Treatment strategies in recent-onset rheumatoid arthritis : the best study

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Chapter 6

Patient preferences for treatment: report from a randomized comparison of treatment strategies in early rheumatoid arthritis (BeSt trial)

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ABSTRACT

Objectives. To determine treatment preferences among patients with recent onset rheumatoid arthritis participating in a randomized controlled trial comparing four therapeutic strategies.

Methods. A questionnaire was sent to all 508 participants of the BeSt trial, treated for an average of 2.2 years with either sequential monotherapy (group 1), step-up combination therapy (group 2), initial combination therapy with tapered high-dose prednisone (group 3), or initial combination therapy with infliximab (group 4). Treatment adjustments were made every 3 months to achieve low disease activity (DAS ≤ 2.4). The questionnaire explored patients' preferences or dislikes for the initial therapy.

Results. In total, 440 patients (87%) completed the questionnaire. Despite virtually equal study outcomes at 2 years, more patients in group 4 reported much or very much improvement of general health: 50%, 56%, 46% and 74% in groups 1-4, respectively (overall, $P<0.001$). Almost half of the patients expressed no preference or aversion for a particular treatment group, 33% had hoped for assignment to group 4 and 38% had hoped against assignment to group 3. This negative perception was much less prominent in patients actually in group 3. Nevertheless, 50% of patients in group 3 disliked having to take prednisone, while only 8% in group 4 disliked going to the hospital for intravenous treatment.

Conclusions. Within the limitations of our retrospective study, patients clearly preferred initial combination therapy with infliximab and disliked taking prednisone. After actual exposure, this preference remained, but the perception of prednisone improved. Patient perceptions need to be addressed when administering treatment.

INTRODUCTION

Several therapeutic strategies have been advocated to obtain disease control in patients with recent onset rheumatoid arthritis. In this respect, combinations of disease modifying anti-rheumatic Drugs (DMARDs) and biologic drugs have demonstrated to be more effective than single DMARD therapy (1-9). In addition, the side effect spectrum of combination therapy and biologic agents is acceptable when compared to monotherapy. It is obvious that the costs of medication are substantially higher for the new TNF-blocking agents than for prednisone. State of the art health economical evaluations are needed to determine whether there are rewards in terms of utilities and societal costs.

By contrast, the successful implementation of these strategies in daily clinical practice will also depend on any preferences or dislikes patients have for different therapies. Studies on this topic thus far have focussed on the patient's perception of the quality of care (10) and outcome measurements (11;12) more than on the patient's preference for the prescribed medication. A study that evaluated patient trade-offs between specific drug characteristics for a number of DMARDs revealed that older patients with established rheumatoid arthritis prefer drugs with the least short-term toxicity (13).

Considerable information is available on the efficacy and toxicity of treatment strategies in recent onset rheumatoid arthritis, but the most effective strategies can have various disadvantages for the patients that should be taken into account. DMARD combination therapy implies taking many pills and biologics require parenteral administration. To learn the opinion of the patients with recent onset rheumatoid arthritis enrolled in the BeSt study (Behandel Strategieën; in English, treatment strategies), a questionnaire on the subject of patient preferences for treatment modalities was used. We compared the patients' specific likes and dislikes towards the treatment they received with objective study outcomes.

PATIENTS AND METHODS

Patients

The BeSt study was designed and conducted by rheumatologists participating in the Foundation for Applied Rheumatology Research (FARR), in 18 peripheral and 2 university hospitals in the Western part of the Netherlands. Between April 2000 and August 2002, patients with recent onset rheumatoid arthritis, as defined by the American College of Rheumatology (ACR) 1987 criteria (14), were recruited. Patients were ≥18 years of age, with a disease duration ≤2 years, and had active disease with ≥6/66 swollen joints, ≥6/68 tender joints and either an erythrocyte sedimentation rate (ESR) ≥28 mm/hr or a visual analogue scale (VAS) global health ≥20 mm (on a scale of 0-100 mm where 0=best, 100=worst). Patient enrolment criteria have been described in detail previously (9). The

Medical Ethics Committee at each participating centre approved the study protocol and all patients provided written informed consent before enrolment.

Patients were allocated to one of four treatment groups by variable block (9-13) randomisation, stratified per centre. Treatment groups were sequential monotherapy starting with methotrexate (group 1), step-up combination therapy also starting with methotrexate (group 2), initial combination therapy with methotrexate, sulphasalazine and a tapered high-dose prednisone (group 3) and initial combination therapy with methotrexate and infliximab (group 4). For patients failing on their medication (defined as a Disease Activity Score (DAS) >2.4) (15), or in case of intolerable side effects, the treatment protocol described a number of subsequent treatment steps. If the DAS was ≤2.4 for at least 6 months, medication was gradually tapered until one drug remained in a maintenance dose. The DAS was measured every 3 months by a trained nurse who remained blinded for the treatment received (9).

Table 1. Questionnaire on the subject of patient preferences for treatment strategies

1. Has the treatment for rheumatoid arthritis improved your general health?
2. If yes, how much? Hardly Little Moderately Much Very much
3. Do you feel your current state of health is acceptable for the next year, taking in mind the way you feel at this moment and the medication you have to take for it?
4. Was there, before you started with the BeSt study, one particular group you hoped to be assigned to? No Yes, I hoped for group 1 Yes, I hoped for group 2 Yes, I hoped for group 3 Yes, I hoped for group 4
5. Was there, before you started with the BeSt study, one particular group you hoped not to be assigned to? No Yes, I hoped not group 1 Yes, I hoped not group 2 Yes, I hoped not group 3 Yes, I hoped not group 4
6. Suppose you would present with rheumatoid arthritis at this moment and treatment would have to be initiated, what kind of treatment would you choose to start with? One well known antirheumatic drug A combination of well known antirheumatic drugs without prednisone A combination of well known antirheumatic drugs with prednisone A combination of well known antirheumatic drug with a new intravenous drug*
7. The treatment gave me a rapid relief of symptoms†
8. I disliked having to take prednisone†
9. I disliked going to the hospital for intravenous treatment†

*'A new intravenous drug' refers to infliximab, the only available new intravenous drug for the treatment of rheumatoid arthritis at that time.

†Patients could mark these statements if they agreed.

Study design and intervention

In November 2003, an ad-hoc questionnaire comprising multiple-choice questions and yes/no statements (Table 1) was sent along with a stamped envelope to all patients enrolled in the BeSt study. In an accompanying letter, the importance of knowing the patient's preference for a specific treatment was pointed out and all patients were asked to complete and return the form. Using the same terms as in the patient information leaflet provided at the start of the BeSt study, it was stated that patients presenting with rheumatoid arthritis are usually treated with monotherapy or step-up combination therapy, but that there are indications that initial combination therapy or the newest intravenous drug infliximab might be more effective. The patients had not yet been informed about the results of the BeSt study.

The results of the questionnaire were compared with results of the Health Assessment Questionnaire (HAQ) (16), the DAS and the VAS global health, which were assessed every 3 months by a blinded trained nurse.

Statistical analysis

The data obtained from the multiple-choice questions and statements, and categorical patient variables such as gender and rheumatoid factor were analysed using the chi-square test. Measures with a Gaussian distribution, expressed as mean and standard deviation (SD), were analyzed using a one-way analysis of variance. When overall tests were statistically significant, a post-hoc least significant difference test was used for the HAQ and Tukey's honestly significant difference test was used for DAS and VAS global health to correct for multiple testing (9).

RESULTS

Overall, 440 out of 508 patients (87%) completed and returned the questionnaire (85%, 83%, 87% and 93% in groups 1 through 4, respectively). The patients had been in the BeSt study for a mean (SD) period of 2.2 (0.6) years at the time the questionnaire was distributed. There were no statistically significant differences in baseline characteristics between those patients who completed the questionnaire and those who did not (Table 2).

BeSt study results

After 2 years of therapy, patients in all groups had comparable functional and clinical outcomes. Patients who received initial combination therapy with prednisone or infliximab had a significantly more rapid improvement of physical function and relief of clinical signs and symptoms compared with patients who received sequential monotherapy or step-up combination therapy (Figure 1) (9). Importantly, these measurements included patient reported outcomes such as HAQ and patient assessment of global health by VAS.

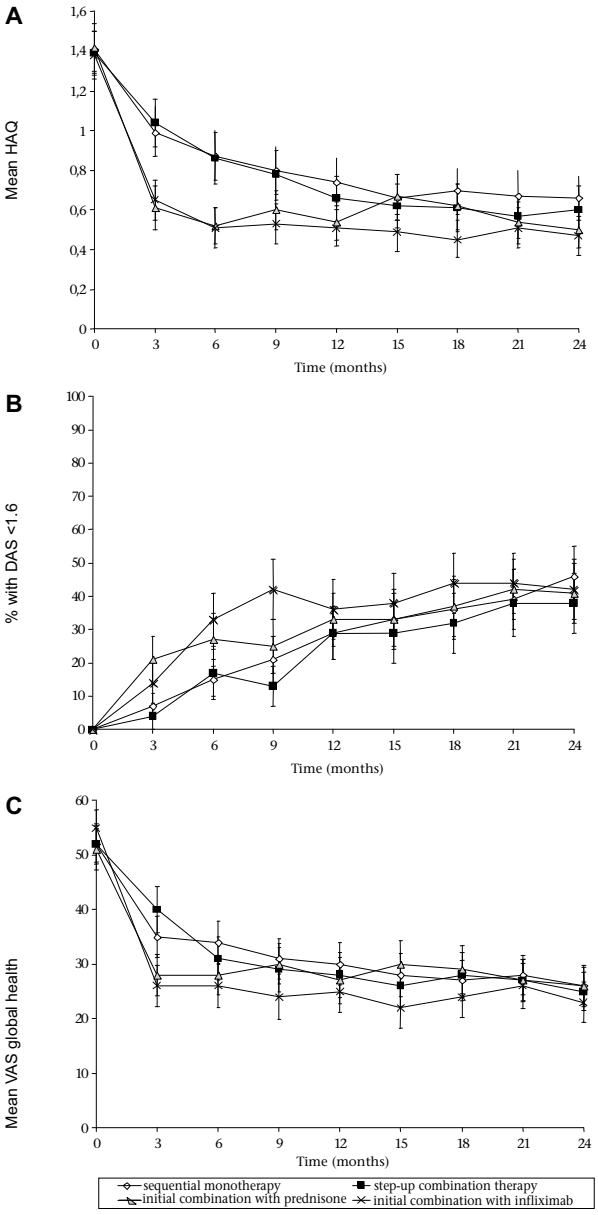

Figure 1. Clinical outcomes of the BeSt study for each treatment group during 2 years of follow-up. (A) Mean Health Assessment Questionnaire (HAQ). (B) Percentage of patients in clinical remission (DAS <1.6). (C) Mean Visual Analogue Scale (VAS) global health.
Error bars represent 95% confidence intervals. See Patients and Methods for description of treatment groups.

Table 2. Baseline characteristics of the patients who completed and returned the questionnaire (completers) and those who did not (non-completers)*

	Completers N=440	Non-completers N=68
Female (%)	301 (68)	42 (62)
Age, mean (SD) years	55 (13)	53 (16)
Symptom duration, median (IQR) weeks	23 (13-51)	24 (15-65)
RF-positivity (%)	284 (65)	45 (66)
ESR, mm/h	41 (28)	38 (28)
DAS, mean (SD)	4.4 (0.9)	4.5 (0.6)
HAQ, mean (SD)	1.4 (0.7)	1.4 (0.8)
SHS, median (IQR)	4.0 (1.5-8.5)	4.0 (1.0-10.3)

*RF, rheumatoid factor; ESR, erythrocyte sedimentation rate; DAS, disease activity score; HAQ, health assessment questionnaire; SHS, total Sharp-van der Heijde Score for radiographic joint damage; SD, standard deviation; IQR, interquartile range; there were no statistically significant differences between the completers and the non-completers.

Patient satisfaction and preferences

Significantly more patients in group 4 stated their general health had improved much to very much since the initiation of the treatment: 50%, 56%, 47% and 74% of patients in groups 1 through 4, respectively (all pairwise comparisons with group 4 $P \leq 0.001$; other comparisons, P=NS). Significantly more patients in groups 3 and 4 reported a rapid relief of symptoms: 52%, 54%, 78% and 85% of patients in groups 1 through 4, respectively (all pairwise comparisons between group 1 or 2 and group 3 or 4, $P<0.001$; other comparisons, P=NS). The majority of patients felt that their current state of health together with the medication they had to take was acceptable for the next year, but the patients in group 3 were less satisfied: 85%, 88%, 72% and 85% of patients, respectively (all pairwise comparisons with group 3, P=0.05; other comparisons, P=NS). These responses correspond with the levels of disease activity (DAS), with the observation that patients in group 3 more often had a low DAS while reporting not to be satisfied with their state of health (Figure 2). Patients were asked whether, at the start of the treatment, they had hoped to be assigned to a particular treatment group. Pretrial preference was increased for the treatment actually received. Overall, 44% of patients reported not to have had a preference for any of the treatment groups. Preference for group 1 was expressed by 17 (16%) patients in group 1, and by 18 (5%) patients in groups 2, 3 and 4. Preference for group 2 was expressed by 8 (8%) patients in group 2, and by 12 (4%) patients in groups 1, 3 and 4. Preference for group 3 was expressed by 22 (19%) patients in group 3 and by 5 (2%) patients in groups 1, 2 and 4. Finally, preference for group 4 was expressed by 74 (62%) patients in group 4 and by 71 (22%) patients in groups 1, 2 and 3 (Table 3). For interpretation of group 2 it should be noted that at the two-year time point 31% of patients still received monotherapy.

Conversely, 4% of patients had hoped not to be assigned to group 1, 1% had hoped

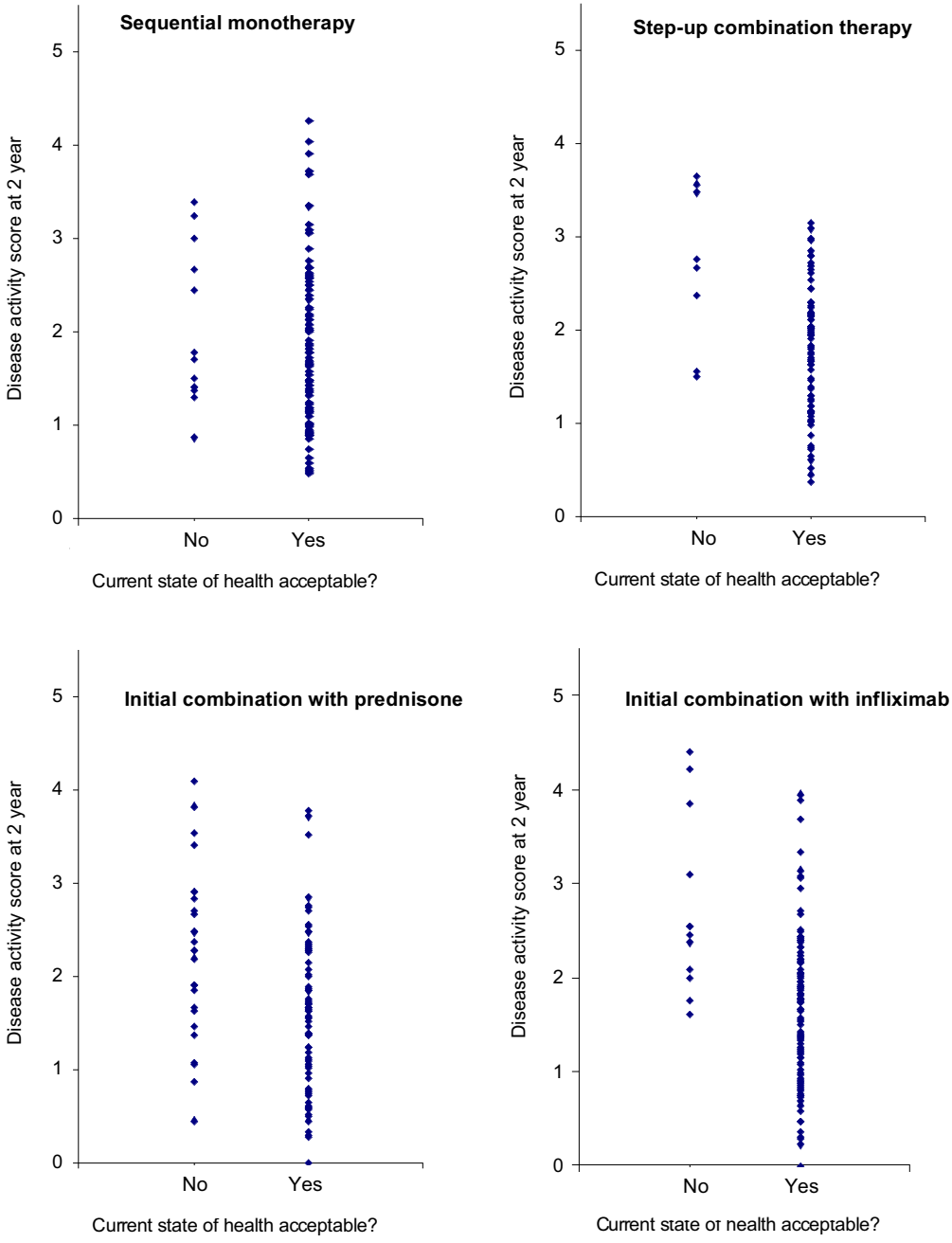

Figure 2. Scatter plots of Disease Activity Score at 2 year and the answer to the question whether or not patients find their current state of health acceptable for the next year, for all four treatment groups.

Table 3. Results of questionnaire on the subject of patient preferences for treatment strategies*

	Sequential monotherapy (group 1)	Step-up combination therapy (group 2)	Initial combination with prednisone (group 3)	Initial combination with infliximab (group 4)	Total
Was there, before you started with the BeSt study, one particular group you hoped to be assigned to?					
No preferred group	48 (45)	55 (55)	57 (50)	35 (29)	195 (44)
Hoped for group 1	17 (16)	11 (11)	4 (4)	3 (3)	35 (8)
Hoped for group 2	5 (5)	8 (8)	5 (4)	2 (2)	20 (5)
Hoped for group 3	3 (3)	0 (0)	22 (19)	2 (2)	27 (6)
Hoped for group 4	27 (25)	23 (23)	21 (18)	74 (62)	145 (33)
No answer	6 (6)	3 (3)	6 (5)	3 (2)	18 (4)
Was there, before you started with the BeSt study, one particular group you hoped not to be assigned to?					
No preferred group	45 (42)	49 (49)	62 (54)	46 (39)	202 (46)
Hoped not group 1	3 (3)	2 (2)	10 (8)	4 (3)	19 (4)
Hoped not group 2	0 (0)	2 (2)	2 (2)	1 (1)	5 (1)
Hoped not group 3	48 (45)	40 (40)	25 (22)	54 (45)	167 (38)
Hoped not group 4	4 (4)	4 (4)	8 (7)	8 (7)	24 (6)
No answer	6 (6)	3 (3)	8 (7)	6 (5)	23 (5)
If you presented with rheumatoid arthritis at this moment and treatment would have to be initiated, what kind of treatment would you choose to start with					
One well known antirheumatic drug	40 (38)	33 (33)	12 (10)	9 (8)	94 (21)
Combination without prednisone	18 (17)	29 (29)	28 (24)	9 (8)	84 (19)
Combination with prednisone	2 (2)	3 (3)	46 (40)	3 (2)	54 (12)
Combination with infliximab	43 (40)	27 (27)	26 (23)	95 (80)	191 (44)
No answer	3 (3)	8 (8)	3 (3)	3 (2)	17 (4)

*Data are number (percentage) of patients. See Patients and Methods for description of treatments groups.

not group 2, 38% had hoped not group 3, 6% had hoped not to be assigned to group 4 and 46% did not have a particular group they disliked (Table 3). For this question an effect of group allocation was only clear in group 3: 22% of patients who actually received this treatment had hoped not to be assigned to group 3, whereas this percentage was much higher (≥40%) in the other groups.

Furthermore, we asked patients which treatment they would prefer if diagnosed with rheumatoid arthritis today. Overall, 21% of patients would choose treatment with one well known antirheumatic drug, 19% would choose a combination without prednisone, 12% would choose a combination with prednisone and 44% of patients would choose a combination with the newest intravenous drug, implying treatment with 'a combination with infliximab' (Table 3). Infliximab was the only new intravenous antirheumatic drug available at the time of the study and was mentioned in the introduction of the questionnaire as being a new intravenous drug. Therefore, the remainder of the text infliximab will be used.

Half of the patients who were treated with initial combination therapy including prednisone (group 3) reported to dislike having to take prednisone. At the time this question was asked, 8% of the patients in group 3 actually received prednisone. Among the patients in groups 1, 2 and 4, 15%, 20% and 9%, respectively, reported that they disliked having to take prednisone and 6%, 13% and 6%, respectively, received low dose prednisone (up to 7.5mg/day) at that time (all pairwise comparisons with group 3, P<0.001; group 2 vs 4, P=0.023; other comparisons, P=NS). Eight percent of patients treated with initial combination therapy with infliximab disliked having to go to the hospital for intravenous treatment (overall, P=NS). At the time of the questionnaire, 19% of the patients in group 4 were still treated with infliximab. Among the patients in groups 1, 2 and 3, 2%, 3% and 2%, respectively, stated that they disliked having to go to the hospital for intravenous treatment. When the question was asked, 27%, 8%, and 10% of the patients in groups 1 through 3, respectively, actually received treatment with infliximab.

There were no differences in adherence to the treatment protocol between patients who expressed their dislike for their allocated treatment group and patients who did not. In group 3, 25 patients expressed their dislike for allocation to group 3. Of these patients 3 (12%) lost adherence to the treatment protocol. Of the remaining 90 patients in group 3, 11 (12%) lost adherence to the treatment protocol. In group 4, 8 patients expressed their dislike for allocation to group 4. None of these patients lost adherence to the treatment protocol. In total 5 patients lost adherence in group 4. Outcomes were comparable between patients with or without strong dislikes for a certain group (data not shown).

DISCUSSION

This study, in setting of effective to highly effective therapy in patients with recent onset rheumatoid arthritis, documents important discrepancies between patient perceptions and preferences on the one hand, and measured outcome of treatment on the other. The results are robust as patient outcome measurements were state-of-the-art, response rates to the questionnaire were high, and the answers to the questions were consistent. On the one hand, the majority of patients who completed the questionnaire reported that, since receiving treatment for rheumatoid arthritis in the BeSt trial, their general health had improved much to very much. More patients treated with initial combination therapy with prednisone (group 3) or infliximab (group 4) reported a rapid relief of symptoms after starting treatment than patients treated with sequential monotherapy (group 1) or step-up combination therapy (group 2). Based on these assessments, the patients' perceptions appear to be consistent with the more objective outcomes of the BeSt study, which showed that all patients improved remarkably in terms of disease activity and functional ability and that the patients in groups 3 and 4 improved more rapidly than those in groups 1 and 2. On the other hand, there is a marked difference in most of the questionnaire results between group 3 and group 4, even though the DAS and HAQ results and even the VAS global health of these patients are virtually overlapping and there were no significant differences in adverse events (9). Fewer patients in group 3 than in group

4 report 'much to very much improvement' of their general health, and fewer patients in group 3 than in group 4 found their current state of health including the drugs they have to take acceptable for the next year. There were no differences in adherence between patients with or without strong dislikes for a certain treatment group, but this is in a trial setting with intense monitoring and disease activity driven treatment adjustments.

The dislike of prednisone, which appears strong and widespread, revolves around (mis)information about possible side effects, whereas of the newer TNF-blocking agents information appears to focus on the efficacy and less on possible (future) side effects. The perception can be (partially) modified by experience, as shown by careful comparison of group 3 with the other groups. Patients who actually received prednisone showed more preference and less aversion to this drug, despite still 'disliking taking prednisone', and more patients would choose a strategy with prednisone if their rheumatoid arthritis started today. Patients would have more realistic expectations if they receive the proper information about the benefits and risks of prednisone in the dosages used in rheumatoid arthritis treatment. For infliximab it is obvious that more patients prefer this drug, and this preference is increased in those who actually received the drug. This study has important limitations. First and foremost, the questionnaire explored opinions and preferences two years after the start of therapy rather than up front. It is clear from the responses that patients were unable to fully recall their pre-trial preferences and that these were confounded with their experience in the trial. The only other (unlikely) explanation is that the otherwise well balanced groups were highly unbalanced for treatment preference and that by chance many patients were allocated to the group they preferred.

We have to ask ourselves whether we have influenced the patients' responses by suggestive wording of the questions. For instance, 'newest intravenous drug' was used to reflect the words used in the original patient information leaflet for the trial. Put in contrast to 'well known antirheumatic drugs', we worried that it might evoke a sense of risk and uncertainty, but given the received response for the patients it might have had a more positive connotation. The negative connotation of 'dislike' could have been sensed more strongly in combination with 'having to take prednisone' than with 'going to hospital for intravenous treatment' instead of 'having to use infliximab'. Also, the yes/no statements could have had more answer categories and few questions were posed specifically on the other DMARDs. Nevertheless, the negative perception of prednisone and the positive perception of infliximab are unmistakeable.

The implementation of new treatment strategies for patients with rheumatoid arthritis is primarily based on the comparison of treatment effects, side effects and costs. However, perceptions of patients should be addressed as these perceptions surely impact on treatment adherence and ultimately treatment decisions in future daily practice.

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COMPETING INTERESTS

CFA has received a fee for speaking at a conference by Schering-Plough, the manufacturer of infliximab; FCB has received lecture fees from Schering-Plough; BAD has received funds for research and lecture fees from Schering-Plough.

REFERENCES

1 Boers M, Verhoeven AC, Markusse HM, van de Laar MA, Westhovens R, van Denderen JC, et al. Randomised comparison of combined step-down prednisolone, methotrexate and sulphasalazine with sulphasalazine alone in early rheumatoid arthritis. *Lancet* 1997;350:309-18.

2 Breedveld FC, Emery P, Keystone E, Patel K, Furst DE, Kalden JR, et al. Infliximab in active early rheumatoid arthritis. *Ann Rheum Dis* 2004;63:149-55.

3 Calguneri M, Pay S, Caliskaner Z, Apras S, Kiraz S, Ertenli I, et al. Combination therapy versus monotherapy for the treatment of patients with rheumatoid arthritis. *Clin Exp Rheumatol* 1999;17:699-704.

4 Genovese MC, Bathon JM, Martin RW, Fleischmann RM, Tesser JR, Schiff MH, et al. Etanercept versus methotrexate in patients with early rheumatoid arthritis: two-year radiographic and clinical outcomes. *Arthritis Rheum* 2002;46:1443-50.

5 Gerards AH, Landewe RB, Prins AP, Bruyn GA, Goei The HS, Laan RF, et al. Cyclosporin A monotherapy versus cyclosporin A and methotrexate combination therapy in patients with early rheumatoid arthritis: a double blind randomised placebo controlled trial. *Ann Rheum Dis* 2003;62:291-6.

6 Marchesoni A, Battafarano N, Arreghini M, Panni B, Gallazzi M, Tosi S. Radiographic progression in early rheumatoid arthritis: a 12-month randomized controlled study comparing the combination of cyclosporin and methotrexate with methotrexate alone. *Rheumatology* 2003;42:1545-9.

7 Mottonen T, Hannonen P, Leirisalo-Repo M, Nissila M, Kautiainen H, Korpela M, et al. Comparison of combination therapy with single-drug therapy in early rheumatoid arthritis: a randomised trial. *Lancet* 1999;353:1568-73.

8 St Clair EW, van der Heijde DM, Smolen JS, Maini RN, Bathon JM, Emery P, et al. Combination of infliximab and methotrexate therapy for early rheumatoid arthritis: a randomized, controlled trial. *Arthritis Rheum* 2004;50:3432-43.

9 Goekoop-Ruiterman YP, de Vries-Bouwstra JK, Allaart CF, van Zeben D, Kerstens PJ, Hazes JM, et al. Clinical and radiographic outcomes of four different treatment strategies in patients with early rheumatoid arthritis (the BeSt study): a randomized, controlled trial. *Arthritis Rheum* 2005;52:3381-90.

10 Jacobi CE, Boshuizen HC, Rupp I, Dinant HJ, van den Bos GA. Quality of rheumatoid arthritis care: the patient's perspective. *Int J Qual Health Care* 2004;16:73-81.

11 Ahlmen M, Nordenskiold U, Archenholtz B, Thyberg I, Ronnqvist R, Linden L, et al. Rheumatology outcomes: the patient's perspective. A multicentre focus group interview study of Swedish rheumatoid arthritis patients. *Rheumatology* 2005;44:105-10.

12 Strand V, Cohen S, Crawford B, Smolen JS, Scott DL. Patient-reported outcomes better discriminate active treatment from placebo in randomized controlled trials in rheumatoid arthritis. *Rheumatology* 2004;43:640-7.

13 Fraenkel L, Bogardus ST, Concato J, Felson DT, Wittink DR. Patient preferences for treatment of rheumatoid arthritis. *Ann Rheum Dis* 2004;63:1372-8.

14 Arnett FC, Edworthy SM, Bloch DA, McShane DJ, Fries JF, Cooper NS, et al. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. *Arthritis Rheum* 1988;31:315-24.
15 van der Heijde DM, van 't Hof MA, van Riel PL, van de Putte LB. Development of a disease activity score based on judgment in clinical practice by rheumatologists. *J Rheumatol* 1993;20:579-81.
16 Siegert CE, Vleming LJ, Vandenbroucke JP, Cats A. Measurement of disability in Dutch rheumatoid arthritis patients. *Clin Rheumatol* 1984;3:305-9.