Intervention

Effectiveness of a group-based intervention to change medication beliefs and improve medication adherence in patients with rheumatoid arthritis: A randomized controlled trial

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A B S T R A C T

Objective: To assess the effect of a group-based intervention on the balance between necessity beliefs and concern beliefs about medication and on medication non-adherence in patients with rheumatoid arthritis (RA).

Methods: Non-adherent RA patients using disease-modifying anti-rheumatic drugs (DMARDs) were randomized to an intervention or control arm. The intervention consisted, amongst others, of two motivational interviewing-guided group sessions led by the same pharmacist. Control patients received brochures about their DMARDs. Questionnaires were completed up to 12 months follow-up.

Results: 123 patients (mean age: 60 years, female: 69%) were randomized. No differences in necessity beliefs and concern beliefs about medication and in medication non-adherence were detected between the intervention and control arm, except at 12 months’ follow-up: participants in the intervention arm had less strong necessity beliefs about medication than participants in the control arm (b: −1.0 (95% CI: −2.0, −0.1)).

Conclusion: This trial did not demonstrate superiority of our intervention over the control arm in changing beliefs about medication or in improving medication adherence over time.

Practice implications: Absent intervention effects might have been due to, amongst others, selection bias and a suboptimal treatment integrity level. Hence, targeting beliefs about medication in clinical practice should not yet be ruled out.

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1. Introduction

Adherence to disease-modifying anti-rheumatic drugs (DMARDs) in patients with rheumatoid arthritis (RA) is not optimal and ranges from 22% to 107% [1–5]. As non-adherence can reduce treatment efficacy and can intensify disease activity, pain, joint damage and a lower quality of life [6–8], interventions to improve adherence are warranted.

Existing interventions to improve medication adherence in chronic diseases are mostly complex and of limited effect [9]. To date, three studies have assessed the effectiveness of a medication adherence intervention in RA [10–12]. Only one of these studies demonstrated a slight improvement in adherence to β-penicillin-mine following a patient education program [11], but this program was intensive (51 individuals × six sessions × 30 min).

Time-efficient and effective adherence interventions are, thus, needed. Therefore, we developed a short, group-based intervention to improve medication adherence in non-adherent patients with RA using DMARDs [13]. Of the five WHO domains comprising
possible targets for adherence improving interventions (i.e., the socio-economic, healthcare system, condition-related, therapy-related and the patient-related domain) [14], our intervention focusses on the patient-related domain. It aims to improve adherence by resolving patients’ practical barriers to taking medication, and by improving patients’ individual balance between necessity beliefs and concern beliefs about medication. Despite the apparent association between these beliefs and medication adherence [15–22], they have seldom been the main focus of adherence-improving interventions [13].

This randomized clinical trial evaluated the effectiveness of our group-based intervention on medication beliefs (primary outcome of interest) and adherence in non-adherent patients with RA.

2. Methods

2.1. Design

This is a single-center, researcher-blinded randomized clinical trial. Participants were randomly allocated to two arms at a ratio of 1:1, and were asked to complete questionnaires at baseline (T0), and at one week (T1), six months (T2), and one year (T3) after the second group session (Section 2.3). In addition to questionnaires, pill data were used to assess medication adherence. This trial was approved by the local medical ethical board (CMO 2009/090; NCT00968266), and has been reported according to the CONSORT guidelines [23].

2.2. Participants and recruitment

Patient inclusion took place between September 2009 and February 2011 at the Sint Maartenskliniek (SMK Nijmegen, the Netherlands), a clinic specialized in rheumatology, rehabilitation and orthopedics.

Consecutive, adult patients having RA for at least one year according to the 2010 ACR-criteria [24] and using at least one DMARD were screened for eligibility by their rheumatologist during regular outpatient visits. Patients with severe mental or physical constraints or illiterate in the Dutch language were excluded. Eligible patients filled in an informed consent form and questionnaires (including the Compliance Questionnaire Rheumatology for adherence assessment (CQR)) [25] at home. Subsequently, as we only wanted to include non-adherent patients, patients taking ≤80% of prescribed medication according to the CQR were telephonically invited for trial participation. Interested patients were scheduled for an intake meeting with one of the two involved researchers [BvdM/HZ]: trial information was discussed and written informed consent was obtained.

2.3. Interventions

2.3.1. Intervention arm (arm 1: sessions)

The systematic development of the intervention (based on the Intervention Mapping framework) [26] and its content is published by Zwikker et al. in this journal [13].

The intervention consisted of two motivational interviewing (MI) guided [27] group sessions (one week apart, with 5–7 RA patients), designed to improve patients’ balance between necessity beliefs and concern beliefs about medication and to resolve patients’ practical barriers to medication taking. During the Intervention Mapping process, beliefs about medication and practical barriers were selected as intervention targets by an interdisciplinary expert group, based on a (1) literature study, (2) cross-sectional study, and (3) focus groups. MI was chosen as central communication style, amongst others, for its suitability to explore patients’ individual ambivalence regarding necessity – and concern beliefs about medication.

Two pharmacists alternately led the pair of sessions. During these sessions, the participants made an inventory of their own medication beliefs and practical barriers to take medication. These were non-judgmentally discussed in the group, with co-participation of a rheumatologist during the second session. Participants were encouraged to provide constructive feedback and solutions. The session closed with handing out brochures about the DMARDs that the patients were using.

Four of nine pairs of sessions were randomly audio-recorded and analyzed: an independent assessor checked treatment integrity in terms of potential omission errors in the intervention content [28] and the degree of patient-centeredness (or MI ‘ambiance’ as measured with the validated BECCI-instrument [29], see Appendix I).

Supplementary material related to this article can be found, in the online version, at http://dx.doi.org/10.1016/j.pec.2013.12.002.

2.3.2. Control arm (arm 2: brochures)

Participants allocated to the control arm received brochures at home about the DMARDs they were using at the time, with a request to thoroughly read the brochures.

2.4. Trial randomization and implementation

Appendix Figure I presents the randomization and implementation process. (See online Supplementary Material).

A blinded, computer-generated randomization list was obtained [BvdB] for subjects in permuted blocks of 10 [30]. Based on order of inclusion and availability, patients were allocated to one of nine clusters between 2009 and 2011 (one cluster consisted of 12–14 patients, half of whom were allocated to arm 1 and the other half to arm 2). The researcher was responsible for data collection and – analyses, and remained blind to treatment allocation.

2.5. Measures

2.5.1. Baseline characteristics (T0)

Socio-demographic factors measured were age, sex, living with others, educational level, and employment status. Clinical factors measured were disease duration and physical functioning (such as physical abilities and pain severity, see Appendix Table I).

Electronic hospital/pharmacy data were used to assess the types of DMARDs used at baseline, and to assess the presence of anti-CCP and rheumatoid factor values in the participants (descriptive use only).

2.5.2. Primary measures (T0, T1, T2, T3)

Beliefs about medication were measured using the validated Beliefs about Medicines Questionnaire [19], which consists of two parts. Part one, the BMQ ‘specific’, has two subscales of five items each, measuring patients’ beliefs about the necessity of prescribed medication (e.g., “Without my medicines I would be very ill”), and their concerns about potential adverse consequences of taking the medication. Within the subscales, items are scored from 5 (strongly agree) to 1 (strongly disagree) and are summed to obtain a total score ranging from 5 to 25. Higher scores indicate stronger beliefs. By subtracting the concerns score from the necessity score, a necessity-concerns differential score can be calculated (ranging from −20 to +20, where positive scores mean that patients perceive that benefits of medication outweigh costs, and vice versa).
Part two, the BMQ ‘general’, assesses general beliefs about pharmaceuticals as a class of treatment [20], and also has two subscales of four items each. The ‘overuse’ subscale includes beliefs about the way in which medicines are endorsed by doctors (e.g., “Doctors place too much trust on medicines”). The ‘harm’ subscale includes beliefs about the potential of medication to harm (e.g., “Medicines do more harm than good”). The scoring method is identical to the BMQ ‘specific’: total subscale scores range from 4 to 20.

2.5.3. Secondary measures (T0, T1, T2, T3)

Medication non-adherence was assessed with the Compliance Questionnaire Rheumatology [25]. The CQR is able to detect whether a patient takes <80% of prescribed medication (binary score) with a sensitivity of 62% and a specificity of 95%.

Non-adherence was also measured using a dichotomized score of the five-item Medication Adherence Report Scale (MARS [31], non-adherent when total score <23 [22,41]) and using pharmacy refill data [42]. Using these data, Medication Possession Ratios (MPR: days of DMARD supply divided by the number of days within an observation period) were calculated [32]. (Calculation) details about the non-adherence measures and other secondary measures that might be affected by our intervention [17] are provided in Appendix Table I [33–40].

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All questionnaires used were validated and had a sufficient level of internal consistency in this RA sample (alpha: 0.68–0.95). Reminders were sent to stimulate patients to fill in the questionnaires.

2.6. Sample size and data analyses

To detect a difference in the BMQ differential score of two points at 12 months’ follow-up between the two arms [15], we aimed to include 60 participants in each arm (based on an alpha of 0.05, beta of 0.2, a pilot-derived SD of 3.9, and taking 28% drop-outs into account).

Data analyses were based on the intention-to-treat principle [23], and on complete cases. For all outcomes except refill rates (MPRs), intervention effects were analyzed using generalized estimating equations (GEE [43]) with robust standard errors [44], two-sided p set at 0.05, and an assumed unstructured correlation working matrix. Beforehand, severely skewed outcomes were dichotomized (MARS and SIMS, cut-off at 95% of their scales [22,41]). Furthermore, one fixed set of confounders was selected from the baseline measures (selected when visually unbalanced between the arms [45], univariately associated with one outcome measure, and when not strongly correlated to other potential confounders). Time was handled as a dummy variable [46].

Intervention effects as assessed by refill data, and differences between the non-adherent trial participants and the non-adherent patients who refused to participate were tested by means of t-tests (unequal variances assumed) or Chi-square tests. Baseline scores of the initial sample and the remained sample at 12 months’ follow-up were compared using standardized mean differences to assess the influence of attrition on the study results [47]. All data analyses were verified by a statistician.

3. Results

3.1. Participants and attrition

1819 RA patients were assessed for eligibility; the participant flow trough the trial is depicted in Fig. 1. The 123 non-adherent, randomized patients did not differ in terms of baseline characteristics and outcome measures from the 118 non-randomized, non-adherent patients.

Overall attrition in the baseline sample up to 12 months after baseline was 8.9%, and had no influence on the main outcomes of this study.

3.2. Baseline sample characteristics

Most participants were female and lived together with others. A quarter of the total sample was highly educated. Also, participants had a mean disease duration of >14 years (Table 1). Descriptive data on all outcome measures at baseline and follow-up are presented in appendix Table I.

Supplementary material related to this article can be found, in the online version, at http://dx.doi.org/10.1016/j.pec.2013.12.002.

3.3. Effects of the intervention

Table 2 presents outcomes regarding beliefs about medication and non-adherence at baseline and 12 months’ follow-up, and the corresponding adjusted effect sizes.

Generally, no differences in BMQ scores were detected between both arms over time. Only at 12 months’ follow-up, participants in the intervention arm did have less strong necessity beliefs about medication than participants in the control arm.

No differences between the two arms could be detected for other secondary outcome measures, except pain and accepting illness cognitions: at one week follow-up, participants in the intervention arm reported less pain (adjusted b: −7.8, 95% CI −13.7, −1.8), and stronger accepting illness cognitions (unadjusted b: 0.9, 95% CI 0.1, 1.8, adjusted b not significant) than those in the control arm.

3.4. Additional analyses

Three additional analyses were performed.

First, we studied changes in outcomes between the intake meeting and baseline, since we noted that non-adherence had changed between these moments (decreased from 100% of patients being non-adherent, to 65%). It appeared that the balance between necessity – and concern beliefs about medication had improved (paired t-test, difference 0.9, 95% CI –0.1, 1.8). Also, the amount of change in CQR adherence in the participants depended on the researchers involved in the inclusion procedure (44% of patients included by researcher ‘A’ became adherent at baseline, versus 25% of patients included by researcher ‘B’; p = 0.03). This association was also reflected in the refill rates: the mean refill rate was 98% at baseline, and 104% at 12 months’ follow-up in those patients included by researcher ‘A’ versus 100% and 93% by researcher ‘B’, respectively (p < 0.05, paired two sample t-test).

Second, in a sensitivity analysis, we found that the direction of our results did not change when excluding patients who were medication-adherent at baseline.

Third, treatment integrity analyses were performed (Appendix I). 49% of the intervention content, as described in the intervention protocol [13] was conducted. In practice, participants had a greater need for education about medication than for discussions about medication use; the intervention leaders felt it was important to serve this need. The degree of patient-centeredness during the intervention was 3.1 on a scale of 0 (‘not at all’) to 4 (‘a great extent’).

4. Discussion and conclusion

4.1. Discussion

This study evaluated the effects of a short, group-based intervention, which primarily aimed to change the balance in
beliefs about medication, and subsequently, to improve medication adherence to DMARDs in non-adherent patients with RA. However, the intervention was not superior to the control arm in changing beliefs or improving adherence.

Our results are in line with the systematic review by Haynes and colleagues [9], which states that most existing interventions to improve medication adherence are not particularly effective. However, our results do not correspond with the studies by Clifford and Bender [15,48], who found that their telephone interventions elicited more positive beliefs about medication and better adherence than the control condition. Since baseline measures were missing [15] or no long term effects had been examined [48] in these studies, however, our results seem to be more solid. To place our results in context, more studies about the effectiveness of targeting beliefs about are needed, though.

There are several explanations for the absence of intervention effects.

First, there may not have been sufficient room for improvement in beliefs and adherence: beliefs and adherence had already favorably changed before the actual intervention took place. This might have been due to the phenomenon of ‘regression to the mean’ [49], Hawthorne effects [50], but also to our intake meeting [51], a notion supported by the correlation between the change in adherence and the two researchers involved during intake.

Second, although we established a good level of patient-centeredness, the total treatment integrity level of our intervention was suboptimal. This might have affected our study results. In contrast, it is still unknown to what extent a suboptimal treatment integrity level affects treatment outcomes [28], so more research into the topic of treatment integrity is needed.

Table 1: Baseline study sample characteristics.a

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Arm 1 [sessions], n = 63</th>
<th>Arm 2 [brochures], n = 60</th>
</tr>
</thead>
<tbody>
<tr>
<td>Socio-demographic characteristics</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>60.4 (12.1)</td>
<td>59.3 (11.3)</td>
</tr>
<tr>
<td>Female</td>
<td>42 (66.7%)</td>
<td>43 (71.7%)</td>
</tr>
<tr>
<td>Living with others</td>
<td>44 (72.1%)</td>
<td>50 (84.8%)</td>
</tr>
<tr>
<td>Higher educationab</td>
<td>15 (24.6%)</td>
<td>15 (25.4%)</td>
</tr>
<tr>
<td>Currently employed/studyingc</td>
<td>28 (48.2%)</td>
<td>31 (51.7%)</td>
</tr>
<tr>
<td>Clinical characteristics</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Disease duration (years)</td>
<td>15.3 (10.5)</td>
<td>14.2 (9.1)</td>
</tr>
<tr>
<td>DMARDs used (1–3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 DMARD</td>
<td>25 (41.7%)</td>
<td>36 (61.0%)</td>
</tr>
<tr>
<td>2 DMARDs</td>
<td>29 (48.3%)</td>
<td>17 (28.8%)</td>
</tr>
<tr>
<td>≥ 3 DMARDs</td>
<td>6 (10.0%)</td>
<td>6 (10.2%)</td>
</tr>
<tr>
<td>Route of DMARD administration</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oralab</td>
<td>43 (71.7%)</td>
<td>34 (57.6%)</td>
</tr>
<tr>
<td>Parenteralc</td>
<td>41 (68.3%)</td>
<td>38 (64.4%)</td>
</tr>
<tr>
<td>Rheumatoid factor (positive)</td>
<td>29 (78.4%)</td>
<td>30 (79.0%)</td>
</tr>
<tr>
<td>Anti-CCP (positive)</td>
<td>24 (72.7%)</td>
<td>24 (68.6%)</td>
</tr>
<tr>
<td>RADAI disease activity (0–10)</td>
<td>2.5 (1.7)</td>
<td>2.5 (1.9)c</td>
</tr>
<tr>
<td>VAS pain score (0–100mm)</td>
<td>27.2 (19.2)</td>
<td>26.8 (21.0)</td>
</tr>
<tr>
<td>HAQ Disability Index (0–3)d</td>
<td>1.0 (0.7)</td>
<td>0.9 (0.7)</td>
</tr>
</tbody>
</table>

Note: a Data are means (SD) or numbers (%).

b Higher education means having at least a bachelor's or master's degree.

c Azathioprine, hydroxychloroquine, leflunomide, methotrexate, prednisone/ prednisolone or sulfasalazine.

d Adalimumab, depotmedrol, etanercept, methotrexate, abatacept, infliximab, or mabthera. Four patients received infusion mono-therapy.

e >10% missing data. Number of non-missing cases in intervention and control arm is 37/38 for the rheumatoid factor, 33/35 for anti-CCP, and 51/52 for the RADAI score, respectively.

f Higher scores = greater disability/disease activity/pain.
Table 2
Adjusted effect sizes for beliefs about medication and medication non-adherence, 12 months after the intervention.\(^a\)

<table>
<thead>
<tr>
<th>Measures</th>
<th>T0: baseline, n = 119</th>
<th>T3: 12-month follow-up, n = 115</th>
<th>Adjusted effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Arm 1 (sessions)</td>
<td>Arm 2 (brochures)</td>
<td>Arm 1 (sessions)</td>
</tr>
<tr>
<td><strong>Beliefs about medication</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMQ specific necessity (5–25)(^d)</td>
<td>18.8 (3.6)</td>
<td>18.8 (3.3)</td>
<td>18.2 (3.8)</td>
</tr>
<tr>
<td>BMQ specific concerns (5–25)(^d)</td>
<td>13.3 (3.4)</td>
<td>14.3 (3.3)</td>
<td>12.8 (3.5)</td>
</tr>
<tr>
<td>BMQ differential (−20 to +20)(^d)</td>
<td>5.6 (4.7)</td>
<td>4.6 (4.8)</td>
<td>5.5 (5.1)</td>
</tr>
<tr>
<td>BMQ general overuse (4–20)(^d)</td>
<td>11.0 (2.5)</td>
<td>11.1 (2.7)</td>
<td>10.6 (2.8)</td>
</tr>
<tr>
<td>BMQ general harm (4–20)(^d)</td>
<td>9.9 (2.5)</td>
<td>10.0 (2.6)</td>
<td>9.8 (2.5)</td>
</tr>
<tr>
<td><strong>Measures</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CQR, non-adherent</td>
<td>36 (62.1%)</td>
<td>40 (67.8%)</td>
<td>28 (50.9%)</td>
</tr>
<tr>
<td>MARS, non-adherent</td>
<td>32 (54.2%)</td>
<td>33 (56.9%)</td>
<td>30 (54.6%)</td>
</tr>
<tr>
<td>% Refill adherence</td>
<td>94.4%</td>
<td>103.1%</td>
<td>96.6%</td>
</tr>
</tbody>
</table>

\(^a\) Descriptive data are means (SD) or numbers (%). Effect sizes (except for refill rate adherence) adjusted for age, sex, living with others yes/no, disease duration, parenteral medication yes/no, and baseline depression score (HADS).
\(^b\) Regression coefficient or odds ratio (OR) with 95% confidence interval for the difference in outcome values between the intervention arm and control arm at 12 months’ follow-up, corrected for baseline. Control arm = reference category. OR: odds of being non-adherent at 12 months’ follow-up is smaller (OR < 1) or bigger (OR > 1) for participants in the intervention arm in comparison with participants in the control arm.
\(^c\) Higher scores indicate stronger beliefs.
\(^d\) Positive scores mean that necessity beliefs about medication are stronger than concern beliefs about medication, and vice versa.
\(^e\) p value ≤0.05.
\(^f\) The mean change in refill adherence in participants in the intervention arm minus the mean change in refill adherence in participants in the control arm.

Third, this trial suffered from selection bias by including patients with a long disease duration (mean: >14 years). Modifying existing beliefs and adherence behaviors in patients with such a long disease duration might be harder to establish than forming new beliefs and behavior in recently diagnosed RA patients who are, essentially, busy with adopting a new lifestyle [52].

Last, ineffectiveness of our intervention might be due to focusing on patient-related factors only, while non-adherence is also caused by other types of factors according to the WHO [14]. Targeting beliefs about medication in RA patients, however, still remains an understandable choice according to a recent systematic review of Pasma et al. [53], indicating beliefs about medication to be one of the most relevant and modifiable determinants of non-adherence in RA patients.

This study has both limitations and strengths regarding internal validity. Non-adherence rates differ according to the questionnaires and the refill rates, for example (60% versus 1.5% non-adherence). The refill rate, however, is a medication possession measure, rather than a medication adherence measure [54]. Moreover, a strong feature of this trial is the combination of three different adherence measures [55]. Neither the self-report questionnaires nor the refill rate data showed superiority of the intervention arm over the control arm in changing beliefs or adherence, indicating robustness of findings.

This study has also strengths and limitations regarding external validity. A limitation is that we do not know if our non-adherent trial participants represent non-adherent RA patients in general, since no comparison material is available. A strength was the low attrition rate in our trial [56].

4.3. Practice implications

Beliefs about medication are relevant and modifiable determinants of non-adherence in RA patients. Hence, the potential value of targeting beliefs about medication and practical barriers to take medication in improving medication adherence should not yet be ruled out in clinical practice. Ineffectiveness of our intervention, namely, might have been due to selection bias, Hawthorne effects, and a suboptimal level of treatment integrity. Further research on other types of interventions which are embedded in clinical practice (non-trial setting) and with early RA-patients is warranted.

I confirm all patient/personal identifiers have been removed or disguised so the patient/person(s) described are not identifiable and cannot be identified through the details of the story.

Conflict of interest

None.

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biologic indicator.

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