.4%, n = 8). Six (0.6%) patients did not answer.
Accessibility to health care staff
Sixty per cent of patients were examined from two to four times per year and 27.3% had a medical examination five or more times per year.

Disease activity
In this cohort of RA patients, the RADA1 mean score was 4.61 (2.18) and 13.2% of the patients had a score of >7. The mean scores per RADA1 item were also analyzed.

The ‘global disease activity in the last 6 months’ was 5.67 (2.63), the ‘disease activity in terms of current swollen and tender joints’ was 5.57 (2.70) and ‘arthritis today pain’ was 5.12 (2.72). The most frequent joints involved were wrists and fingers. Almost half of the patients (45.8%) reported a morning stiffness for >1 h and the number of joints involved averaged 9.04 (4.78).

Patient preferences
The i.v. and s.c. routes of administration were preferred for 50.2 and 49.8% of the patients, respectively. Patients who preferred the i.v. (n = 403) or s.c. (n = 399) route of administration were compared. The distribution of treatment preferences did not differ by sex, age or disease duration.

Preferences were not significantly associated with the category and the total number of drugs currently used. There was no significant difference between patients satisfied and not satisfied by the current therapy in the choice of the route of administration of the drug.

However, patients who were not satisfied with current treatment due to side effects were more likely to prefer s.c. than i.v. administration (59 vs 41%, respectively). No correlation was observed either between patient preference and accessibility to health care staff, or confidence with the physician.

Considering the RADA1 items, only the ‘arthritis today pain’ [4.51 (2.37)] vs 4.19 (2.24); P = 0.047] and ‘articular pain’ (P = 0.023) were clearly associated with patient choice of the i.v. route.

When asked about reasons for their preferences, patients gave a total of 3570 answers, grouped into 14 thematic categories (Table 1).

<table>
<thead>
<tr>
<th>Categories</th>
<th>I.v. (n = 403), n (%)</th>
<th>S.c. (n = 399), n (%)</th>
<th>Total (n = 802)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Convenience</td>
<td>183 (45)</td>
<td>220 (55)</td>
<td>403</td>
</tr>
<tr>
<td>Frequency of administration</td>
<td>244 (60)</td>
<td>20 (5)</td>
<td>264</td>
</tr>
<tr>
<td>Preparation of drugs</td>
<td>165 (40)</td>
<td>35 (8)</td>
<td>200</td>
</tr>
<tr>
<td>Convenience of hospital/home treatment</td>
<td>227 (56)</td>
<td>325 (81)</td>
<td>552</td>
</tr>
<tr>
<td>Easy to use</td>
<td>118 (29)</td>
<td>142 (35)</td>
<td>260</td>
</tr>
<tr>
<td>Anxiety about having injections</td>
<td>152 (37)</td>
<td>0 (0)</td>
<td>152</td>
</tr>
<tr>
<td>Safety of hospital administration</td>
<td>312 (77)</td>
<td>2 (0)</td>
<td>312</td>
</tr>
<tr>
<td>Interference with everyday life</td>
<td>99 (24)</td>
<td>167 (41)</td>
<td>266</td>
</tr>
<tr>
<td>Reassuring effect of the doctor’s presence</td>
<td>270 (66)</td>
<td>0 (0)</td>
<td>270</td>
</tr>
<tr>
<td>Safety</td>
<td>62 (15)</td>
<td>37 (9)</td>
<td>99</td>
</tr>
<tr>
<td>Needle phobia or dislike of needles</td>
<td>46 (11)</td>
<td>30 (7)</td>
<td>76</td>
</tr>
<tr>
<td>Painful administration</td>
<td>33 (8)</td>
<td>52 (13)</td>
<td>85</td>
</tr>
<tr>
<td>Self-administration</td>
<td>144 (35)</td>
<td>100 (25)</td>
<td>244</td>
</tr>
<tr>
<td>Difficulty/discomfort to reach hospital</td>
<td>0 (0)</td>
<td>387 (96)</td>
<td>387</td>
</tr>
</tbody>
</table>

Determinants of preferences
Only relative convenience of i.v. and s.c. treatments and the confidence with home s.c. treatment were significantly related to preference. The percentage of patients preferring i.v. or s.c. administration in the determination of patients’ preference increased steadily with the perception of relative convenience of the two routes of administration (P < 0.0001 by chi-square test). Administrations by i.v. and s.c. were preferred by ~50% of the patients rating i.v. and s.c. as equally convenient (relative convenience = 0).

Favourite site of drug administration, favourite drug and possibility of self-administration
For those who chose i.v. infusion, the vast majority of patients (81.3%) stated their preference for administration at a hospital, whereas for who chose s.c. injection, 65% of patients preferred administration at home.

Moreover, patients’ confidence with home s.c. administration was analysed: 56% of the patients preferring s.c. injection were not completely confident with home administration and only 21.9% were keen to perform self-administration. On the contrary, 75.7% of patients...
preferred the drug to be administered by health care personnel (55%), relatives (39.4%) or others (5.6%). In the questionnaire, we described the different posologies of s.c. routes, but we did not ask the patient the preference between these posologies, to compare in an unquestionable way the preference between the different routes.

Discussion

RA patient’s experience of, and physician’s effort to achieve, the best treatment, may sometimes lead to discrepant opinions about drug choice [12], and clinicians are not always in a position to advise patients about treatment options based on what they would accept for themselves [8, 13, 14].

Despite similar survival rates during treatment in patients treated with different anti-TNF drugs, the adherence to treatment in different populations is higher for either i.v. or s.c. treatment [15, 16], compared with standard therapies. Nevertheless, the choice of therapeutic agent may be affected by the efficacy, safety, tolerability, route of administration and costs.

To the best of our knowledge, this is the first study addressing patients’ preferences for the route of administration in a population of RA patients being evaluated for anti-TNF treatment. In Italy, the eligibility criteria for anti-TNF therapy are active disease (DAS > 3.7 or DAS28 > 5.1) in patients with failure to achieve adequate DMARDs therapy (including MTX 15 mg/week for 3 months). Italian public health care guarantees as a whole primary care independent of financial factors, making it easier to empower patient choice and examine the factors that influence it; moreover, the availability of infusion spaces is guaranteed in all the prescriber centres; there are no differences of time of access or waiting list to start therapy. Therefore, in Italy, it is very difficult to evaluate the indirect costs of s.c. vs i.v. therapy.

The RADAI index was chosen because it reflects a patient’s perception of signs and symptoms, and represents RA in ‘real life’ [17]. The fact that almost all RA patients (97.6%) agreed to participate and completed the questionnaire demonstrates their willingness to be involved in decision making and to know all the information about anti-TNF drugs.

Patients showed good adherence to therapy and a widespread positive perception of care by their own rheumatologist, independent of the treatment outcome. Nevertheless, a percentage of patients (38%) were not satisfied with the current treatment and expressed the need to reassess their clinical situation in order to reshape the therapeutic strategy.

By analysing the data in our population, patient preferences were exactly split between the s.c. and i.v. routes of administration, without any difference in either gender, age, RA duration or in the category or total number of drugs used. Surprisingly, the distance of the patient from the hospital did not influence the choice of the two routes of administration. However, patients not satisfied with current treatment due to side effects were more likely to prefer s.c. administration, probably because they consider this method to be less aggressive.

Considering the RADAI items, only the ‘arthritis today pain’ and ‘articular pain’ items were significantly associated with the choice of i.v. route, probably due to the image of more speed of action of this option. The other items and the total score did not correlate with patient preference. Patients preferred i.v. administration.
especially because of perceived improved safety of hospital administration, the reassuring effect of the doctor’s presence, the frequency of administration, the convenience of treatment at hospital and smaller number of injections (Fig. 1). These reasons might indicate a solid trust of patients in health structures, preferring the i.v. route of administration at hospital. The frequency of treatment seems a determining factor in patient choice, and the lower number of administrations might seem the pivotal element for the choice of i.v. route [18, 19].

On the other hand, the other group of patients preferred the s.c. route especially because of the convenience of treatment at home and no interference with everyday life (n = 167; Table 1). These answers might identify a profile of a patient with logistic difficulties or a patient with a lesser trust in health structure. In a few cases, s.c. choice was probably induced by the profession, or by personal ability to perform a s.c. injection.

In other diseases, the fear of side effects at home was reported as a determining factor for preferring the i.v. over s.c. route [20]. In our cohort, a number of patients (33%) who chose s.c. administration were not completely confident with home administration and only a limited percentage of them (21.9%) was willing to perform self-administration. On the contrary, a large number of patients preferred the drug to be administered by another person such as relatives or health care personnel.

From this analysis, you may deduce that the profile of patient eligible for s.c. therapy could be those with confidence in self-administration techniques or a well-trained caregiver.

On the whole, the preference towards i.v. and s.c. routes identifies different patient profiles: some patients choose i.v. for safety, rapidity of action and reassurance, whereas some prefer s.c. for convenience and confidence with self-administration.

Our study had several unique features. First of all, unlike previous studies, all patients completed the questionnaire before the treatment was started. This study reflects the expectations of patients before starting any biologic drugs: it might be intriguing to compare the perceptions of patients about the therapy after a specific period of care. This informed-model of decision making is very useful in approaching RA patients. Therefore, understanding patient needs provides the physician with the basis for the right therapeutic choice [21, 22].

**Rheumatology key messages**

- No significant difference was found in patients by sex, age, disease duration or previous therapy.
- Some patients choose the i.v. route for safety, rapidity and reassurance, whereas others choose the s.c. route for convenience.

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