

Discordant perspectives of rheumatologists and patients on COBRA combination therapy in rheumatoid arthritis

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Objective. The COBRA therapy (combination therapy in early rheumatoid arthritis) has proven to be an effective treatment for early RA, but is rarely prescribed. A survey showed reluctance of Dutch rheumatologists to apply COBRA therapy in early RA. The present qualitative study was carried out to further explore the reservation of Dutch rheumatologists towards prescribing COBRA therapy and include patients' view on (components of) COBRA therapy.

Methods. Two focus group discussions were undertaken for rheumatologists ($n_1 = 8$, $n_2 = 7$) and two for patients ($n_1 = 4$, $n_2 = 8$). In addition, in-depth interviews were conducted with 11 rheumatologists and 1 patient. These were taped and transcribed. Two independent researchers identified themes and these were discussed with three other researchers.

Results. Rheumatologists were positive concerning effectiveness of COBRA therapy, but highly concerned about their patients' possible negative reaction to the large amount of pills to be prescribed. In addition, rheumatologists perceived lack of time explaining and prescribing COBRA therapy and felt uncomfortable prescribing high doses of prednisolone. Patients were positive about an aggressive combination therapy such as COBRA, and they had no qualms taking many pills if this could improve their prognosis. Patients associated prednisolone with negative side-effects, but were also aware of the benefits and the need of prednisolone in rough times. A decrease in the amount of pills after intensive treatment was highly appreciated.

Conclusion. Rheumatologists and patients differed in opinion about the use of COBRA therapy. Rheumatologists were particularly concerned about their patients' reaction towards them prescribing such an aggressive and complex therapy, whereas patients, while aware of the side-effects, were most interested in suppressing illness symptoms and reducing future damage regardless of the amount of pills.

KEY WORDS: Rheumatoid arthritis, Combination therapy, Qualitative, Focus group, Patient perspective, COBRA therapy, Glucocorticoids.

Introduction

In the last decade, knowledge on the optimal treatment of RA has greatly increased. Nowadays, it is generally accepted that initial combination therapy and biologic agents are more effective than single DMARD therapy [1–5], although evidence is not conclusive yet [6]. As biologic agents are not commonly introduced at the onset of disease, combination therapy constitutes the obvious choice for treatment of early RA.

The COBRA therapy (combination therapy in early rheumatoid arthritis) is a step-down combination strategy comprising SSZ (2 g/day), MTX (7.5 mg/week) and prednisolone (initially 60 mg/day, tapered in 6 weekly steps to 7.5 mg) (Fig. 1). COBRA therapy has been shown to be very effective in the treatment of early RA. The original trial reported in 1997 showed that treatment with COBRA therapy leads to faster suppression of disease activity and delay in the rate of radiological progression in early RA, compared with traditional monotherapy with SSZ [7]. Disease activity was almost immediately improved in patients using the COBRA therapy, toxicity was low and costs of the treatment were equal to those of SSZ monotherapy [8, 9]. Five-year follow-up by Landewé *et al.* [10] showed that damage control persists for up to 5 yrs after treatment, independent of subsequent DMARD use and disease activity.

More recently, the BeSt trial, comparing clinical and radiographic outcomes of four treatment strategies, showed equal effectiveness of COBRA therapy to initial combination therapy of high-dose MTX with infliximab. This resulted in earlier functional improvement and less radiographic damage after 1 yr, compared

with sequential monotherapy or step-up combination therapy [11, 12].

Despite this irrefutable evidence for effectiveness of COBRA therapy, former research showed reluctance of Dutch rheumatologists to apply COBRA therapy in early RA [13]. The average attitude towards the COBRA therapy was positive, and was mainly caused by high scores on the items effectiveness and safety. However, COBRA therapy was also perceived as somewhat complex to administer. In contrast to this positive attitude, most respondents did not intend to prescribe COBRA therapy in the near future.

In order to better understand this discrepancy and to include patients' view on COBRA therapy, we performed the present qualitative study.

Methods

To investigate the opinions and beliefs regarding all aspects of COBRA combination therapy, a qualitative approach was used, combining focus group discussions and semi-structured in-depth telephone interviews. Focus group research is qualitative research that gathers rich, descriptive data from participants convened in small, homogeneous groups, focusing on a specific topic. The emphasis is on understanding participants' experiences, attitudes, perspectives and assumptions through interaction between respondents [14]. The idea is that every finding is equally important regardless of the number of times mentioned. The nature of in-depth interviews is more structured than that of focus group discussions and focuses deeply on the opinion of the individual.

Participants

Rheumatologists (main focus of research). Opinions and beliefs of rheumatologists towards COBRA therapy were the main focus of our study. First, a random selection of 17 rheumatologists working in the two academic hospitals and the Jan van Breemen

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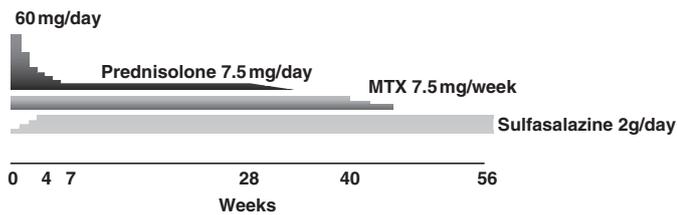


FIG. 1. COBRA combination therapy.

Institute in Amsterdam were invited to participate in a focus group discussion. This resulted in a group of eight participants. Second, all rheumatologists who had participated in the original COBRA trial ($n = 10$) were invited for a focus group discussion. These rheumatologists formed a group of seven participants.

Third, the research team identified opinion leaders from the Dutch rheumatology field, based on their role as professor of rheumatology, an educator of new rheumatologists or a rheumatologist working in a large peripheral hospital. Due to their busy schedules, they were invited for an in-depth telephone interview. Out of 20 invited opinion leaders, 11 accepted.

Patients. Firstly, the rheumatologists of the research team invited eight patients with established RA from their own practice; one rheumatologist selected two patients exposed to COBRA therapy; one rheumatologist invited two patients currently on anti-TNF therapy and two rheumatologists both selected two patients exposed to prednisolone. This resulted in a group with four patients, one with COBRA experience, two with at least anti-TNF experience and one with at least prednisolone experience.

Secondly, 32 patients who were active members of the national patient rheumatic association in the central region of The Netherlands were invited. These patients, listed as tutors and volunteers to help new patients with rheumatic diseases, formed a group of eight participants. In addition, one patient unable to take part in the group was invited for an in-depth telephone interview.

Invited participants (rheumatologists and patients) who did not attend informed us that they were unable to meet at the appointed date.

Data collection

The structure of the focus group discussions and in-depth interviews is shown in Table 1. The study focused mainly on the rheumatologists as the prime target for implementation efforts. Thus, for the rheumatologists data collection continued until saturation was reached. In contrast, we felt it was important to research patient opinion, but did not seek saturation. In all contacts with patients, a short scenario was presented in which they were asked to imagine that they came to the rheumatologist for the first time with their complaints and that the COBRA therapy was explained to them (see supplementary data, available at *Rheumatology Online*). Participants were reassured that what they said during the focus groups and interviews would be anonymously reported. Before the start, all participants gave their informed consent. All focus group discussions and in-depth interviews were conducted, taped and transcribed by the same researcher (L.vT.), who was not involved as a rheumatologist or in the clinical care management of any of the patient participants. Under Dutch law, this research does not need approval from an ethical review board. This study was conducted between May 2005 and June 2006.

Data analyses

During the focus group discussions and interviews, the responses of the participants were thoroughly investigated through the formulation of questions like: ‘Why do you do that?’ or ‘In what

TABLE 1. Basic structure of the focus group discussions and interviews

Rheumatologists
How do you treat most of your early RA patients?
Did you ever use COBRA combination therapy or a related combination therapy?
What are the advantages of COBRA combination therapy in the treatment of early RA?
What are the disadvantages of COBRA combination therapy in the treatment of early RA?
How do you feel about SSZ, MTX and prednisolone?
How do you feel about the dosage in which these medications are used in the COBRA therapy?
Do you think there is enough scientific evidence to support the COBRA therapy?
What should be changed regarding the COBRA therapy, to make you prescribe it more often to early RA patients?
Patients
What is your experience regarding the treatment of your arthritis?
With what treatment have you had a good experience, with what treatment a bad experience?
How do you feel about SSZ, MTX and prednisolone? What is your experience with these drugs?
What aspects of treatment are important to you?
Presentation of COBRA scenario (see supplementary data available at <i>Rheumatology online</i>)
Feedback on COBRA scenario

The nature of in-depth interviews is more structured than that of focus group discussions.

way do you mean this?’ The data were analysed according to the interpretative phenomenological analysis (IPA) method [15, 16], which not only shows the content of the qualitative data, but also searches for underlying cognitive and emotional concepts. The IPA method is a data driven, bottom-up approach that avoids prior assumptions to minimize bias. To further reduce the chance of bias, transcripts were cross-validated through researcher triangulation: two independent researchers (L.vT. and A.P.) systematically searched for themes in the first group, forged connections between themes, then moved on to the next group. After all the transcripts were analysed, the two independent researchers agreed to the same set of major themes. Further data exploration created new categories that were grouped in the themes. Themes were discussed and agreed upon by three other researchers. All transcripts were analysed using the same techniques with opinions and feelings towards components of the COBRA therapy being the main focus of the analytical procedure. Data analysis was carried out using NVivo software for coding. Because of the qualitative nature of the data, frequencies are stated in broad terms (some, many, all), and no statistical tests were used.

Results

Twenty-six rheumatologists participated, with a mean number of 23 yrs of experience (median 25; range 1–34). Nineteen rheumatologists were males. Thirteen patients with rheumatic diseases [RA ($n = 11$), PsA ($n = 1$) and juvenile inflammatory arthritis ($n = 1$)] participated. The mean duration of disease for patients was 22 yrs (median 21; range 1–50). Three patients were males.

The results of rheumatologists and patients are discussed separately and presented using summaries and quotes (rheumatologists are shortened to ‘R’ and patients are shortened to ‘P’).

Rheumatologists

Most rheumatologists treated their early RA patients with MTX, starting with 7.5 or 10 mg during the first weeks, and increasing this to a maximum of 25 within 2 or 3 months. For patients with a very active disease, some added glucocorticoids, preferably by injection in the affected joint(s), otherwise prednisolone orally up to 15 mg as bridge therapy. The major determinants for a rheumatologist’s choice of medication were the patient’s disease activity and prognostic factors. In addition, comorbidity, personal desires of a patient, the duration and location of disease, and age

of a patient were taken into account. On average, rheumatologists saw two to three newly diagnosed RA patients per month. Participants rarely prescribed COBRA therapy and were unfamiliar with its exact treatment schedule. Four main themes could be identified: patient-related concerns; personal perceived barriers (practical and emotional); societal implications; and perceived value of scientific evidence.

Patient-related concerns. Rheumatologists emphasized the negative aspects of the COBRA therapy for the patient. Their main concern was the large number of tablets that has to be taken (the three drugs SSZ, MTX and prednisolone, with additional folic acid and bisphosphonates) and the kind of tablets (large tablets of SSZ).

R-F: 'I personally would find it extremely annoying to swallow such large pills.'

They were worried about their patients' opinion about themselves (the practising physician) and they expected that their patients would strongly oppose the use of prednisolone; in addition, rheumatologists felt uncomfortable with the possibility of a bloated 'Cushing face'.

R-G: 'The patient leaves the room and says: "this doctor is completely nuts. I enter with pain in my wrist and I leave with 8 different kinds of tablets!"'

R-J: 'Very often it depends on the patient. When you mention the word [prednisolone] it makes their hair stand on end.'

On the other hand, rheumatologists also saw great advantages of aggressive combination therapy for the patient:

R-T8: 'The first blow is half the battle, if you can simply convince the patient and improve their condition.'

Personal perceived barriers. In the discussion of positive and negative aspects of COBRA therapy, two types of personal perceived barriers were identified: practical or workload-related barriers and emotional barriers.

Some rheumatologists felt that explaining COBRA therapy to a patient took so much effort and time:

R-J: 'It takes a lot of talking to convince a patient that this is very good for him.'

R-C: 'Way too much work, I only have 10 minutes...'

Emotional statements were made about the COBRA therapy as a whole, but especially the use of high-dose prednisolone in the COBRA therapy gave emotional resistance.

R-T2: 'The dose of prednisolone, as physician I'd rather start with 20 or 30 mg, it's a matter of feeling, you, know, but it feels more comfortable than 60 mg.'

R-A: 'An essential point is simply, do you want to implement this schedule yes or no. And my feeling is, I'm just not going to do it. If deep in your heart you are not convinced that this is the schedule I'd like to give to my patient, regardless of how good the results are, then there isn't much point to it, if I'm honest.'

R-T5: 'It's more the fear, "in the doctor's mind". The fear lingers a bit, you can't get it out of your head completely.'

Societal implications. Only one rheumatologist felt that as a doctor he had the obligation towards society to rather choose a cheap effective therapy as opposed to an expensive effective therapy.

R-M: 'Because I feel we as professionals have a certain responsibility to society; if we can achieve the same effect with fewer financial resources we should do so.'

Perceived value of scientific evidence. Scientific evidence was regarded as very important. It was generally accepted that the COBRA trial and the BeSt trial showed that COBRA combination therapy is very effective, both in the short term and the long term.

R-C: 'With this schedule you KNOW that after 5 years there are fewer erosions than with sulfasalazine alone.'

However, much discussion focused on components of the COBRA therapy: the effectiveness of the combination of MTX and SSZ was put in doubt, since a study of Haagsma *et al.* [17] showed that SSZ and MTX in combination are as effective as both drugs alone. Rheumatologists doubted the value of SSZ in the treatment schedule, especially because SSZ was maintained as the anchor drug in the original COBRA trial. SSZ was perceived as old-fashioned and currently replaced by high dosages of MTX. The dosage of 7.5 mg MTX in the COBRA therapy was perceived as ineffective. Additionally, they felt there was no evidence that a dosage of 20 mg prednisolone would be less effective than 60 mg.

Even though some rheumatologists saw great advantages, most rheumatologists were not convinced that treating their patient with COBRA therapy was the best for them:

R-T9: 'The greatest disadvantage is the feeling one has of doing things that are not necessary and that unnecessarily complicate matters. If one is convinced that all those three things are necessary, then of course one can explain it and create a system to make it clear to the patient. But it is more that one isn't convinced that giving this combination in this particular way is really necessary.'

Patients

The patients, mostly with long-standing disease, still remembered that in their early stages it took quite some time before the disease had been diagnosed and treatment initiated; they recalled having had a difficult period thereafter, experiencing many different types of DMARDs.

In general, after the diagnosis had been made and the treatment had been explained, patients were glad that something could be done about it, and had more faith in facing the future. Therefore, patients wanted their rheumatologists to start as actively and aggressively as possible with a therapy that would improve their prognosis.

P-C: 'I started with methotrexate, four tablets, well it gradually became more, and I thought "give me as much as possible", because I really revived, wasn't as tired anymore, the pain became bearable and finally went away.'

When the therapy is effective and patients regained quality of life, the desire to decrease the number of pills that has to be taken becomes important.

P-I: 'I was really happy that I could leave off a medication like that once in a while.'

Two themes were identified: RA treatment: experiences, side-effects, fear and future expectations—and faith in physician.

RA treatment: experiences, side effects, fear and future expectations. In general, patients, being aware of the negative side-effects of the medication prescribed, greatly appreciated all kind of medication for the treatment of RA, because life without medication would be very complicated or even impossible

P-F: 'I have regained quality of life, while it was completely gone for a long time, so I am really happy that I'm alive at this time and that these drugs are available.'

Only few patients remembered using SSZ. It was not regarded as a very important DMARD. Patients, who had used it, reported that it did not work very well. The tablet size was no issue to them, neither was the large number of tablets that had to be taken:

P-I: 'No, no, nothing wrong with that [red: about the size of the tablets]; but it's hard to digest, like "there it is".'

P-G: 'I have no trouble with it at all, at breakfast I just knock them back all at once.'

MTX was a much more widely known drug; a patient's first introduction to the drug was generally perceived as a bit scary, because of the use of MTX in oncology. Opinions about the use of MTX varied a lot; some perceived it as being very effective, others as scary and uncomfortable because of the stomach pains after intake:

P-F: 'I remember, I was terrified, because I had to take corticosteroids and an oncological drug, it was intense.'

P-C: 'It was a miracle drug for me, because I was like a vegetable, and suddenly I was jumping around again like the person I thought I was.'

P-A: 'I don't feel well on MTX; it makes you very tired and also my stomach bothers me a lot.'

Prednisolone was associated with negative side-effects, all affecting appearance, and this was regarded as being a big issue. On the other hand, many patients had experienced great improvements on prednisolone and perceived it as being highly effective. Two patients, who experienced the worst side-effects of prednisolone over many years, felt it to be a drug they could always count on when other drugs failed.

P-I: 'In the early 70s, it gave me a rather bloated face.'

P-F: 'They say that if you use it for long, you gain weight because you feel hungry all the time, and indeed I gained 5 kilos, and can't take them off...'

P-K: 'It's the only drug that helps. That shows again that it is really a fantastic drug.'

Some patients felt disappointed to not be able to live without it:

P-G: 'Because I suffer from osteoporosis, mainly from using prednisone, that is corticosteroids, we tried to completely cut down my prednisone intake, but for some reason that didn't work...'

Fear of medication was based on reading the information leaflet, reactions from their social circle and on witnessing negative side-effects of the drugs in other patients:

P-C: 'Yes, and your social circle reacts strangely in my opinion: What, prednisone? Don't start with that!...'

P-J: 'My orthopaedist said: "arthritis patients actually have 2 diseases, that is arthritis and methotrexate"; I have always remembered that. If a doctor talks this way about a drug...'

P-E: 'Yes, on our holiday, someone was injected with MTX on Thursday and he was sick from it all of Friday and Saturday, well, I thought, "I'll never take that rubbish".'

The main expectation of treatment was equal for all patients: less pain, more functionality and an improved quality of life. Work and a social life were very important determinants of quality of life. Patients mainly focused on quality of life in the near future, but the limitation of further bone damage was also regarded as being important.

P-C: 'What I expect is, the pain has to go, and the terrible fatigue, and then I still don't know what to expect in terms of deformed hands and so on...'

P-F: 'Most important is that you can join in on things like this meeting again, that I could go back to work, maybe only for 3 hours a day, but I felt that I got a piece of my life back.'

Trust in physician. The relationship between the rheumatologist and the patient was regarded as being important to patients.

P-H: 'My rheumatologist told me: "hang on to me, we're really watching over you very carefully". That was very reassuring for me. It gives you some faith after all, because you really have no other choice.'

P-B: 'You shouldn't talk about it with others; you just need a doctor you can trust, who is an expert. I never listen to those people any more, I don't ask, I don't listen. I say, I have a good doctor, thank you very much.'

An arthritis nurse was also regarded as supportive and valuable in case of uncertainties:

P-G: 'If I do have questions in between, I can call my arthritis nurse, who in turn will contact my rheumatologist. It is great to be sure of that.'

Discussion

This qualitative study shows a large discrepancy between what patients actually feel about COBRA therapy (mostly positive) and what rheumatologists think they feel (mostly negative). Together with perceived practical problems in prescribing the therapy and personal emotions on the part of the rheumatologists, these are clues to explain why COBRA therapy is so rarely prescribed.

Rheumatologists were positive about the effectiveness of COBRA therapy, but highly concerned about their patients' possible negative reaction to the large amount of pills to be prescribed. In addition, rheumatologists perceived lack of time explaining and prescribing COBRA therapy and felt uncomfortable prescribing high doses of prednisolone.

On the other hand, patients were positive about an aggressive combination therapy such as COBRA therapy, and they had no qualms taking many pills if this would give immediate relief or might improve their prognosis. Patients associated prednisolone with negative side-effects (especially affecting looks), but they were also aware of its benefits and the need of prednisolone in rough times. A decrease in the amount of pills after intensive treatment was highly appreciated.

In conceptualizing why the difference between doctors and patients occurred, two major issues came up: first, it was found that doctors feared to fail in the eyes of their patients in prescribing such a disagreeable therapy. Second, it appears that rheumatologists formed their opinion and feelings concerning COBRA therapy overlooking the initial burden of the disease. Their concerns towards the therapy appeared more in line with the desires of a hypothetical patient in a later stage of the disease, but not with the desires of newly diagnosed patients for whom COBRA therapy is intended. Patients stated they based their opinions on their own experience at the start of the disease and concluded that taking a lot of pills felt a whole lot better than the pain and constraints they were facing with the disease. So, at the start of the disease, patients just want relief of their pain and return to life the way it was. Their major concern about the therapy is that it has to work, agreeable or not. Other concerns, such as decreasing the amount of pills, are for later.

Several studies have reported differences in perceptions between rheumatologists and patients [18, 19]. In rheumatology, differences between assessments of physician global and patient global are well known. The rheumatologist might observe a large improvement in joint count and ESR, whereas the patient fails to experience improvement in pain or global well-being [20, 21]. The importance of the patient's perspective is increasingly recognized, as can be seen in the success of the patient perspective programme in the OMERACT (Outcomes in Rheumatology) initiative. As an example, the OMERACT community has accepted that fatigue is a relevant and important symptom in RA and should be measured in all trials [22, 23]. Our findings

reinforce that also in case of prescribing COBRA therapy rheumatologists should take note of the real patient's perspective on COBRA therapy as described in this article and not act according to their own pre-conceived opinion of that perspective.

Another important factor that determines rheumatologists' reluctance towards the use of COBRA therapy for early RA is the workload. Dutch rheumatologists have only 10 or 15 min to explain the diagnosis and start a treatment; it is very difficult to explain the patient about the ins and outs of all the drugs involved in this short time.

It is remarkable that only one rheumatologist mentioned the cost-effectiveness of COBRA therapy. Former research showed that COBRA therapy provided additional disease control at lower or equal cost compared with SSZ [8, 9] and it is obviously cheaper than most new alternative drugs. Still, cost-effectiveness was not an issue for rheumatologists. Key opinion leaders potentially have an important role in promoting conventional treatment regimens and raising cost awareness. Their actual role could be an interesting area for future research.

Patients routinely associate prednisolone with an unfavourable appearance; a problem faced daily by rheumatologists. However, our study shows that, although patients experience negative side-effects of the use of prednisolone, they are also highly aware of its strong positive effect, something to count on when all else fails. The latter is largely overlooked by the rheumatologists.

The BeSt study also reported a negative perception of patients towards prednisolone: a questionnaire exploring preferences of patients 2 yrs after the trial (retrospectively) reported that 38% of all patients had hoped not to be randomized into the COBRA arm [24]. This perception was much less prominent for the patients who actually received prednisolone during the trial. Possibly this same effect is seen in our study; because all the participating patients had experience with RA treatment and many of them with prednisolone, their negative perceptions towards this drug are probably less profound than without such experience. In contrast, most of the BeSt patients expressed preference for infliximab. However, we feel this comparison is hard to interpret: the questionnaire contained leading questions and was administered *post hoc*, as the authors admit in their discussion.

A limitation of this study is that the patients participating in the group discussion were already very experienced, with average disease duration of 22 yrs. These patients appreciated the benefit of early and active treatment, because they themselves were treated in a time when therapy was not as advanced as it is now. On the other hand, these patients, including the active members of the national patient rheumatic association, were of great value to the discussions, because they have daily contact with new inexperienced patients in advising and helping them with uncertainties and were thus very well able to understand and express the patient position. Also, practical concerns limited the possibility of patient data collection so this data may be incomplete.

This study shows that practical and emotional constraints make rheumatologists reluctant towards prescribing COBRA therapy in their own practice. Information about patients' opinions on COBRA therapy needs to be disseminated among rheumatologists. We are working to improve uptake by specific information materials, pre-printed prescription orders, training of the arthritis consultant and by the dissemination of research findings as presented in this and other papers.

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Supplementary data

Supplementary data are available at *Rheumatology Online*.

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Rheumatology key messages

- Rheumatologists were convinced that COBRA therapy is effective, but perceive practical problems and negative emotions in prescribing COBRA therapy.
- Patients were positive about aggressive combination therapy such as COBRA if this might improve their prognosis, regardless of the amount of pills and in full awareness of the potential side-effects.

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