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ORIGINAL RESEARCH

To treat or not to treat? Current attitudes on treatment aimed at modifying the disease burden in clinically suspect arthralgia: a survey among participants of the TREAT EARLIER trial and healthcare professionals

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ABSTRACT

Objectives While awaiting therapies accomplishing rheumatoid arthritis (RA)-prevention in individuals at-risk, recent evidence supports that a 1-year methotrexate treatment may lead to sustained reduction in disease burden and subclinical joint inflammation in patients with clinically suspect arthralgia (CSA). We aimed to study the previously unexplored attitudes of CSA patients and rheumatologists on 1-year DMARD treatment in the arthralgia phase to reduce the disease burden, while not preventing RA.

Methods CSA patients who participated in the TREAT EARLIER trial, thus being expert by experience, were informed on the trial results. Thereafter they completed an anonymous questionnaire about their attitudes on treatment in the CSA phase. We used the same approach for Dutch healthcare professionals in rheumatology.

Results The majority of trial participants (85%) considered the effects of the 1-year treatment as found in the TREAT EARLIER trial, beneficial in the symptomatic at-risk stage. 79% would recommend a 1-year methotrexate course to others with comparable joint complaints. Two-thirds indicated RA prevention and improving disease burden to be equally important treatment goals in the CSA phase. Most healthcare professionals (88%) were inclined to prescribe 1-year treatment to CSA patients aimed at long-term improvement of symptoms and functioning, while not preventing RA development. 59% believed the profits of a 1-year methotrexate course to outweigh disadvantages, for example, side effects.

Conclusions A considerable willingness exists among CSA patients and rheumatologists to start a 1-year treatment resulting in long-term improvement of symptoms and functioning, while not preventing RA. This emphasises the need for more research optimising treatment regimens and disease monitoring in

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Recently, the TREAT EARLIER trial revealed that a 1-year methotrexate treatment may lead to sustained reduction of at least 1-year post-treatment in disease burden for patients with clinically suspect arthralgia (CSA) and subclinical joint inflammation, while not preventing rheumatoid arthritis (RA).

⇒ Although a number of well-designed studies have been published about perspectives on RA prevention, it was previously unknown if treatment aimed at lowering the disease burden would be acceptable and desirable by CSA patients and healthcare professionals in rheumatology.

WHAT THIS STUDY ADDS

⇒ A considerable willingness exists among CSA patients and healthcare professionals in rheumatology to start a 1-year treatment aimed at modifying the disease burden, while not preventing RA.

⇒ Not only RA prevention, but also sustained improvement of the disease burden are considered relevant treatment goals in the CSA phase to pursue in future research.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ The data of the current survey study emphasise the need of further research on treatment regimens aiming at modifying the disease burden in symptomatic individuals at risk, to avoid treatment that may have harms that outweigh benefits, especially while awaiting treatment leading to RA prevention.

individuals at-risk to facilitate such treatment decisions in the future, while avoiding an intervention, either limited or for a prolonged period, which may have harms that outweigh benefits.

Trial registration number The Netherlands Trials Registry (NTR4853-trial-NL4599). EudraCT number: NL2014-004472-35.

INTRODUCTION

Rheumatoid arthritis (RA) is among the most prevalent, disabling and burdensome chronic autoimmune diseases, requiring long-term immunosuppressive treatment.[1] This forms a clear rationale for research on interventions aimed at RA prevention and disease modification. Physical impairment in the symptomatic phase before the onset of clinical arthritis, clinically suspect arthralgia (CSA), can be as severe as at the stage of RA diagnosis, and can already result in work limitations.[2 3] Therefore, this symptomatic at-risk stage provides a unique opportunity to study treatment effectiveness in RA prevention and disease modification.

Understanding the perceptions of individuals with joint symptoms that are considered at risk for progression to RA is of great importance for effective clinical translation of trial outcomes.[4] While several trials on RA preventions were ongoing, a considerable number of well-designed studies has been published on perspectives of first degree relatives of RA patients (FDRs), CSA and RA patients on possible future treatment to prevent RA.[5–12] Qualitative research concluded that potential RA prevention may outweigh uncertainty about the risk of RA and treatment harms in FDRs.[5] In addition, pharmacological treatment was more often found appropriate after symptom onset.[6 7] A quantitative, stated choice survey by Finckh *et al* found the willingness to take preventive therapies in FDRs to be 7%, 30% and 38% for an assumed risk of RA of 1%, 20% and 40%, respectively.[8] Predicted uptake by individuals at risk was reported the highest for oral methotrexate (46%) in another large study among FDRs.[9] Perspectives of healthcare professionals on the subject are less often studied. A qualitative study, also involving rheumatologists, revealed that the opinion of the healthcare professional is an important attribute for the willingness of patients and FDRs to take preventive treatments.[10] Moreover, in the two quantitative studies that included rheumatologists, rheumatologists seemed to be somewhat more inclined to start preventive treatment compared with individuals at risk.[11 12]

Recently, the TREAT EARLIER (TREAT Early Arthralgia to Reverse or Limit Impending Exacerbation to Rheumatoid arthritis) study showed that a temporary treatment with a 1-year course of methotrexate tablets leads to a sustained improvement in symptoms, functioning and MRI-detected inflammation, while not preventing RA.[13] The available studies on preferences of stakeholders, as mentioned above, all used hypothetical scenarios on RA prevention and also did not include improvement of the burden of disease in CSA patients as a possible treatment aim. It is, therefore, unknown if treatment aimed at lowering the disease burden would be acceptable and desirable by CSA patients and rheumatologists. This study, therefore, aimed to explore attitudes and preferences of CSA patients on the results of the TREAT EARLIER trial and the future of treatment on the CSA phase. Second, since previous research revealed that the opinion of the healthcare professional is an important attribute for individuals at risk and less often studied, we additionally explored attitudes and preferences of healthcare professionals on the subject.

METHODS

Study population

The study population consisted of two groups of important stakeholders: CSA patients who participated in the TREAT EARLIER trial and healthcare professionals in rheumatology. Both groups were asked to participate in an anonymous survey after they attended a meeting in which the results of the TREAT EARLIER trial were presented by the research team: the information meeting for trial participants and the annual meeting for Dutch clinical rheumatologists, respectively. All trial participants were invited for the information meeting, which was held online, in order to encourage attendance of participants who lived further away from the Leiden University Medical Centre (LUMC). Both meetings were held within 2 weeks in September 2022.

The TREAT EARLIER trial was a randomised, double-blind, 2-year proof-of-concept trial, in which patients with CSA-detected and MRI-detected subclinical joint inflammation were randomly assigned (1:1) to a single intramuscular glucocorticoid injection and methotrexate tablets or placebo injection and tablets during 1 year.[13] Subsequently, all participants were followed for a second year without treatment. Adults aged 18 years or older with arthralgia at risk of developing RA were eligible for trial enrolment across 13 rheumatology outpatient clinics in the southwest region of the Netherlands. We used a two-level definition to identify patients predisposed to develop RA. First, patients needed to have recent-onset (within the past year) arthralgia that was suspected of progressing to RA according to the treating rheumatologist (ie, CSA). CSA, a complex of clinical symptoms and signs, was identified by rheumatologists using pattern recognition, as no single symptom is sufficiently specific for imminent RA. Second, an MRI scan of their hands or forefeet had to show subclinical joint inflammation. Development of RA was the primary endpoint of the trial. Secondary endpoints were patient-reported functioning, symptoms and work-related limitations.[13] The trial was conducted double-blinded, but after the trial was completed, participants were informed on their allocated treatment during the study. Trial screening, all study visits and assessment of endpoints occurred at a single centre, the LUMC, Leiden, Netherlands. This ensured a similar level of care for all trial participants.

Survey

For trial participants, the survey was preceded by a 30 min presentation on the trial results. The presentation started with a short background on RA, CSA, the trial inclusion criteria (CSA+ subclinical joint inflammation on MRI), and the rationale of the trial. The research question of the trial was introduced as follows: can a 1-year treatment in the CSA phase prevent RA[1] and/or improve symptoms and functioning,[2] and do any positive treatment effects persist after the 1-year treatment? We showed and explained the survival curves on RA development ('RA was not prevented'). Next, we presented the findings on sustained improvement of joint pain, morning stiffness, functioning (Health Assessment Questionaire (HAQ)-score), presenteeism at work and MRI-detected inflammation ('improvement during the 1-year treatment, which continued after the treatment was ended in the second year of the study'). Then, we addressed the incidence and nature of side effects of methotrexate as observed in the trial. We ended the presentation with the main conclusion of the trial: a 1-year course of methotrexate tablets leads to a sustained improvement in symptoms, functioning and MRI-detected inflammation, while not preventing RA. After this presentation, trial participants were asked to fill in a short survey comprising five questions with multiple response options about the main treatment effects revealed in the trial and the most important outcomes for future studies (exact phrasing of these questions can be found in online supplemental file S1). Since the survey was completely anonymous and the survey results could, therefore, not be directly coupled to the trial data of individual participants, the first two questions inquired on the allocated study treatment and RA development. Next, participants were asked if they found the effects of a 1-year methotrexate treatment to be beneficial to CSA patients, and if they would recommend this treatment to other CSA patients with similar complaints as themselves. Respondents could answer agree, disagree or neutral to this third and fourth question. The fifth question inquired on the most important goal(s) of treatment in at-risk individuals, where patients could chose RA prevention, lowering disease burden or both to be of equally major relevance. After these questions, patients were invited to share any further comments on the subject, in a final open question or live during the meeting. This study is not qualitative or mixed methods in nature, but some quotes of participants were added to the results for illustrative purposes. A complete overview of all answers on the open question can be found in online supplemental file S2.

A comparable survey was held among healthcare professionals, also composed of five questions (exact phrasing of these questions can be found in online supplemental file S1). First, respondents were asked if they had already prescribed DMARDs in the past to symptomatic patients at high risk of RA, but without clinical arthritis detectable at physical examination (answer options: often, sometimes, never). Second, they were asked to fill in on a 5-level Likert scale how likely they were to prescribe a 1-year methotrexate treatment to CSA patients in the future pursuing sustained improvement of disease burden, while not preventing RA. This was followed by a 5-level Likert scale inquiring if the benefits of a 1-year treatment with methotrexate as given in the trial would outweigh the disadvantages, such as side effects. Next, respondents could point out what treatment goals they would value most in clinical practice: RA prevention, lowering disease burden and/or lowering subclinical inflammation on imaging (multiple answers could be given). Finally, healthcare professionals could indicate reasons that would currently be considered discouraging for starting temporary treatment (eg, 1-year course of MTX) in the CSA phase. Next to prespecified answer options (scarce scientific evidence at the current moment, insufficient treatment effect, inability to prevent RA, burden of the treatment for patients, and nothing is withholding me), respondents could formulate their own answer to this question.

Analyses

We assessed the answers given in the two surveys using descriptive statistics. As participants' answers could have possibly been influenced by the allocated study treatment or RA development, we also performed stratification on these aspects among the answers given by trial participants. Similarly, the extent to which rheumatologists were already prescribing DMARDs to CSA patients in the past might have influenced their current interpretation of the TREAT EARLIER results. Hence, stratification on this element was performed among the answers given by the rheumatologists.

RESULTS

Trial participants

Fifty-three participants attended the information meeting on the trial results, all attendees completed the survey. Thirteen participants reported to have progressed to RA. This corresponded to a percentage of progressors of 25% among respondents, which is comparable to 19% of participants who developed RA in the total population during the trial.[13] Twenty-nine (55%) reported to have been treated with active medication (single glucocorticoid injection and 1-year course of methotrexate tables) and 23 (43%) with placebo medication during the trial. One participant did not report the treatment allocation. Among the total population of 236 trial participants, mean age was 47,[12] 65% was female, median symptom duration was 27 weeks (12≥27), median tender joint count was 3[1–8] and 23% was ACPA positive. Baseline characteristics were well balanced between the treatment and placebo group.[13]

After having been presented the main treatment effect found in the trial (a sustained improvement in symptoms, functioning and MRI-detected inflammation in the second year of the study, while not preventing RA), the vast majority

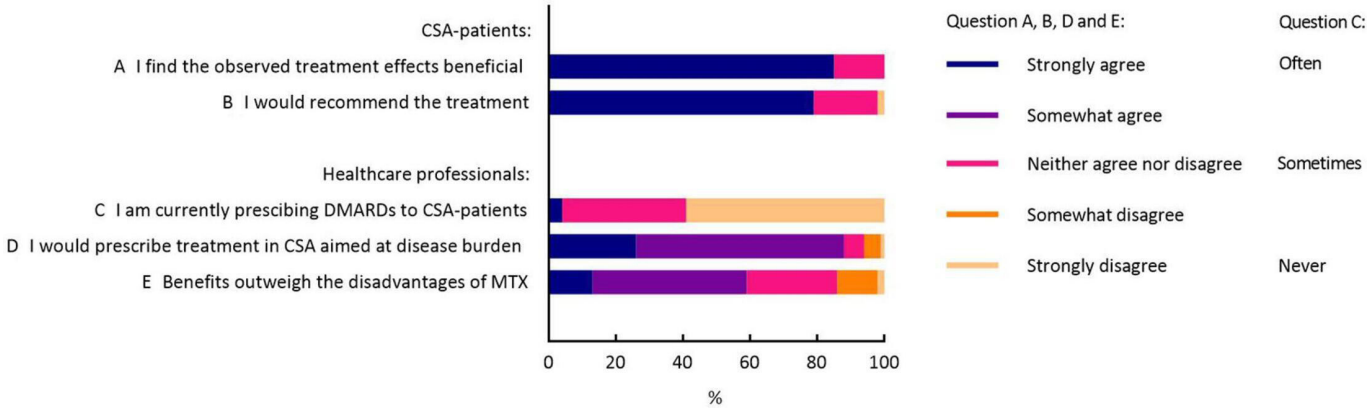

Figure 1 Attitudes of CSA patients and healthcare professionals on treatment in the CSA phase. Full phrasing of the questions was as follows: (A) I think that the effects of a 1-year methotrexate treatment, as observed in the TREAT EARLIER trail, would be beneficial to CSA patients, (B) Now I know the results of the trial, I would recommend this treatment to other CSA patients with similar complaints, (C) Have you prescribed DMARDs in the past to symptomatic patients you considered at high risk of developing RA, but who did not have (yet) developed detectable clinical arthritis at physical examination? (D) I would prescribe a 1-year methotrexate treatment to CSA patients in the future, pursuing sustained improvement of disease burden, while not preventing RA, (E) I think that the benefits of a 1-year course of methotrexate as given in the trial would outweigh the disadvantages, such as side effects. CSA, clinically suspect arthralgia; RA, rheumatoid arthritis, DMARD: disease modifying anti-rheumatic drug, MTX: methotrexate.[13]

of respondents (85%) answered that these treatment effects, would be beneficial for future CSA patients in clinical practice. The remaining 15% felt neutral on the topic, while nobody disagreed with the statement (figure 1A). Among respondents who reported to have taken the active treatment or placebo, comparable percentages of participants addressed the treatment as beneficial: 87% for placebo and 83% for treatment. Among participants who had progressed to RA, the proportion of patients reporting that the studied treatment would be beneficial was lower (62%), compared with non-progressing CSA patients (96%). These results were further illustrated by reactions of participants after the survey (for a complete overview of all comments and reactions of participants, we refer to online supplemental file S2). One participant commented on this: '*This treatment can reduce pain and other problems, that is definitely valuable*'. Another participant further commented '*How severe should CSA-complaints be to start medication? It is also a treatment with potential side effects, so I think the balance is important*'.

Over three-quarters of respondents (79%) would recommend the study treatment to others with similar complaints. Nineteen per cent were not sure about this and 2% would discourage others to start the treatment (figure 1B). In the final open question, a respondent wrote: '*I think that the trial results are good news for CSA-patients in the future*'. In respondents who were treated with active medication, the percentage who would recommend the treatment was slightly higher (83%) than respondents who were treated with placebo (74%). Participants who had developed RA were somewhat less likely to recommend the treatment (69%) compared with non-progressing CSA patients (84%).

When asking about major treatment goals that should be pursued, most participants (66%) addressed prevention of RA and long-term improvement in symptoms and functioning as equally important. Some patients indicated either only RA prevention (17%) or disease burden (17%) to be of major importance (figure 2). Respondents who have been treated with methotrexate more often considered RA prevention an important goal to pursue (93%) compared with participants who have received placebo (73%). When comparing progressors and non-progressors to RA, results were similar; in both groups of patients about two-thirds indicated RA prevention and lowering the disease burden as equally important (62% and 68%, respectively).

Healthcare professionals

A total of 211 healthcare professionals completed the survey after having been informed about the results of the TREAT EARLIER trial in a 15 min presentation commonly held at scientific conferences. In their current practice, 4% of healthcare professionals were already used to prescribing DMARD therapy to CSA patients on a regular base, and 37% did so sometimes. Fifty-eight per cent answered to have never prescribed DMARDs to patients before the onset of clinical arthritis (figure 1C). Notably, prescription of DMARDs to patients before the development of clinical arthritis is currently not recommended in national or international guidelines.[14]

Subsequently, we then assessed healthcare professionals' view on treatment of patients at risk for RA development considering the results of the TREAT EARLIER trial. To the statement 'I would prescribe a 1-year treatment for CSA patients pursuing long-term improvement of symptoms and functioning, while not preventing RA development', 26% strongly agreed, 62% somewhat agreed, 6% neither agreed nor disagreed, 5% partly disagreed and 1% strongly disagreed (figure 1D). Among the respondents who strongly agreed, 61% had never prescribed DMARDs before

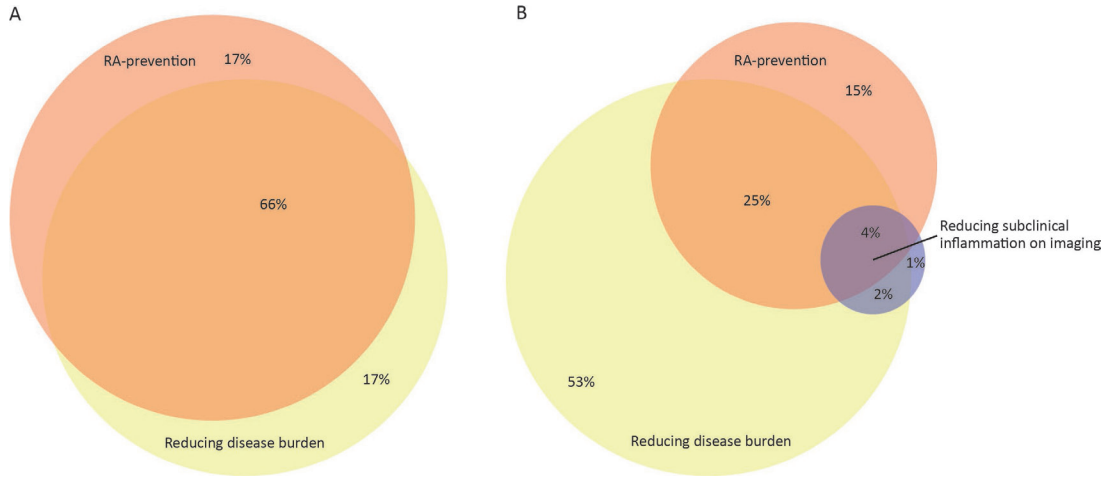

Figure 2 Most important goal(s) of future treatment in CSA patients, according to CSA patients (A) and healthcare professionals (B). Each circle represents a treatment goal: prevention of RA development (red), sustained improvement of disease burden (symptoms, functioning and work-related problems) (yellow), reducing subclinical inflammation on imaging (MRI or ultrasound) (blue, this option was only proposed to healthcare professionals). The size of the circles reflect the percentage of respondents who selected this outcome to be of considerable importance. The overlapping areas of circles depict the respondents who chose multiple treatment goals. CSA, clinically suspect arthralgia; RA, rheumatoid arthritis.

to CSA patients, and among respondents who partly agreed this was 59%. Thus, whereas 41% of rheumatologist occasionally treated CSA patients with DMARDs in their practice before, the percentage that would possibly be willing to treat CSA patients with DMARDs in order to reduce the disease burden increased to 88%. To the statement 'profits of a 1-year course of methotrexate outweigh disadvantages, such as side effects' 13% of healthcare professionals strongly agreed and 46% partly agreed. Twenty-seven per cent felt neutral on this point, 12% partially and 2% strongly disagreed (figure 1E).

Assessing what treatment goals were regarded as most important for clinical practice (multiple answers could be given) revealed that 84% considered long-term improvement in symptoms and functioning as critical, 44% indicated RA prevention and 7% considered reducing imaging-detected subclinical inflammation as of major importance (figure 2).

Finally, we evaluated reasons that would be considered discouraging by healthcare professionals for prescribing a 1-year treatment to CSA patients. Four per cent indicated that there were no reasons for not starting treatment in CSA patients. Healthcare professionals would most often consider side effects as a reason for not starting treatment (63%). About one-third of respondents addressed the scarce numbers of randomised controlled trials published on the topic (34%), as well as the negative findings on RA prevention until this date (38%) as reasons for not wanting to start treatment. About one-fourth indicated that the treatment effect was insufficient (26%). The following reasons to withhold treatment were indicated several times in the open answer option: trouble with identifying at-risk patients in clinical practice (eg, scarce availability of MRI), wanting to await data on cost-effectiveness or long-term outcomes. The importance of shared decision-making was also mentioned more often. A complete overview of all free-text answers to this question are given in online supplemental file S3.

DISCUSSION

We reported results of a survey conducted among both CSA patients and healthcare professionals in rheumatology, following publication of the main results of the TREAT EARLIER trial.[13] The results of this trial are both negative and positive in nature, since RA was not prevented, while sustained improvements of symptoms, physical functioning and MRI-detected joint inflammation were observed to ~1-year postdrug use. Because of these results, we aimed to gain insight into the attitudes of patients and healthcare professionals in a therapy pursuing long-term improvement of disease burden in CSA patients with MRI-detected subclinical joint inflammation and whether they would be willing to adopt this in daily practice. Our findings reveal that a considerable willingness exists among CSA patients and their rheumatologist to start such a time-limited treatment, although findings need to be validated in a broader CSA population besides trial participants. Not only RA prevention, but also sustained improvement of the disease burden were considered relevant treatment goals. Since the TREAT EARLIER trial is the first to show that a time-limited use of methotrexate may lead to at least 1-year improvements after treatment stop, there are still important knowledge lacunae to be filled before such a therapy could be responsibly implemented in clinical practice, to avoid an intervention, either limited or for a prolonged period, which may have harms that outweigh benefits. These include, for example, a way of monitoring disease activity and treatment response in the CSA phase as well as optimising the duration and dosage of therapy. Concluding, the data of the current survey study and

TREAT EARLIER trial emphasise the need of further research on treatment regimens aiming at modifying the disease burden in symptomatic individuals at risk, especially while awaiting treatment leading to RA prevention.

In earlier research studying perspectives on RA prevention, the willingness to take preventive treatment among at-risk individuals varied between studies, influenced, for example, by differences in assumed risk for RA and side effects in the hypothetical vignettes. To our best knowledge, Harrison *et al* quantified the highest percentage for predicted uptake (84%) of therapy among at-risk individuals.[9] Other studies reported much lower percentages, that is, Finckh *et al* found approximately one-third of FDRs would be willing to take preventive therapy.[8 11] Interestingly, in the current study, the percentage of CSA patients willing to take a 1-year treatment aimed at sustained improvement in disease burden instead of RA prevention, was comparable to the highest proportions previously reported in literature for RA prevention.[8 9 11] The high willingness found in our survey study may relate to several reasons. First, at-risk individuals in the TREAT EARLIER trial were symptomatic and had subclinical joint inflammation on MRI. Earlier research suggested higher acceptance of pharmacological interventions among symptomatic individuals than among asymptomatic individuals.[6 7] Additionally, patient respondents in the current study had participated in the TREAT EARLIER trial itself, and might, therefore, inherently be somewhat more inclined to choose pharmacological treatment, compared with CSA patients who did not want to participate in an intervention trial. Recent research indeed showed differences between enrollees and nonenrollees in a trial on, for example, concerns about medication effects.[15] Therefore, attitudes among trial participants in the current study, definitely need to be validated in other CSA patients. As also mentioned in figure 1 of the publication on the results of the TREAT EARLIER trial, 89 (23%) of the CSA patients who were eligible for the trial did not want to participate.[13] Hypothetically, if these patients would have participated in this survey and have negative perspectives on its outcomes; still over half of respondents would find the treatment beneficial and would recommend it to others. Participants in the current study have actually taken the treatment and experienced the effects. It is, therefore, important to note the positive attitudes from these patients, especially since the attitudes from patients who have received 'true methotrexate' were even slightly more positive compared with the patients who have been treated with placebo.

With respect to treatment goal, interestingly, the tendency to start treatment aimed at lowering the disease burden was larger among rheumatologists than CSA patients. This is in line with the earlier research focusing on RA prevention, in which rheumatologists seemed to be somewhat more inclined to start treatment than individuals at risk.[11 12] van Boheemen *et al* found that at 30% baseline risk of RA, 53% of seropositive arthralgia patients and 74% of rheumatologists would be willing to start a preventive treatment with no side effects.[11] Similarly, Harrison *et al* concluded that 38% of RA patients and FDRs preferred not to start preventive treatment, compared with 12% of rheumatologists.[12] The notion, that, regardless of the pursued treatment goal, willingness of CSA patients to take therapy may differ from rheumatologists' tendency to prescribe therapy, is important to take into consideration, especially since both groups of stakeholders address shared discission-making as important.[10] Interestingly, in an earlier publication from 2020, the proportion of UK rheumatologist who reported to prescribe DMARDs to anti-CCP positive individuals with subclinical inflammation on ultrasound in their current practice was fairly higher (73%), compared with the proportion of Dutch healthcare professionals who reported to have prescribed DMARDs in the past to CSA patients (4% often, 37% sometimes) in the current survey.[16] This might indicate that in general, Dutch rheumatologists could inherently be somewhat hesitant to start pharmacological treatment in at-risk patients in comparison to their UK colleagues.

The current study has some important limitations. The first concerns the generalisability of the survey results. As described earlier, trial participants might inherently have more positive attitudes towards pharmacological treatment. Therefore findings need to be validated in a broader CSA population besides trial participants. Another limitation of our study is that data on characteristics of patients and healthcare professionals who were not attending were not available. We estimate that over 60% of the total number of rheumatologists in the Netherlands filled in the survey. Among trial participants, the proportion who attended the information meeting was lower: 22% (53 of the 236 trial participants), all of whom completed the survey. A selection bias among respondents can therefore not be ruled out. In particular in trial participants, it might be possible that those with either positive or negative personal experiences during the study are more inclined to attend an information meeting on the trial results. Reassuringly, the proportion of patients who reported to have developed RA, and to have received active treatment was in agreement with the proportions in the original trial, suggesting that bias on these points is less likely.

Another limitation concerns the confined number of questions. This was done as a smaller number of questions was considered less burdensome for the participants who had already filled in a large number of lengthy questionnaires on patient-reported outcomes during the trial and its observational follow-up. Similarly, a shorter questionnaire made it possible to address many healthcare professionals. Nevertheless, the lower number of questions limited the opportunities to study many attributing factors. This is subject for future research.

Because of the anonymous nature of the survey, linking the survey results to clinical trial data, such as treatment adherence or autoantibody status, was not possible, which could be considered a limitation. Anti-citrullinated

protein antibody (ACPA) status and treatment adherence might have had influence on the perceived benefits of the trial treatment by participants. However, presumably, the treatment adherence as well as the proportion of ACPA-positive and ACPA-negative within respondents of the survey was in line with the complete trial population, as the percentage of patients who reported to have participated in the treatment arm and the proportion who reported to have developed RA and in the survey was also similar to the trail. The ability to express opinions completely anonymously also had advantages in our view, because it may have made it easier to give honest answers and promoted the fact that all participants completed the questionnaire.

While this study evaluated perspectives of patients and healthcare professionals, the societal perspective was not yet included and cost-effectiveness of DMARD treatment during the CSA phase needs to be determined in future research.

Some rheumatologists addressed risk prediction in individuals at-risk as a potential hurdle to initiate treatment in CSA patients in the future. Likewise, one participant preferred to have information about the severity of CSA and to include this in any future treatment decision-making. Risk prediction models for the development of RA have been generated in different risk cohorts and an EULAR/ACR task force is currently deriving a validated risk stratification method.[17–19] This may allow information about risk to be incorporated into treatment decisions in future studies and clinical practice.

This study on patients' and rheumatologists' attitudes and preferences is the first that used real world scientific evidence on treatment efficacy in an at-risk stage of RA. Another strength is that the CSA patients in the current study are experts by experience on having CSA symptoms and taking methotrexate tablets for 1 year. The high number of healthcare professionals who participated in the current study (n=211), especially compared with earlier research studying a group of 49 rheumatologists at the most, could also be considered as a strength.[11 12 16]

In conclusion, the current study shows a potential perceived relevance of treatment regimens aiming at modifying disease burden in the CSA phase, especially while awaiting treatment accomplishing RA prevention. More research is needed before these treatment regimens can be responsibly implemented in clinical practice. Treatment monitoring methods that enable the clinician to monitor treatment response and that assists in stopping temporary treatment in a targeted and timely manner, must be developed to prevent initiating treatment that has harms that outweigh benefits.

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Contributors DIK, SJHK and AvdH designed the study. DIK, SJHK and AvdH collected the data. All authors interpreted the data and wrote the report. AvdH was the principal investigator. DIK wass responsible for the overall content as guarantor. All authors approved the final version of the manuscript.

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Competing interests AvdH is an editorial board member for RMDopen. Otherwise none.

Patient and public involvement statement Patient partners were involved in the design of the TREAT EARLIER trial.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants and the TREAT EARLIER trial study was carried out in compliance with the Declaration of Helsinki and all patients provided written informed consent. It was approved by the medical ethical committee of the Leiden University Medical Centre (LUMC). Participants gave informed consent to participate in the study before taking part.

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Data availability statement Data are available on reasonable request. Requests for data collected (such as deidentified participant data) can be made to the corresponding author following publication, and requests will be considered on an individual basis.

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