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Original article

Non-adherence in difficult-to-treat rheumatoid arthritis from the perspectives of patients and rheumatologists: a concept mapping study

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Abstract

Objectives. Treatment non-adherence is more frequent among difficult-to-treat (D2T) than among non-D2T RA patients. Perceptions of non-adherence may differ. We aimed to thematically structure and prioritize barriers to (i.e. causes and reasons for non-adherence) and facilitators of optimal adherence from the patients' and rheumatologists' perspectives.

Methods. Patients' perceptions were identified in semi-structured in-depth interviews. Experts selected representative statements regarding 40 barriers and 40 facilitators. Twenty D2T and 20 non-D2T RA patients sorted these statements during two card-sorting tasks: first, by order of content similarity and, second, content applicability. Additionally, 20 rheumatologists sorted the statements by order of content applicability to the general RA population. The similarity sorting was used as input for hierarchical cluster analysis. The applicability sorting was analysed using descriptive statistics, prioritized and the results compared between D2T RA patients, non-D2T RA patients and rheumatologists.

Results. Nine clusters of barriers were identified, related to the healthcare system, treatment safety/efficacy, treatment regimen and patient behaviour. D2T RA patients prioritized adverse events and doubts about effectiveness as the most important barriers. Doubts about effectiveness were more important to D2T than to non-D2T RA patients ($P = 0.02$). Seven clusters of facilitators were identified, related to the healthcare system and directly to the patient. All RA patients and rheumatologists prioritized a good relationship with the healthcare professional and treatment information as the most helpful facilitators.

Conclusions. D2T RA patients, non-D2T RA patients and rheumatologists prioritized perceptions of non-adherence largely similarly. The structured overviews of barriers and facilitators provided in this study may guide improvement of adherence.

Key words: rheumatoid arthritis, difficult-to-treat, treatment non-adherence, patients' perspective, rheumatologists' perspective

Rheumatology key messages

- The importance assigned to adherence barriers differed slightly between D2T and non-D2T RA patients and rheumatologists.
- D2T RA patients prioritized adverse events and doubts about effectiveness as most important adherence barriers.
- A good relationship and treatment information were considered most helpful facilitators of optimal adherence.

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CLINICAL SCIENCE

Introduction

Clinical outcomes of RA patients have significantly improved over the past decades [1]. However, around 5–20% of patients remain symptomatic, despite treatment according to EULAR recommendations [2–5]. These patients can be classified as having difficult-to-treat (D2T) RA [6]. D2T RA is often a multifactorial disease state, in which several factors may contribute to the persistence of signs and/or symptoms [2, 7, 8].

Treatment non-adherence is one of the factors that could contribute to D2T RA [2, 8]. Our recent study confirmed the importance of non-adherence in D2T RA, with significantly higher non-adherence rates in D2T than in non-D2T RA patients (40% *vs* 22%) [8]. An optimal drug response can only be achieved if a patient adheres to treatment instructions; therefore, inflammation may persist in case of non-adherence. In D2T RA, this could eventually result in having used all available DMARDs without (apparently) having any option left. Thus, non-adherence is highly relevant, specifically, as non-adherence is potentially modifiable: if non-adherence can be identified by the healthcare professional (HCP) and adequately addressed, the D2T RA state may be ameliorated [9].

To optimize adherence, insights into perceptions of non-adherence are needed. It is essential to identify both adherence barriers (i.e. any factor inducing suboptimal or non-adherence: causes and reasons for non-adherence) as well as adherence facilitators (i.e. circumstances that could improve adherence) to allow their implementation in treatment strategies [10]. Identification of perceptions of non-adherence has previously been based on patients' opinions [10–12], although few studies have thematically structured patient input. Concept mapping, for example using card-sorting tasks, has been shown to be a valid and reliable method of thematically structuring and prioritizing perceptions from the patients' perspective [13–15]. In this method, patients structure perceptions of non-adherence themselves.

Perceptions of non-adherence may differ between D2T and non-D2T RA patients. This could be due to, for instance, disease-related factors (e.g. a higher number of previously failed drugs and higher disease activity levels in D2T RA) [8], and different adherence barriers may apply to D2T than to non-D2T RA patients [16, 17]. Additionally, perceptions of non-adherence may differ between D2T RA patients and HCPs. This discordance could potentially aggravate the problem. As the role of the rheumatologist is crucial in the treatment of RA and in optimizing adherence, it is important for the HCP to be vigilant regarding the issue of non-adherence in D2T RA and to understand causes and patient-related reasons as well as helpful facilitators. Therefore, identification of perceptions of both patients and rheumatologists is important.

The aim of this study was to thematically structure barriers and facilitators of optimal adherence using concept mapping, and to prioritize and compare these perceptions from the patients' and rheumatologists' perspectives.

Methods

Study design and participants

Consecutive RA outpatients fulfilling the 2010 ACR/EULAR classification criteria for RA [18] and treated according to the current standard of care (treat-to-target) for at least 1 year, had been recruited for a previous, cross-sectional study into factors potentially contributing to D2T RA [8]. These patients had been enrolled from February 2019 to August 2020 at the Department of Rheumatology & Clinical Immunology of the University Medical Center (UMC) Utrecht, the Netherlands. Patients had been classified as having D2T RA if they fulfilled all three criteria of the new EULAR definition [6], in short: (1) previous failure of $\geq$2 biologic and/or targeted synthetic DMARDs with different mechanisms of action; (2) symptoms and signs suggestive of active/progressive disease (e.g. DAS28-ESR $>$ 3.2); (3) management perceived as problematic by the rheumatologist and/or patient. RA patients who did not fulfil all three D2T RA criteria were allocated to the non-D2T RA group. Further details regarding participants and study procedures have been described previously [8].

For the current study on treatment non-adherence, random samples of D2T and non-D2T RA patients were generated by a computer from the sample described above. Patients were invited by telephone for an additional study visit from February 2020 to August 2020. To be eligible, patients had to be fluent in the Dutch language and have no hearing or visual impairments, or reading restrictions.

This study was approved by the medical ethics committee of the UMC Utrecht (18–753) and performed according to the Declaration of Helsinki. Written informed consent was obtained from all participants.

Study procedures

Step 1: Interviews

Semi-structured in-depth interviews were conducted to collect as many statements as possible regarding (A) barriers and (B) facilitators of optimal adherence. Prior to these interviews, a pilot interview was undertaken in collaboration with a patient research partner (N.C.N.) to limit the patient burden and to assess the relevance and comprehensiveness of the questions. Two female researchers (N.M.T.R., E.P.C.v.O.) conducted the interviews, in which a confidential environment was ensured and open-ended questions were asked in accordance with a predetermined interview guide (Supplementary File S1, available at *Rheumatology* online). The first 10 interviews were carried out face-to-face at the outpatient clinic. Due to the COVID-19 outbreak, the subsequent interviews were performed via a video call. All

interviews were audiorecorded for verbatim transcription. Interviews were performed until saturation of information occurred (i.e. when no new information was gained during two consecutive interviews, Supplementary File S2, available at *Rheumatology* online). This study was conducted following the consolidated criteria for reporting qualitative research (COREQ) checklist (Supplementary File S3, available at *Rheumatology* online) [19].

Step 2: Selection of statements

Statements were extracted regarding (A) barriers and (B) facilitators of optimal adherence. The statements were reduced to 40 statements per category, which has been shown to be a manageable number in card-sorting tasks (step 3) [15].

First, unmistakably duplicate statements (in terms of content) were removed (in consensus by N.M.T.R., E.P.C.v.O.). Second, three researchers (N.M.T.R., E.P.C.v.O., R.G.) independently made a selection of 40 statements per category. Statements were removed when they were too similar to another statement, too abstract, vague or inapplicable to all participants. Statements were then divided into three categories: chosen by at least two researchers, chosen by one researcher or not chosen by any of the researchers. Three other researchers (M.C.v.d.G., P.M.J.W., J.M.v.L.) and one patient research partner (N.C.N.) independently reviewed the categorization of the statements using the same criteria and noted whether they agreed with the categorization. Statements that were selected by at least four members were discussed and then selected for the final set of statements after consensus was reached. Lastly, wording and clarity of the statements were discussed and amended if needed.

Step 3: Card-sorting tasks

Twenty D2T and 20 non-D2T RA patients participated in the card-sorting tasks: they sorted the selected barriers and facilitators (randomly numbered and printed on separate cards) by order of content similarity and content applicability. A sample size of 10–20 patients per group has been shown to be a working number for concept mapping and to ensure a variety of opinions [13], and 25–30 participants will likely yield similar results to those of several hundred participants [20].

Due to the COVID-19 outbreak, the methodology was changed into patients sorting at home without supervision by one of the researchers. A detailed manual was created to describe all steps of the card-sorting tasks, a study call was performed that included an extensive explanation, and patients with remaining questions were contacted in an additional call.

In the first card-sorting task, patients sorted the individual cards with different barriers and facilitators printed on them, by order of content similarity. The following rules applied: all statements had to be placed in a group, a statement could only be placed in 1 group, at least 2 and a maximum of 20 statements per group were allowed, and at least 4 and a maximum of 10 groups had to be formed. After the patients completed the sorting, they were asked to describe each group with an overarching word or sentence (i.e. an open card sorting).

In the second card-sorting task, patients sorted the individual cards with different barriers and facilitators printed on them, by order of content applicability (importance and helpfulness, respectively) into five predetermined groups. Group one had to contain statements that were least applicable to the individual and group five contained statements that were most applicable to the individual (i.e. forced closed card sorting). The following rules applied: all statements had to be placed in a group, a statement could only be placed in one group, and all five groups had to contain eight statements.

Additionally, rheumatologists of the Utrecht RA Cohort Study group performed the second card-sorting task, now using an online questionnaire (OptimalSort, Optimal Workshop, Wellington, New Zealand). They sorted the barriers and facilitators by order of content applicability to the general population of RA patients.

Statistical analyses

The similarity of statements was classified using hierarchical cluster analysis, a statistical technique for classifying similar objects into separate clusters [21]. The cells of the input proximity matrix included the frequency of statements not being sorted into the same group. The number of statements that were not sorted into the same group was squared to get squared Euclidean distances. Then, Ward's method was used to cluster the most similar statements. At the end, a set of clusters was derived and presented as a dendrogram and agglomeration schedule, which showed which statements were combined in each stage of the process. The project group (N.M.T.R., M.C.v.d.G., P.M.J.W., E.P.C.v.O., N.C.N., J.M.v.L., R.G.) decided on the final number of clusters using the output of the hierarchical cluster analysis. The main criterion to decide on the final set of clusters was that clusters comprised statements with a consistent content that diverged from the content of other clusters.

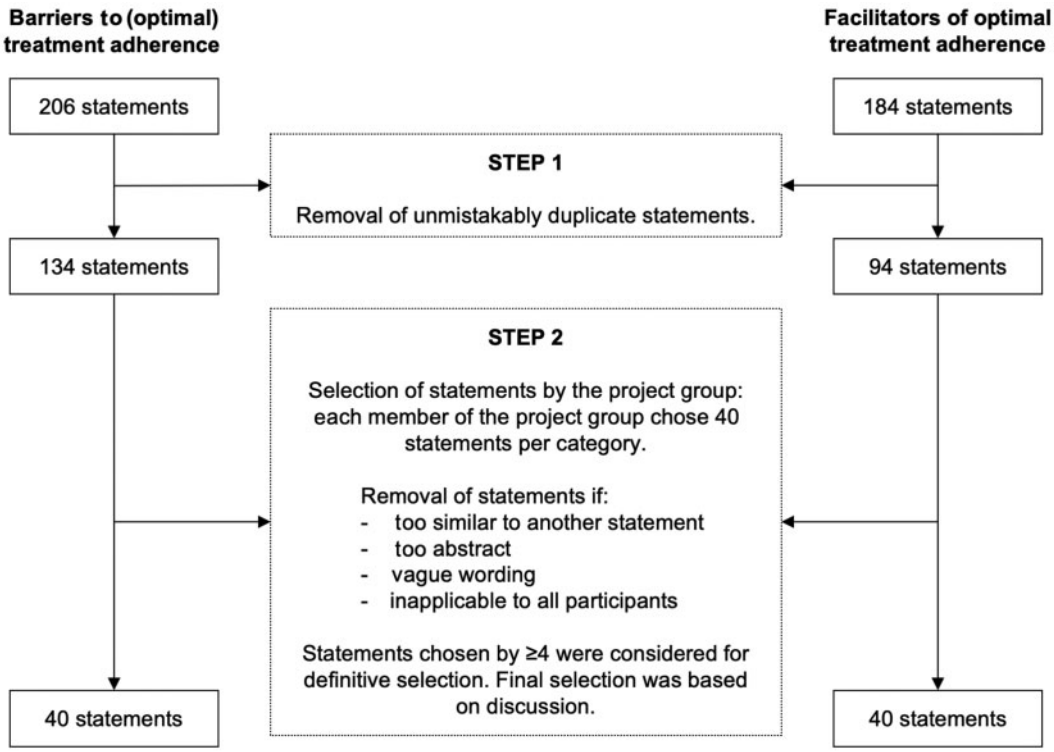
Patient characteristics and applicability of statements and clusters were summarized descriptively. Results of D2T patients were compared with those of non-D2T RA patients and rheumatologists, and tested for statistically significant differences using independent T-, Mann–Whitney U, Fisher's exact or χ^2 tests for continuous (depending on distribution), binary and categorical variables, respectively. Two-sided tested *P*-values <0.05 were considered statistically significant. Statistical analyses were performed using IBM SPSS Statistics v24 (IBM Corp, Armonk, NY, USA).

Results

Interviews

Saturation of information occurred after 14 RA patients (7 D2T and 7 non-D2T RA patients) participated in the

Fig. 1 Flow chart of selection of statements



Project group: N.M.T.R., M.C.v.d.G., P.M.J.W., E.P.C.v.O., N.C.N., J.M.v.L. and R.G.

in-depth interviews. All invited patients chose to participate. Patient characteristics were similar to those of the total previous study population [8], ensuring heterogeneity and representativeness of the sample (Supplementary Table S1, available at *Rheumatology* online). The median duration of interviews was 21 min (interquartile range 19–31 min).

Selection of statements

A total of 390 statements were collected: 206 barriers and 184 facilitators of optimal adherence (Fig. 1). From these, 155 duplicates were removed (65 barriers and 90 facilitators). From the remaining statements, a final set of 40 statements per category was derived (Supplementary Tables S2–3, available at *Rheumatology* online).

Card-sorting tasks

Patients

Fifty RA patients were invited and, of these, 40 patients participated (20 D2T and 20 non-D2T RA patients). Patient characteristics were similar to those of the total previous study population [8], ensuring heterogeneity and representativeness of the sample (Table 1). DMARDs of different administration routes were prescribed, as well as different numbers of drugs.

Non-adherence in the form of a discrepancy between supplied and prescribed drugs was more frequent among D2T than among non-D2T RA patients (this difference was statistically significant in the total previous study population; statistical significance was not tested in the participants of the card-sorting task because of the smaller sample size, Table 1). The self-reported level of adherence (according to a questionnaire) did not differ between D2T and non-D2T RA patients, as described previously [8].

Rheumatologists

Of 52 invited rheumatologists, 20 participated in the card-sorting task. Four of them were still in training. The participating rheumatologists each treated an estimated mean of 189 unique RA patients per year.

Barriers to (optimal) treatment adherence: structured overview

Patients sorted the barriers into a mean of 6.3 groups (range 4–10). In total, 246 groups were created and 245 groups were named. Twenty-nine labels were used by more than one patient, e.g. relationship with the physician, discipline, adverse events, usability issues, distrust.

After discussing the results of the hierarchical cluster analysis, the project group chose the 9-cluster option with four overarching categories (Fig. 2a). Options of 5, 7, 8 and 10 clusters were also considered. Decreasing the number of clusters below 9 resulted in the combination of clusters *adverse events* and *doubts about safety*, the combination of clusters *doubts about effectiveness*, *low disease activity* and *cost–utility evaluation*,

TABLE 1 Characteristics of patients who participated in the card-sorting task in comparison with the total previous study population [8]

	Patients who participated in the card-sorting task		Total previous study population	
	D2T RA ($n = 20$)	Non-D2T RA ($n = 20$)	D2T RA ($n = 52$)	Non-D2T RA ($n = 100$)
(Socio-)demographics				
Age, years, mean (S.D.)	60.4 (8.6)	61.1 (7.8)	60.2 (11.4)	64.5 (10.9)*
Female, *n* (%)	15 (75)	14 (70)	38 (73)	72 (72)
Education, *n* (%)				
None	0 0	0 0	1 (2)	0 0[a]
Primary school	1 (5)	0 0	3 (6)	2 (2)
Secondary school/secondary vocational education	11 (55)	5 (25)	30 (58)	48 (49)
High vocational education/university	8 (40)	15 (75)	18 (34)	49 (49)
Work participation, *n* (%)				
Paid work	2 (10)	7 (35)	7 (14)	23 (23)[a]
Paid work and partly work disabled	2 (10)	2 (10)	3 (6)	2 (2)
Fully work disabled	7 (35)	3 (15)	16 (31)	17 (17)
Retired	5 (25)	6 (30)	16 (31)	43 (44)
Other	4 (20)	2 (10)	10 (19)	14 (14)
Disease characteristics				
Disease duration, years, median (IQR)	18.5 (13.0–27.8)	11.5 (5.3–27.8)	17.0 (9.0–25.0)	14.0 (8.0–24.0)
RF positivity, *n* (%)	15 (75)	13 (65)	39 (75)	65 (65)
ACPA positivity, *n* (%)	13 (65)	14 (70)	38 (73)	65 (65)
DAS28-ESR, median (IQR)	3.7 (3.0–4.5)	2.0 (1.4–2.8)	4.1 (3.5–6.1)	2.5 (1.8–3.3)*
Comorbidities, number according to EULAR domains [22], median (IQR)	2 (1–2)	1 (0–1)	2 (1–3)	1 (0–1)*
Drugs				
Failed DMARDs, number, median (IQR)				
csDMARDs	3 (2–3)	1 (0–3)	3 (3–5)	2 (1–3)*
b/tsDMARDs	4 (3–5)	0 (0–0)	4 (3–6)	0 (0–1)*
Current DMARDs, number, median (IQR)	2 (1–2)	1 (1–2)	2 (1–2)	1 (1–2)
csDMARDs, *n* (%)	16 (80)	18 (90)	37 (71)	86 (86)*
bDMARDs, *n* (%)	11 (55)	8 (40)	27 (52)	39 (39)
tsDMARDs, *n* (%)	3 (15)	0 (0)	12 (23)	0 (0)*
Administration route of current DMARDs, *n* (%)				
Oral	17 (85)	18 (90)	45 (87)	86 (86)
s.c.	4 (20)	8 (40)	11 (21)	30 (30)
i.v.	7 (35)	0 0	16 (31)	9 (9)
Current glucocorticoids, *n* (%)	11 (55)	2 (10)	27 (52)	16 (16)*
Current painkillers, *n* (%)	19 (95)	9 (45)	49 (94)	64 (64)
Current other non-antirheumatic drugs, number, median (IQR)	6 (3–8)	2 (1–4)	–	–
Treatment non-adherence				
Level of MARS-5, median (IQR)	24 (22–25)	24 (23–25)	24 (21–25)	24 (23–25)[a]
Discrepancy in supplied and prescribed drugs, *n* (%)	8 (40)	4 (20)	21 (40)	22 (22)[a,*]

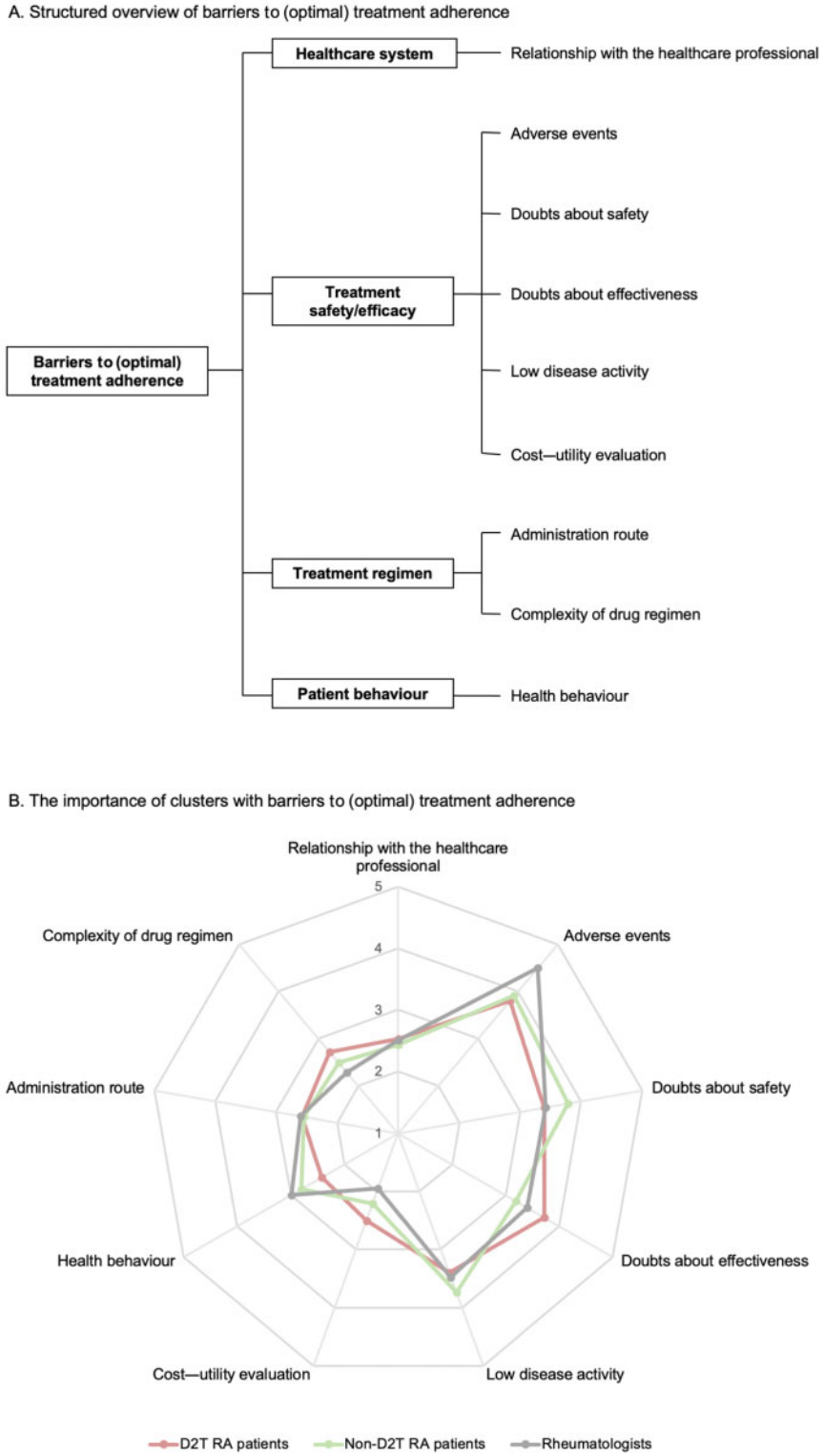
b-: biologic; cs-: conventional synthetic; D2T: difficult-to-treat; DAS28-ESR: DAS assessing 28 joints using ESR; IQR: interquartile range; MARS-5: medication adherence reporting scale (5–25, higher score reflects higher level of adherence); [23] *n*: number; ts-: targeted synthetic; [a]$n = 99$; *$P < 0.05$. In the total previous study population, D2T and non-D2T RA patients were compared. Differences were analysed using independent *t* test, Fisher's exact test, χ^2 test or Mann–Whitney *U* test, as appropriate. Statistical significance was not tested in the participants of the card-sorting task because of the smaller sample size.

and the combination of clusters *administration route* and *complexity of drug regimen*. These clusters were considered to be too distinct to combine. Increasing the number of clusters above 9 separated the cluster *health behaviour*, which did not result in new, clearly distinguishable clusters. Each cluster represented two to eight barriers (Supplementary Table S2, available at *Rheumatology* online).

Barriers to (optimal) treatment adherence: importance

The prioritization of the importance of the barriers is shown in Fig. 2b (details in Supplementary Table S2,

Fig. 2 Barriers to (optimal) treatment adherence



(**A**) The nine clusters are organized in four overarching categories (shown in the contoured boxes). (**B**) Mean scores of importance of clusters. Importance was scored from 1 (least important) to 5 (most important). D2T: difficult-to-treat.

available at *Rheumatology* online). The cluster *adverse events* was the most important barrier in D2T and non-D2T RA patients and rheumatologists. D2T RA patients ranked *doubts about effectiveness* as second-most important and ranked this cluster as more important than non-D2T RA patients [mean (S.D.): 3.7 (0.7) *vs* 3.2 (0.7), $P = 0.02$]. Additionally, D2T RA patients ranked *complexity of drug regimen* as more important than rheumatologists [mean (S.D.): 2.7 (0.9) *vs* 2.3 (0.5), $P = 0.03$]. Conversely, D2T RA patients ranked *health behaviour* as less important than rheumatologists [mean (S.D.): 2.4 (0.7) *vs* 3.0 (0.5), $P < 0.01$].

Facilitators of optimal treatment adherence: structured overview

Patients sorted the facilitators into a mean of 6.2 groups (range 4–10). In total, 252 groups were created and 250 groups were named. Twenty-three labels were used by more than one patient, e.g. pharmacy, help from others, routine, information.

After discussing the results of the hierarchical cluster analysis, the project group chose the 7-cluster option with two overarching categories (Fig. 3a). Decreasing the number of clusters below 7 resulted in the combination of clusters *good relationship with the HCP* and *treatment information*. These clusters were considered to be too distinct to combine. Increasing the number of clusters above 7 separated the cluster *aids*, which did not result in new, clearly distinguishable clusters. Each cluster represented 3–11 facilitators (Supplementary Table S3, available at *Rheumatology* online).

Three facilitators were combined in the cluster *miscellaneous*: *the absence of major life events*, *low personal costs related to drug use* and *a reward after drug use*. Patients' names for this group were, for example, *other* or *external*.

Facilitators of optimal treatment adherence: helpfulness

The prioritization of the helpfulness of the facilitators was largely similar for D2T RA patients, non-D2T RA patients and rheumatologists (Fig. 3b, Supplementary Table S3, available at *Rheumatology* online). *Good relationship with the HCP* was ranked as the most helpful cluster, followed by *treatment information* and *routine and reminders*. *Help from the pharmacy* was more helpful to D2T RA patients than rheumatologists indicated [mean (S.D.): 3.2 (0.8) *vs* 2.7 (0.5), $P = 0.04$].

Discussion

This study delineates the hierarchical structures of barriers and facilitators of optimal treatment adherence. Nine clusters of adherence barriers were identified in four overarching categories: healthcare system, treatment safety/efficacy, treatment regimen and patient behaviour. Additionally, seven clusters of facilitators of optimal adherence were identified in two overarching categories: healthcare system–related and patient-related. D2T and non-D2T RA patients and rheumatologists prioritized the presence of adverse events as the most important adherence barrier. For D2T RA patients as a group, adverse events were followed by doubts about effectiveness, which were a less important barrier for non-D2T RA patients. The facilitators of optimal adherence were prioritized largely similarly by all RA patients and rheumatologists: a good relationship with the HCP, treatment information, and routine and reminders were considered most helpful. Help from the pharmacy was considered significantly more helpful to D2T RA patients than rheumatologists indicated.

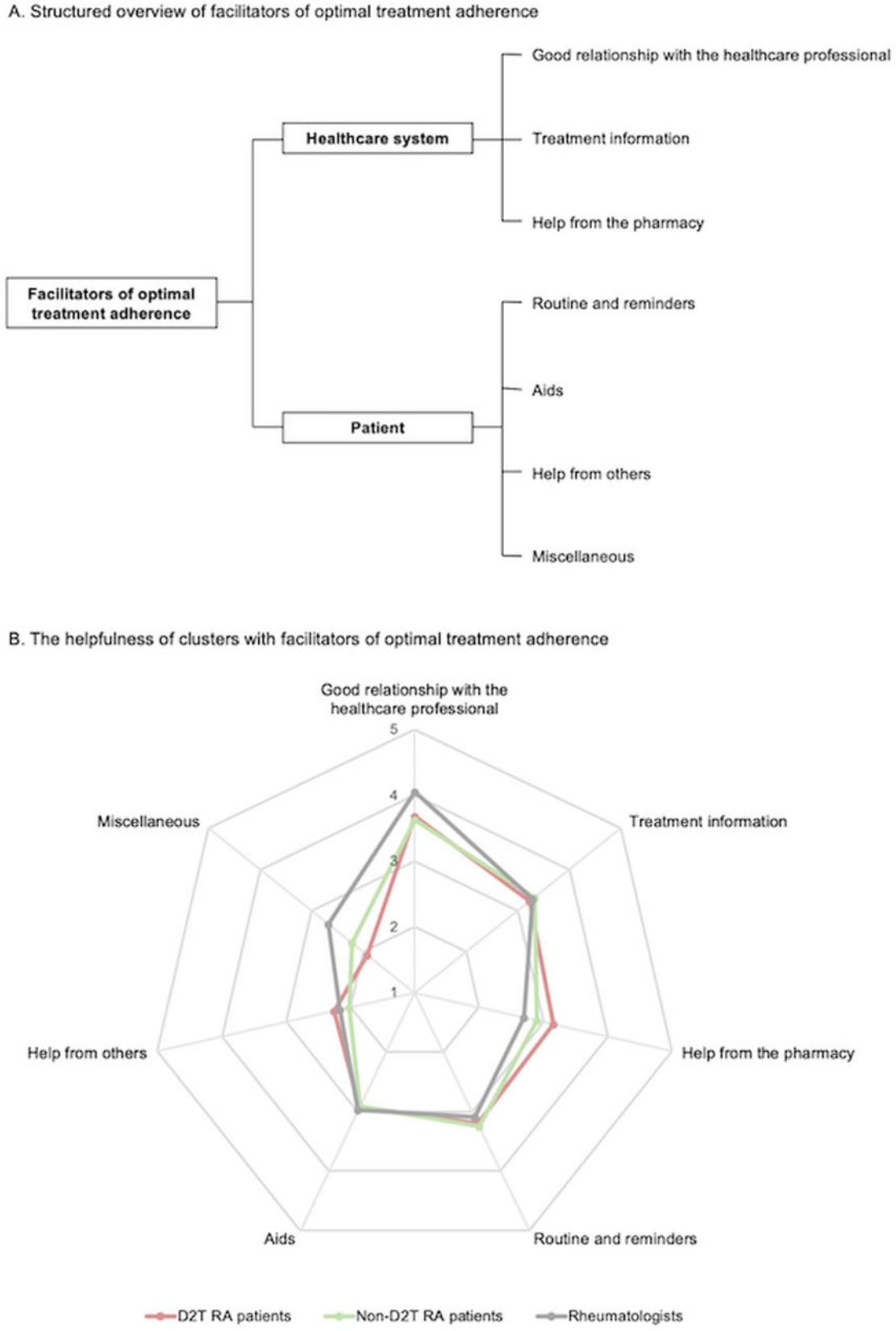
Although our study focused on treatment non-adherence in general, most statements provided by the patients were in fact related to medication adherence, for instance, those in the barrier clusters *adverse events* and *administration route*. This suggests that patients, and perhaps also their rheumatologists guided by EULAR recommendations [5], thought less of adherence to non-pharmacological treatments, for instance lifestyle advice, for which adherence improvement would also be beneficial. The study population of our study among RA patients differs from the recently published EULAR points to consider on treatment non-adherence that included patients with musculoskeletal diseases in general [24].

The World Health Organization described five different dimensions of adherence barriers, which resemble the clusters we identified as well as barriers identified in previous studies: condition-related (*low disease activity*), treatment-related (*adverse events*, *administration route*, *complexity of drug regimen*), patient-related (*doubts about safety*, *doubts about effectiveness*, *health behaviour*), health system–related (cluster *relationship with the HCP*) and socio-economic-related factors (*cost–utility evaluation*) [10–12, 16, 25–29]. Although all the clusters we identified can be placed in these five domains, patients in our study sorted the barriers somewhat differently, resulting in a hierarchical structure with other overarching categories. As our overviews were structured by the patients themselves, they may be preferred in daily practice for screening barriers and facilitators that individual patients consider important and helpful.

Despite the variety in the socio-economic status of participants, few adherence barriers in the socio-economic domain were mentioned during the interviews. Costs were mentioned, but other socio-economic-related barriers that have previously been associated with non-adherence were not brought up in our study (e.g. lack of support from relatives, cultural aspects and religion) [25]. As a hypothesis, this may be related to the Dutch (and Western) culture, with a more prominent focus on individualism instead of collectivism [30–32]. Nevertheless, these socio-economic-related barriers have previously not been confirmed to play a role in non-adherence in RA specifically [27].

The identified facilitators of optimal adherence largely resemble the facilitators in previous studies [11, 16]. However, some facilitators were not specifically

FIG. 3 Facilitators of optimal treatment adherence



(**A**) The seven clusters are organized in two overarching categories (shown in the contoured boxes). (**B**) Mean scores of helpfulness of clusters. Helpfulness was scored from 1 (least helpful) to 5 (most helpful). D2T: difficult-to-treat.

mentioned during the interviews in our study: e.g. experience from others and maintaining autonomy. This may be a result of the relatively long disease duration of the participants (median 14 years in D2T and 17 years in non-D2T RA patients) and their extended experience with drug use. Hence, these other facilitators should be considered in patients with early RA.

Perceptions of barriers and facilitators of optimal treatment adherence were largely similar between all RA patients and rheumatologists, although some differences were identified in the prioritization of adherence barriers. Particularly, D2T RA patients prioritized doubts about effectiveness as an important barrier, which may be explained by their higher number of previously failed drugs and higher disease activity levels [8]. Additionally, the prioritization of adherence barriers among rheumatologists seemed to be more aligned with the prioritization of non-D2T than with those of D2T RA patients. As only 5– 20% of RA patients can be classified as having D2T RA [3, 4, 7], the perceptions of rheumatologists may predominantly be based on non-D2T RA patients. Therefore, our results suggest that D2T RA patients, as a group, should be addressed somewhat differently than non-D2T RA patients, for example, by more explicitly discussing their (possible) doubts about effectiveness and the importance of treatment adherence, to achieve an optimal treatment response. Additionally, perceptions of non-adherence between D2T RA patients and rheumatologists could be further aligned.

However, to the extent that the perceptions of non-adherence may differ between individual patients, we suggest that HCPs should be open to the occurrence of all possible barriers and facilitators. Therefore, a discussion between patients and HCPs remains essential. This is emphasized by the most helpful facilitators we identified: a good relationship with the HCP and treatment information. This discussion can be guided by the structured overviews of barriers and facilitators and should be conducted in all phases of the treatment process [i.e. before treatment initiation, in the treatment initiation phase and in the treatment persistence phase; Table 2 presents an overview of a structured approach to address treatment (non-)adherence]. For D2T RA patients specifically, this discussion should include doubts about effectiveness among other potential barriers. The discussion should also focus on patient information and education. Not only did patients identify treatment information as a helpful facilitator, educational interventions have also been shown to be able to improve adherence [9, 33, 34].

Furthermore, other facilitators could be implemented to optimize adherence. Patients, and D2T RA patients specifically, may benefit from help from the pharmacist (e.g. reminders when drugs should be ordered, a consultation with the pharmacist about drug use). Additionally, the complexity of the drug regimen could be reduced by implementing aids (e.g. a patient-friendly drug strip or pill box). Also, the role of routine and reminders (e.g. linking the moment of drug use to a fixed moment of the day, using apps and e-health) [35] and help from others (e.g. relatives and psychologists) [9] could be discussed. Nevertheless, helpfulness of these facilitators will vary between patients and, therefore, optimizing adherence should be tailored to the individual patient. Additional guidance can be found in the recently published EULAR points to consider on treatment non-adherence [24]. Future studies should address whether the use of these structured overviews in discussions, together with the implementation of these facilitators, will ultimately improve adherence.

A major strength of this study is the combination of qualitative and quantitative methods to thematically structure perceptions of non-adherence. Additionally, a patient research partner was involved in the whole study as a researcher and co-author, providing a patient's opinion on, for example, the selection of statements and the number of clusters. Hence, the influence of the researchers has been minimized. As a limitation, this study was conducted in one country, which may limit generalizability of the results, particularly to non-Western countries. The relatively low level of non-adherence (especially the self-reported values) of participants may be another limitation. However, self-reported non-adherence is known to often underreport non-adherence assessed by other methods, such as a discrepancy between supplied and prescribed drugs [36]. We also found a discrepancy (Table 1 and Supplementary Table S1, available at *Rheumatology* online), in line with previously reported rates [36–39]. Nevertheless, the results might have been even more relevant if only non-adherent patients had participated, although the feasibility of such studies is probably low. The relatively low response rate among rheumatologists (38%) should be considered another limitation. This might be due to the large workload during the COVID-19 outbreak. We do not know whether this could have influenced the results. Furthermore, some patients expressed difficulties in performing the similarity sorting and categorized statements as *not applicable* or *other*. Nevertheless, the influence on the results may be limited, as the face validity of the structured overviews is high.

In conclusion, this study provides structured overviews of perceptions of treatment non-adherence. Adherence barriers were structured into healthcare system–related (relationship with the HCP), treatment safety/efficacy–related (adverse events, doubts about safety, doubts about effectiveness, low disease activity, cost–utility evaluation), treatment regimen–related (administration route, and complexity of drug regimen) and patient behaviour–related barriers (health behaviour). Facilitators of optimal adherence were structured into healthcare system–related (a good relationship with the HCP, treatment information, help from the pharmacy) and patient-related facilitators (routine and reminders, aids, and help from others). On average, the perceived importance of adherence barriers differed only slightly between D2T RA patients, non-D2T RA patients and rheumatologists. The helpfulness of facilitators of

TABLE 2 A structured approach to address treatment (non-)adherence in clinical practice

	Before treatment initiation	During treatment	
		Initiation phase	Persistence phase
Discuss the importance of treatment adherence	**X**	**X**	**X**
Discuss barriers to treatment adherence:	**X**	**X**	**X**
• Adverse events[a]			
• Experience with previous adverse events	X		
• Presence of adverse events		X	X
• Doubts about safety	X	X	X
• Doubts about effectiveness	X	X	X
• Low disease activity[b]			X
• Cost-utility evaluation[c]	X	X	X
• Administration route[a]			
• Thoughts about administration route	X		
• Experience with the administration route		X	X
• Complexity of drug regimen[a]	X	X	X
• Health behaviour[d]	X	X	X
Discuss facilitators of optimal adherence:	**X**	**X**	**X**
• Treatment information			
• Provide information	X		
• Check whether additional information is needed		X	X
• Help from the pharmacy[a,e]	X	X	X
• Routine and reminders	X	X	X
• Aids	X	X	X
• Help from others	X	X	X
Maintain a good relationship between patient and HCP	**X**	**X**	**X**

Our proposed approach to address treatment (non-)adherence in the different phases of the treatment process using the clusters as presented in the structured overviews (Figs 2 and 3). For each individual patient, some of these issues will be more important than other issues. HCP: healthcare professional; [a]mainly or only applicable to medication adherence; [b]patients may doubt the importance of continuing treatment in case of (temporarily) low disease activity; [c]weigh the advantages (e.g. effectiveness) and disadvantages (e.g. adverse events, costs) of treatment; [d]e.g. forgetting to follow treatment instructions or to take drugs; [e]e.g. offer a consultation with the pharmacist about drug use.

optimal adherence was prioritized largely similarly by all RA patients and rheumatologists: good relationship with the HCP and treatment information were most helpful. These findings further indicate the importance of a discussion about non-adherence between patients and rheumatologists in improving adherence.

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Data availability statement

Data are available from the corresponding author upon reasonable request.

Supplementary data

Supplementary data are available at *Rheumatology* online.

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