

# Facilitating the Use of COBRA Combination Therapy in Early Rheumatoid Arthritis: A Pilot Implementation Study

LILIAN H.D. van TUYL, ANNE MARIE C. PLASS, WILLEM F. LEMS, ALEXANDRE E. VOSKUYL, PIT J.S.M. KERSTENS, BEN A.C. DIJKMANS, and MAARTEN BOERS

**ABSTRACT.** *Objective.* COBRA combination therapy is well known and has uncontested efficacy in the treatment of rheumatoid arthritis (RA). However, it is infrequently applied in Dutch clinical practice. Based on qualitative research on opinions of physicians and patients towards COBRA therapy, our study describes the development and pilot testing of an implementation package to facilitate prescription and use of COBRA therapy in early RA.

*Methods.* The implementation package was developed to address specific barriers towards prescription of COBRA therapy and comprised informational handouts (an information booklet and leaflet for patients), preprinted prescription orders, and background information on COBRA therapy for the rheumatologists. Twenty-two rheumatologists agreed to participate, including the arthritis nurse where available. Rheumatologists, nurses, and patients were asked to record their experience. All Dutch arthritis nurses were invited to an educational session on COBRA therapy.

*Results.* Sixteen rheumatologists accompanied by 10 arthritis nurses used the material to prescribe COBRA therapy to a total of 27 patients. Rheumatologists and nurses both gave high marks to the supplied materials. Eighty-eight percent of rheumatologists reported that the material sped up the prescription process, and 65% indicated they would prescribe COBRA therapy more frequently if these materials were available routinely. Patients expressed great satisfaction with the information handouts, rating it 2.8 (standard deviation 0.5) on a scale of -3 (very negative) to +3 (very positive). Most patients (89%) planned to keep the information booklet as a reference and 70% used it as a tool to remember the correct intake of medication. The attitude and perceived capability of nurses towards the guidance of patients with RA receiving COBRA therapy was improved through a brief educational intervention.

*Conclusion.* Rheumatologists, patients, and arthritis nurses all highly appreciated the implementation package and indicated that its availability would increase uptake of COBRA therapy. (First Release June 1 2009; J Rheumatol 2009;36:1380-6; doi:10.3899/jrheum.081078)

## Key Indexing Terms:

RHEUMATOID ARTHRITIS  
NURSING EDUCATION RESEARCH

IMPLEMENTATION RESEARCH  
COMBINATION DRUG THERAPY

Over the past few decades, many clinical trials in rheumatology have shown the effectiveness and safety of different combinations of disease modifying antirheumatic drugs (DMARD) for the treatment of rheumatoid arthritis (RA)<sup>1-6</sup>.

A well known and well documented combination strategy is the COBRA therapy, comprising methotrexate (MTX), sulfasalazine (SSZ), and step-down high-dose prednisolone. This therapy proved to be more effective than SSZ monotherapy in a randomized controlled trial<sup>1</sup>, and the delay of radiographic damage to the joints was still detectable after 5 years' followup<sup>7</sup>. It was recently shown that COBRA therapy is as effective as initial combination therapy of high-dose MTX with infliximab<sup>8</sup>. Further, COBRA therapy is a combination of inexpensive, generic drugs, and is therefore likely to be highly cost-effective compared to the newer biologic treatments; COBRA therapy already proved to be equally cost-effective compared to SSZ monotherapy<sup>9,10</sup>. Although evidence is in favor of COBRA therapy, prescription of this combination therapy for treatment of early RA is not common. This is remarkable, since there is a large body of evidence for the superi-

---

From the Department of Rheumatology, EMGO Institute, and the Department of Epidemiology and Biostatistics, VU University Medical Center; and Jan van Breemen Institute, Amsterdam, The Netherlands.

Supported by the Dutch Arthritis Association.

L.H.D. van Tuyl, MSc, Department of Rheumatology; A.M.C. Plass, PhD, EMGO Institute; W.F. Lems, MD, PhD; A.E. Voskuyl, MD, PhD, Department of Rheumatology, VU University Medical Center; P.J.S.M. Kerstens, MD, PhD, Jan van Breemen Institute; B.A.C. Dijkmans, MD, PhD, Department of Rheumatology; M. Boers, MD, PhD, Department of Epidemiology and Biostatistics, VU University Medical Center.

Address reprint requests to L.H.D. van Tuyl, VU University Medical Center, Department of Rheumatology, De Boelelaan 1117, 1081 HV Amsterdam, The Netherlands. E-mail: L.vanTuyl@vumc.nl

Accepted for publication January 27, 2009.

---

Personal non-commercial use only. The Journal of Rheumatology Copyright © 2009. All rights reserved.

ority of combination therapy over monotherapies<sup>1-6,8</sup>. It has been shown that a multifaceted approach is needed to implement research evidence that does not find its way into clinical practice<sup>11,12</sup>.

To investigate and improve the uptake of COBRA combination therapy in clinical practice, the COBRA implementation study started in 2005, comprising 3 main phases; phase 1: identification of facilitators and barriers among Dutch rheumatologists towards prescribing COBRA therapy; phase 2: followup of the original trial cohort to investigate longterm effectiveness and safety; and phase 3: implementation of COBRA therapy in clinical practice with material facilitating use, including an information booklet and a website<sup>13</sup>.

Identification of facilitators and barriers started with a brief inquiry into the uptake of COBRA therapy in daily practice<sup>14</sup>. The study showed that rheumatologists rarely used COBRA therapy outside trials. It also showed the contradictory perspective of rheumatologists towards COBRA therapy: although they regarded COBRA therapy as effective and safe, rheumatologists indicated it was unlikely that they would treat a patient with COBRA therapy in the near future.

After this brief inquiry, a large qualitative study was conducted to investigate all perspectives and perceived barriers towards the use of COBRA therapy. The opinion of patients towards intensive combination therapy with SSZ, MTX, and prednisolone was also studied<sup>15</sup>. Results again showed that rheumatologists regarded COBRA therapy as effective, but were highly concerned about their patients' possible negative reaction towards the large quantity of pills to be prescribed. In addition, rheumatologists perceived a lack of time for 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 had no qualms about taking many pills if this could improve their prognosis. They associated prednisolone with negative side effects, but were also aware of the benefits and the need for prednisolone in times of difficulty.

With this knowledge on rheumatologists' and patients' opinions, an implementation plan was developed and pilot tested to facilitate prescription and use of COBRA therapy in early RA by the rheumatologist, the patient, and the arthritis nurse.

## MATERIALS AND METHODS

**Study design.** This pilot study was conducted from March to October 2007; feasibility and acceptability of components of the implementation plan used by rheumatologists, arthritis nurses, and patients were assessed cross-sectionally through structured questionnaires. The effect of an educational intervention on arthritis nurses' attitude and perceived capability towards the use of COBRA therapy in their clinical practice was also investigated.

**Subjects.** Rheumatologists were selected based on their attitude towards COBRA therapy, as measured during the questionnaire phase of our study,

as reported<sup>14</sup>. Thirty rheumatologists with a positive attitude towards COBRA therapy were invited to participate in the pilot implementation study, to ensure that they were willing to prescribe the therapy to patients who were eligible for the pilot study. Twenty-two rheumatologists from 14 different centers in The Netherlands accepted our invitation. These 22 rheumatologists were asked to involve the arthritis nurse (if employed in the medical center).

In order to have diversity, all rheumatologists were asked to prescribe COBRA therapy to a maximum of 3 patients, using the provided materials. Inclusion criteria were not strict: all patients could be included if they were diagnosed with RA 2 years or less prior to inclusion, unless they had been treated with COBRA therapy before.

All Dutch arthritis nurses (n ≈ 100) were invited to an education session on COBRA therapy later that year.

**Intervention and materials provided.** Taking into account the perceived barriers of rheumatologists, an implementation package was designed to facilitate prescription of COBRA therapy for rheumatologists (Table 1). The perceived workload was tackled by providing the rheumatologists with 4 tools: (1) a specific COBRA therapy information booklet (Figure 1), including a leaflet with a summary of the first consult in which the therapy is explained. The booklet (20 pages) was developed based on booklets available on the separate drugs SSZ, MTX, and prednisolone. Specific attention was paid to the additional value of combined treatment, the visual representation of intake of drugs by tables and figures, and the recognition of the patients' feelings by an interview with a fictional RA patient coping with the diagnosis of RA. Many of these ideas were provided or confirmed by rheumatologists and patients during the focus group discussions preceding this implementation pilot study<sup>15</sup>; (2) preprinted prescriptions on a sticker patch; (3) an example consult, giving the rheumatologist an idea how to motivate and inform the patient (this was tested during focus group discussions with patients and evaluated as very clear and motivating to patients with early RA<sup>15</sup>); and (4) all patients were referred to the arthritis nurse. This nurse explained the therapy more extensively, answered questions, and called the patient once a week during the first month of therapy to answer any additional questions. Further, the participating rheumatologists and arthritis nurses were informed of the results about the patients' opinion from our qualitative study. Scientific articles on this and related subjects were provided.

Later that year, all Dutch arthritis nurses were invited to an educational seminar on COBRA combination therapy, where they learned more about the therapy during a 2 h interactive session.

**Measurements.** Three similar questionnaires were developed to evaluate the information material and prescription process from the rheumatologist's, nurse's, and patient's point of view.

The information leaflet and the information booklet were evaluated through questions using semantic differentials (annoying vs pleasing; patronizing vs considerate; complex vs simple; important vs meaningless; clear vs unclear; bad vs good; a lot vs a little; confusing vs enlightening; clear vs unreadable; inviting vs boring; well structured vs messy; beautiful vs ugly; realistic vs unrealistic; useful vs unnecessary; boring vs captivating) on a 7-point Likert scale. Thus, a score of -3 indicates a most negative attitude and +3 indicates a most positive attitude towards the question. Every aspect of the material was evaluated by 5 different semantic differentials, thus giving a complete evaluation of that aspect. An open-ended question asked participants for "other remarks" about the material or therapy. The rheumatologists' questionnaire ended with multiple choice questions (yes/no/neutral) about the usefulness of the material provided in the implementation package and the intention of rheumatologists to prescribe COBRA therapy more often if the implementation material was available to them. It also queried whether the consult went faster using the material than without it. The patient questionnaire was similar to the rheumatologist questionnaire, with additional questions about the use of the information leaflet to inform other persons about their disease; the use of the information booklet as a tool to remember the correct intake of all drugs; and eval-

Table 1. Barriers to use of COBRA therapy in clinical practice.

Feature	Implementation Package
Rheumatologist barrier*	
Workload	<ol style="list-style-type: none"> <li>1. Specialized COBRA therapy information booklet</li> <li>2. Preprinted prescription orders</li> <li>3. Example consult</li> <li>4. Refer to arthritis nurse</li> </ol>
Anticipated negative reaction of patient	Dissemination of focus group results among rheumatologists and arthritis nurses: patients are positive about intensive combination therapy such as COBRA. Taking many pills is not regarded as a problem, if this improves longterm prognosis. A decrease in the amount of pills over time is highly appreciated
Fear of prednisolone	Dissemination of scientific articles of the COBRA and BeSt trial
Patient barrier	
Comfort	<ol style="list-style-type: none"> <li>1. Provide information booklet for reference and leaflet for summary</li> <li>2. Offer additional support from an arthritis nurse</li> </ol>
Negative perception of prednisolone	Emphasize the temporary nature (using visual aids in the booklet and leaflet)
Amount of pills	Emphasize the temporary nature (using visual aids in the booklet and leaflet)
Arthritis nurse barrier	
Knowledge on COBRA therapy	<ol style="list-style-type: none"> <li>1. Provide information material about COBRA therapy</li> <li>2. Provide education</li> </ol>

\* Assessed in focus group discussions and interviews.

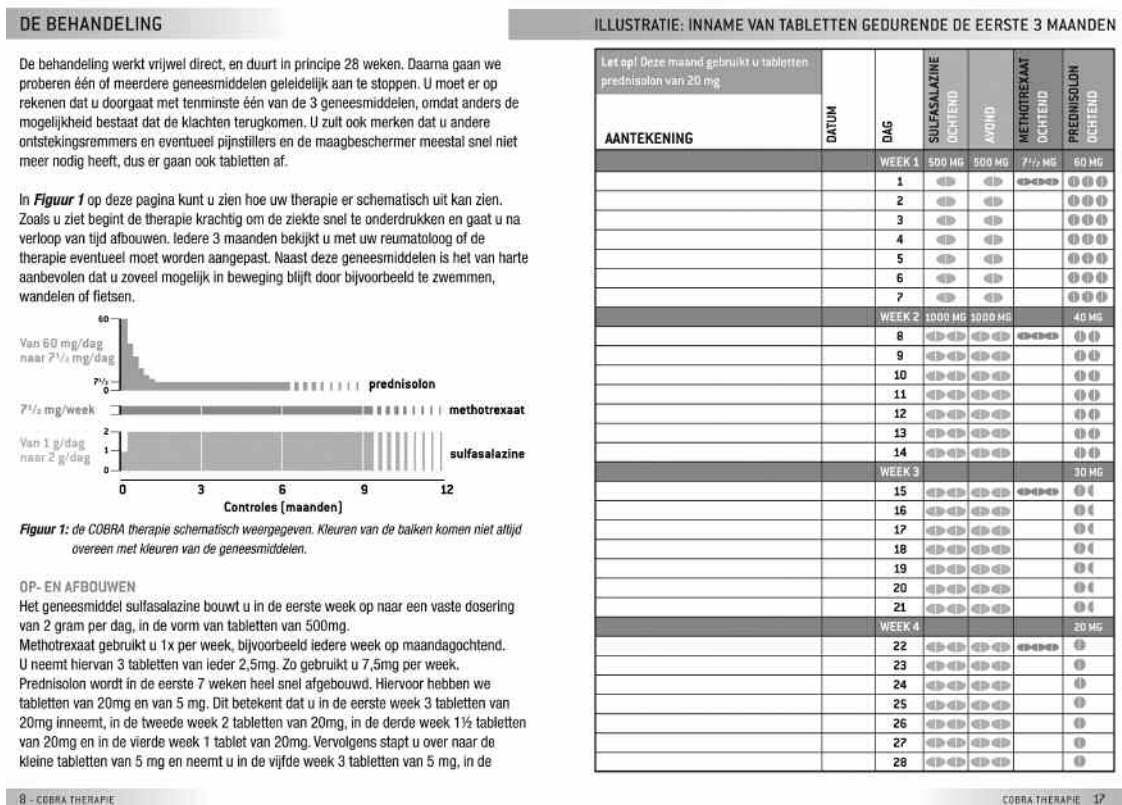


Figure 1. The COBRA therapy information booklet for rheumatologists, arthritis nurses, and patients. A more detailed overview is available at the website, [www.cobrathrapy.nl](http://www.cobrathrapy.nl)

uation of the role of the nurse. Nurses were asked, besides the general questions on the material and process, if they felt that Dutch arthritis nurses had sufficient knowledge on COBRA therapy and if they felt it useful to call the patient every week during the first month of the therapy. Questionnaires were provided by the research team with a post-paid return envelope. Rheumatologists and nurses were asked to fill out the questionnaire direct-

ly after the consultation with the patient. Patients were asked to fill out the questionnaire 2 weeks after beginning COBRA therapy.

Eighty-seven arthritis nurses attended the educational seminar on COBRA therapy. Before the start of the session, all nurses completed a short questionnaire (pre-test) on the basis of the social psychological theory of planned behavior, which explains behavior through behavioral inten-

tion, attitude, social influence, and perceived control<sup>16</sup>. This questionnaire was originally designed in the former phase of our study (phase 1) according to the protocol of Ajzen<sup>14,16</sup>. Questions were based on a 7-point Likert scale, in which value -3 was most negative, value 3 was most positive, and value 0 was neutral. This questionnaire measured the current knowledge, experience, and attitude of arthritis nurses towards COBRA therapy. The final question asked whether nurses felt capable of guiding a patient with early RA who started treatment with COBRA therapy. After a 2 h interactive lecture on modern treatment of RA and the use of COBRA therapy by WL and LvT, the 62 remaining arthritis nurses completed the same questionnaire (post-test).

*Data analysis.* Negatively worded items on questionnaires were recoded for analysis. Results were statistically analyzed by parametrical (t) and non-parametrical (Mann-Whitney) tests where applicable.

The questionnaires that were developed to evaluate the information material and prescription process used multiple semantic differentials (items) to answer a question. Factor analysis was used to see if the items measured the same aspect. In all instances when more than 1 factor was recognized, the reason for this was the same: respondents evaluated not only the content of the material, but also the way the content/material was written. Cronbach's alpha was determined to measure scale reliability. If Cronbach's alpha was  $\geq 0.60$ , the items were combined as 1 scale. If Cronbach's alpha was  $< 0.60$ , the least-matching item was excluded and the

remaining scales were combined. To evaluate the educational seminar for arthritis nurses, differences between pre- and post-test at the group level were analyzed by t-tests.

## RESULTS

Twenty-seven patients were included by a total of 16 rheumatologists from 12 different centers. Additionally, 7 rheumatologists did not see a suitable patient to include within the 5-month study period, and thus evaluated only the information leaflet and booklet. This resulted in a total of 34 evaluations from rheumatologists. There were 13 male and 14 female patients included, with a mean age of 57 years [standard deviation (SD) 15, range 22–78]. One patient was not able to read or write and did not evaluate the material. Ten arthritis nurses evaluated the material and 19 patients consulted the nurse.

*Rheumatologists.* Rheumatologists were very positive about all aspects of the information leaflet and booklet (Table 2). Rheumatologists felt that the information in the leaflet closely resembled the information given by themselves dur-

Table 2. Evaluation of the patient information leaflet and booklet\*.

Scale (items)	Question	Mean (SD) -3 to +3 (range)	Cronbach's alpha (factor)
Rheumatologists (n = 34)			
1 (5)	How does it feel to be able to give a leaflet containing a summary of the first consultation?	2.3 (0.7)	0.80 (1)
2 (3)	How do you evaluate the information provided in the leaflet?	2.3 (0.6)	0.80 (1)**
3 (4)	How do you evaluate the appearance of the leaflet?	2.1 (0.9)	0.95 (1)
4 (5)	What is your opinion on the way the leaflet has been written?	1.6 (0.7)	0.63 (2) <sup>†</sup>
5 (1)	Is the content of the leaflet similar to the first consultation of the rheumatologist?	2.1 (0.5)	Only 1 scale
6 (4)	How does it feel to be able to give an information booklet containing detailed information on the prescribed treatment?	2.0 (1.0)	0.70 (1)
7 (6)	How do you evaluate the interview in the booklet with a newly diagnosed RA patient?	1.7 (0.9)	0.90 (1)
8 (5)	How do you evaluate the medical information provided in the booklet?	2.2 (0.7)	0.83 (2)
9 (5)	How do you evaluate the practical information provided in the booklet?	2.3 (0.5)	0.90 (1)
10 (4)	How do you evaluate the appearance of the booklet?	2.3 (0.6)	0.79 (1)
Patients (n = 26)			
11 (5)	How does it feel to receive a leaflet containing a summary of the first consultation?	2.5 (0.7)	0.90 (1)
12 (4)	How do you evaluate the information provided in the leaflet?	2.4 (0.6)	0.80 (1)
13 (4)	How do you evaluate the appearance of the leaflet?	2.5 (0.6)	0.90 (1)
14 (5)	What is your opinion on the way the leaflet has been written?	2.3 (0.8)	0.84 (2) <sup>†</sup>
15 (1)	Is the content of the leaflet similar to the first consultation of the rheumatologist?	2.6 (0.9)	Only 1 scale
16 (5)	How does it feel to receive an information booklet containing detailed information on the prescribed treatment?	2.8 (0.5)	0.95 (1)
17 (6)	How do you evaluate the interview in the booklet with a newly diagnosed RA patient?	2.2 (0.8)	0.94 (1)
18 (5)	How do you evaluate the medical information provided in the booklet?	2.4 (0.9)	0.83 (1)
19 (5)	How do you evaluate the practical information provided in the booklet?	2.5 (0.6)	0.82 (1)
Arthritis nurses (n = 10)			
20 (2)	How do you evaluate the information provided in the leaflet?	2.6 (0.5)	1.00 (1) <sup>††</sup>
21 (4)	How do you evaluate the appearance of the leaflet?	2.4 (0.6)	0.90 (1)
22 (5)	What is your opinion on the way the leaflet has been written?	2.2 (0.7)	0.60 (2)
23 (6)	How do you evaluate the interview in the booklet with a newly diagnosed RA patient?	2.2 (0.6)	0.90 (2)
24 (4)	How do you evaluate the medical information provided in the booklet?	2.6 (0.5)	0.90 (1)
25 (5)	How do you evaluate the practical information provided in the booklet?	2.3 (0.7)	0.90 (1)
26 (5)	How do you evaluate the appearance of the booklet?	2.4 (0.6)	0.90 (1)

\* On a semantic differential scale from -3 most negative to +3 most positive. \*\* One scale excluded to improve scale reliability. <sup>†</sup> The 2 factors reflect the content of the information in the leaflet and/or booklet vs the way the information has been written. <sup>††</sup> Two items are combined, so Cronbach's alpha is not representative.

ing the consultation [2.0 (SD 0.5) on a scale from -3 to +3]. Rheumatologists were also positive about the opportunity to provide patients with a specific information booklet: 2.0 (SD 1.0). In particular, the use of the practical information during the explanation of COBRA therapy to the patient received high marks and was evaluated as very useful (2.3). Seventy-four percent of rheumatologists actually used the tables and figures from the booklet during the consult. Nearly all rheumatologists (94%) liked to have access to the material as provided in our study while prescribing COBRA therapy. While only 33% liked using the sample consultation, 78% liked using the preprinted prescriptions, and 60% liked to have access to the background material. Eighty-eight percent of rheumatologists indicated that prescribing COBRA therapy went faster with the use of the material provided, and 65% expected to prescribe COBRA therapy to their patients more frequently with this material available to them.

**Patients.** Patients gave high marks to the consultation they had with their rheumatologist, 2.4 (SD 0.8), and were very pleased to receive an information leaflet, 2.5 (SD 0.7) (Table 2). Ninety-six percent of patients indicated they had kept the leaflet (1 patient did not). Patients indicated that the information in the leaflet showed close resemblance to the information given by the rheumatologist during the consult, 2.6 (SD 0.9). Sixty-nine percent of patients indicated that they used the leaflet to inform significant others: mostly family (90%) but also friends or acquaintances (16%), colleagues or employers (11%), and their general practitioner or pharmacist (11%). Another 16% planned to show it to significant others, but had not done so yet. Only 15% indicated that they did not plan to use the leaflet for this purpose. Patients were also pleased to receive an information booklet [2.8 (SD 0.5)]. All patients reported that they had kept the booklet, and 89% planned to use it as a reference. Seventy percent of patients used the booklet to remember the correct intake of their drugs and another 12% planned to use it for this purpose. The practical information in the booklet, like figures and tables, was evaluated positively: 2.5 (SD 0.6) with 2.7 for usefulness and 2.6 for clarity. Further, patients appreciated the effort of the arthritis nurse to call them every week during the first month of therapy, 2.3 (SD 1.1). This was evaluated as being "of additional value": 2.3.

**Arthritis nurses.** Eighty-six percent of the nurses used the tables and figures in the booklet during explanation of COBRA therapy to the patient. Ninety percent of arthritis nurses liked having background information on COBRA therapy as provided during the study. Forty percent thought that their colleagues in The Netherlands would not have sufficient knowledge on COBRA therapy and 80% felt it necessary to call the patient weekly one time during the first month of therapy.

Eighty-seven arthritis nurses started the educational session on COBRA therapy and completed the pre-test ques-

tionnaire; 62 attended the session until the end and completed the post-test questionnaire. The pre-test results showed that 85% of the nurses were familiar with COBRA therapy before announcement of the session and that 31% had experience with guiding patients on COBRA therapy. Forty-eight nurses (55%) had enough knowledge about COBRA therapy to be able to answer the attitude questions, although 56 (64%) answered the perceived-capability question. The pre-test results show that COBRA therapy was perceived as effective and safe, but somewhat complex (Table 3). This is consistent with the initial opinion of rheumatologists, found in phase 1 of our study<sup>14</sup>. Items on effectiveness and safety significantly improved after the educational session. Perceived capability to guide a patient with COBRA therapy improved significantly, from a negative -0.3 to a positive 1.4 ( $p < 0.001$ ).

## DISCUSSION

This article describes a pilot implementation study that was developed to facilitate prescription and use of COBRA therapy, a combination therapy of inexpensive, generic drugs, in early RA by the rheumatologist, the patient, and the arthritis nurse. The implementation material was developed based on thorough qualitative research on perceived barriers and facilitators of rheumatologists and patients towards COBRA therapy. The rheumatologists, patients, and nurses all highly appreciated the implementation material provided to them. Rheumatologists reported that in using this material, workload regarding prescribing COBRA therapy had gone down significantly. The majority (88%) of rheumatologists indicated that prescribing COBRA therapy went faster with the use of the material. Moreover, 65% of the participating rheumatologists indicated that they would prescribe COBRA therapy to their patients more often, if they had access to the material that was provided to them within the

Table 3. Pre- and post-test results of an educational intervention on attitudes towards COBRA therapy of arthritis nurses. 7-point Likert-scale: -3 most negative, 3 most positive.

Question	Attitude (range -3 to +3)	
	Pre-test (n = 48) <sup>††</sup>	Post-test (n = 62)
1. Ineffective/effective	1.1 (0.8)*	1.8 (0.7)* <sup>†</sup>
2. Unsafe/safe	0.6 (0.9)*	1.1 (0.9)* <sup>†</sup>
3. Complex/simple	-0.4 (1.1)*	-0.7 (1.1)*
4. Patient-unfriendly/patient-friendly	0.3 (1.1)	0.5 (1.1)*
5. Unsympathetic/sympathetic	0.3 (0.9)*	0.7 (0.9)* <sup>†</sup>
6. Unnecessary/necessary	0.9 (0.9)*	1.2 (1.0)*
7. Bad/good	0.6 (1.1)*	0.8 (1.4)*
8. Capability	-0.3 (1.8)*	1.4 (1.1)* <sup>†</sup>

\* Significantly different from the neutral point of 0 with  $p < 0.05$ .

<sup>†</sup> Significantly different from the pre-test value with  $p < 0.05$ . <sup>††</sup> During pre-test, 48 arthritis nurses knew enough about COBRA therapy to answer questions 1 to 7; 56 arthritis nurses answered question 8.

framework of the study. Arthritis nurses were also positive and no longer doubted whether their knowledge on COBRA therapy was sufficient to advise patients after the educational session. Our study shows that the attitude and perceived capability of the nurses towards the guidance of patients with RA starting COBRA therapy can be improved through a brief educational intervention.

Our goal of increasing prescription rate of COBRA therapy in daily practice by facilitating its use by rheumatologists, patients, and arthritis nurses seems feasible with the current implementation material.

A disadvantage of our study is that there was no control group included in the design, and no pre- and post-measurement design for evaluating the material. Although all questions to participants were aimed at comparing the situation with the material to the situation without the material, the consequence of our design choice is that we cannot compare the effect of the implementation package with current daily practice, in which no material or support is available when rheumatologists want to prescribe COBRA therapy.

Further, our knowledge of barriers and facilitators from the arthritis nurses' point of view was limited at the start of the implementation, for we initially focused on doctors and patients. In retrospect, it would have been better to involve nurses in a prior stage of the study. Nevertheless, their opinion on how to improve COBRA prescription in daily practice was not overlooked. The ideas that were brought up by the nurses proved to be very useful in completing the implementation process.

The educational session showed that knowledge of arthritis nurses on COBRA therapy was limited. Only 48 of the 87 nurses who started the session were able to answer the attitude questions about COBRA therapy, while all nurses who attended the session until the end ( $n = 62$ ) were able to answer the same questions. Unfortunately, the questionnaires were anonymous, so we cannot be sure if the same nurses who filled out the questionnaire before the start of the session also completed it at the end.

Importantly, the rheumatologists who participated in this pilot study had a positive attitude towards COBRA. We felt it necessary to address this group, because rheumatologists reluctant to use the therapy would probably not cooperate in the short duration of this trial. It is possible that rheumatologists with a very negative attitude towards COBRA therapy would still not use it in practice, even if the material tested in our study was available to them. In this case, workload or fear for the patients' perception was not the real barrier for them, which would have made this group unsuitable to test the implementation material. Groel, *et al* have done extensive research in the field of implementation and showed that the compliance of Dutch general practitioners with recommended guidelines was lower when recommendations were incompatible with clinicians' norms and values and if they were disruptive of routine practice<sup>17</sup>. A well

known theoretical model that explains the uptake of knowledge is Rogers's diffusion of innovations model; besides characteristics of the innovation itself (such as its relative advantage, compatibility, complexity, flexibility, and costs or risks attributed to the innovation), the diffusion process may be further influenced by the individual characteristics of the 5 adopter categories: the so-called innovators are followed by the early adopters; next comes the larger group of early majority, then late majority, followed by the so-called "laggers," who will never be persuaded to adopt a new strategy<sup>18</sup>.

Lessons learned from our pilot study are that a larger, more controlled study on the implementation of a treatment strategy should include a more diverse group of rheumatologists (from all stages of the diffusion of innovations model), allow more time for inclusion of patients, and specify the facilitators and barriers from the nurses' point of view in an earlier stage.

Our implementation strategy might be applicable to other strategies with low uptake. Substitution of branded drugs for generic drugs is a "hot" topic in which there are large economic interests of healthcare systems<sup>19</sup>. Health insurance companies might be interested to cooperate in national implementation.

Rheumatologists, patients, and arthritis nurses all highly appreciated the materials provided and indicated that the use of these would stimulate prescription of the COBRA therapy, which is a "high dosage generic drug therapy," in the future. Thus, with an effective therapy that is unpopular in the eyes of the physician, or is not promoted by pharmaceutical companies, like generic drugs, we suggest that an implementation approach of identifying and addressing barriers with tailored materials can overcome those barriers and increase uptake of the therapy.

[A website has been developed where patients, rheumatologists, and arthritis nurses can find information on COBRA therapy, as well as all the information material (booklet, leaflet, preprinted prescriptions, background information) used in this study: [www.cobratherapy.nl](http://www.cobratherapy.nl)]

## ACKNOWLEDGMENT

We thank all nurses, patients, and rheumatologists who participated in the study.

## REFERENCES

1. Boers M, Verhoeven AC, Markusse HM, 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. Dougados M, Combe B, Cantagrel A, et al. Combination therapy in early rheumatoid arthritis: a randomised, controlled, double blind 52 week clinical trial of sulphasalazine and methotrexate compared with the single components. *Ann Rheum Dis* 1999;58:220-5.
3. Mottonen T, Hannonen P, Leirisalo-Repo M, et al. Comparison of combination therapy with single-drug therapy in early rheumatoid arthritis: a randomised trial. FIN-RACo trial group. *Lancet* 1999;353:1568-73.

4. O'Dell JR, Haire CE, Erikson N, et al. Treatment of rheumatoid arthritis with methotrexate alone, sulfasalazine and hydroxychloroquine, or a combination of all three medications. *N Engl J Med* 1996;334:1287-91.
5. Capell HA, Madhok R, Porter DR, et al. Combination therapy with sulfasalazine and methotrexate is more effective than either drug alone in patients with rheumatoid arthritis with a suboptimal response to sulfasalazine: results from the double-blind placebo-controlled MASCOT study. *Ann Rheum Dis* 2007;66:235-41.
6. Lehman AJ, Esdaile JM, Klinkhoff AV, Grant E, Fitzgerald A, Canvin J. A 48-week, randomized, double-blind, double-observer, placebo-controlled multicenter trial of combination methotrexate and intramuscular gold therapy in rheumatoid arthritis: results of the METGO study. *Arthritis Rheum* 2005;52:1360-70.
7. Landewe RB, Boers M, Verhoeven AC, et al. COBRA combination therapy in patients with early rheumatoid arthritis: long-term structural benefits of a brief intervention. *Arthritis Rheum* 2002;46:347-56.
8. Goekoop-Ruiterman YP, De Vries-Bouwstra JK, Allaart CF, et al. Comparison of treatment strategies in early rheumatoid arthritis: a randomized trial. *Ann Intern Med* 2007;146:406-15.
9. Korthals-de Bos IBC, van Tulder MW, Boers M, et al. Indirect and total costs of early rheumatoid arthritis: a randomized comparison of combined step-down prednisolone, methotrexate, and sulfasalazine with sulfasalazine alone. *J Rheumatol* 2004;3:1709-16.
10. Verhoeven AC, Bibo JC, Boers M, Engel GL, van der Linden S. Cost-effectiveness and cost-utility of combination therapy in early rheumatoid arthritis: randomized comparison of combined step-down prednisolone, methotrexate and sulphasalazine with sulphasalazine alone. COBRA Trial Group. *Combinatietherapie Bij Reumatoïde Artritis. Br J Rheumatol* 1998;37:1102-9.
11. Grimshaw JM, Shirran L, Thomas R, et al. Changing provider behavior: an overview of systematic reviews of interventions. *Med Care* 2001;39 Suppl:II2-45.
12. Grol R. Improving the quality of medical care: building bridges among professional pride, payer profit, and patient satisfaction. *JAMA* 2001;286:2578-85.
13. COBRA therapy.nl. Amsterdam: VU University Medical Center and the Jan van Breemen Institute; 2008. [Internet. Accessed March 6, 2009] Available from: <http://www.cobrathrapy.nl>
14. van Tuyl LH, Plass AM, Lems WF, Voskuyl AE, Dijkmans BA, Boers M. Why are Dutch rheumatologists reluctant to use the COBRA treatment strategy in early rheumatoid arthritis? *Ann Rheum Dis* 2007;66:974-6.
15. van Tuyl LHD, Plass AMC, Lems WF, et al. Discordant perspectives of rheumatologists and patients on COBRA combination therapy in rheumatoid arthritis. *Rheumatology* 2008;47:1571-6. Epub 2008 Aug 18.
16. Ajzen I. Attitudes, personality and behaviour. London: Open University Press; 1988.
17. Grol R, Dalhuijsen J, Thomas S, Veld C, Rutten G, Mekkink H. Attributes of clinical guidelines that influence use of guidelines in general practice: observational study. *BMJ* 1998;317:858-61.
18. Rogers E. Diffusion of innovations. New York: Free Press; 1983.
19. Haas JS, Phillips KA, Gerstenberger EP, Seger AC. Potential savings from substituting generic drugs for brand-name drugs: medical expenditure panel survey, 1997-2000. *Ann Intern Med* 2005;142:891-7.