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Mulligen, E. van; Bour, S.S.; Goossens, L.M.A.; Jong, P.H.P. de; Rutten-van Mölken, M.; Helm-van Mi, A. van der

Ann Rheum Dis 84 (2025) 68–76

Contents lists available at ScienceDirect

Annals of the Rheumatic Diseases

journal homepage: https://www.sciencedirect.com/journal/annals-of-the-rheumatic-diseases

Undifferentiated arthritis

Is a 1-year course of methotrexate in patients with arthralgia at-risk for rheumatoid arthritis cost-effective? A cost-effectiveness analysis of the randomised, placebo-controlled TREAT EARLIER trial

Elise van Mulligen[1,2,*], Sterre S. Bour[3], Lucas M.A. Goossens[3], Pascal Hendrik Pieter de Jong[2], Maureen Rutten-van Mölken[3,4], Annette van der Helm-van Mil[1,2]

[1] *Rheumatology, Leiden University Medical Center, Leiden, The Netherlands*
[2] *Rheumatology, Erasmus Medical Center, Rotterdam, The Netherlands*
[3] *Health Technology Assessment, Erasmus School of Health Policy and Management, Rotterdam, The Netherlands*
[4] *Erasmus Universiteit Rotterdam Institute for Medical Technology Assessment, Rotterdam, Zuid-Holland, The Netherlands*

ARTICLE INFO

Article history:
Received 18 June 2024
Accepted 4 September 2024

Keywords:
Treatment
Methotrexate
Rheumatoid Arthritis
Economics

ABSTRACT

Objectives: Rheumatoid arthritis (RA) has a considerable disease burden with life-long physical limitations, reduced work productivity and high societal costs. Trials on arthralgia at-risk for RA are therefore conducted, aiming to intercept evolving RA and reduce the disease burden. A 1-year course of methotrexate in patients with clinically suspect arthralgia (CSA) caused sustained improvements in subclinical joint inflammation and physical impairments. Since the cost-effectiveness of treatment in CSA has never been investigated, we investigated whether methotrexate is cost-effective.

Methods: Cost-effectiveness was assessed using the TREAT EARLIER trial. 236 patients with CSA with subclinical joint inflammation were randomised to 1-year treatment with methotrexate, or placebo, and followed for 2 years. Cost-effectiveness was analysed by computing costs and effects. For costs, both a societal perspective (healthcare-productivity and work-productivity costs) and a healthcare perspective (healthcare costs only) were used. For effects, quality adjusted life years (QALYs) were used.

Results: Treatment increased QALYs by 0.041 (95% CI −0.050 to 0.091), and reduced costs with €−4809 (95% CI −12 382 to 2726) over the course of 2 years using a societal perspective, with a probability of 88.1% that treatment was cost-effective. From a healthcare perspective, the cost-difference between treatment and placebo was estimated at €−418 (95% CI −1198 to 225).

Conclusion: A fixed treatment course in individuals with arthralgia at-risk for RA and MRI-detected subclinical joint inflammation resulted in better work productivity, lower healthcare costs and improved quality of life over the course of 2 years; with the largest gain in productivity costs. This is the first evidence that methotrexate treatment aiming at secondary prevention in arthralgia at-risk for RA is cost-effective.

*Correspondence to Elise van Mulligen.
E-mail address: e.van_mulligen@lumc.nl (E. van Mulligen).
Handling editor Josef S. Smolen

https://doi.org/10.1136/ard-2024-226286

WHAT IS ALREADY KNOWN ON THIS TOPIC

- Recent trials in people with arthralgia at risk for rheumatoid arthritis (RA) have shown that the severity of symptom burden and imaging-detected joint inflammation can show sustained improvements after disease-modifying anti-rheumatic drug (DMARD) treatment.
- There is an ongoing debate whether people with arthralgia at risk for RA should be treated with DMARDs, however, the economic effects of an intervention in the arthralgia at risk phase are unknown.

WHAT THIS STUDY ADDS

- This is the first study reporting on the cost utility of an intervention in arthralgia at-risk for RA; 2-year follow-up data from the total population studied in the TREAT EARLIER trial was studied.
- A 1-year course of methotrexate in the at-risk phase of RA resulted in less costs (mainly less work productivity costs, also lower healthcare costs) and a small improvement in quality of life.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

- Fixed-interval treatment with methotrexate in patients with arthralgia at risk for RA and subclinical joint inflammation is cost-effective and has benefits for patients and society. This may impact the debate on the treatment of people with arthralgia who are at risk for RA at a societal level and at an individual patient level.

INTRODUCTION

Rheumatoid arthritis (RA) is the most prevalent chronic autoimmune disease affecting 1% of the population. Annual societal costs (including healthcare costs and work productivity loss) are approximately €45 billion within Europe [1–3]. According to current recommendations, RA can be diagnosed once clinically apparent arthritis occurs. Subsequent treatment with disease-modifying anti-rheumatic drugs (DMARDs) aims to suppress inflammation, reduce joint destruction and disability. However, the processes underlying RA development begin much earlier. Autoimmunity can develop years before diagnosis, often in an asymptomatic stage. Subsequently, symptoms may arise while clinically apparent arthritis is still absent. A pattern of symptoms and signs that carries an increased risk of RA is described as clinically suspect arthralgia (CSA) [4]. In the CSA phase, symptoms and physical impairments can be significant and result in significant work productivity losses [5,6]. The symptomatic at-risk stage is considered as a window-of-opportunity when treatment could induce sustained improvements.

Recent trials have shown that the disease course could be modified if DMARD treatment is provided in people with arthralgia at risk for RA [7,8]. The TREAT EARLIER trial demonstrated that methotrexate, the first-line treatment of RA, modified the disease course [9]. This was shown by a sustained reduction of subclinical joint inflammation, improvements in pain, functioning and work productivity [9]. These improvements were present in individuals who developed RA, but also in those who did not, and were present both in autoantibody-positive and autoantibody-negative individuals. Very recently, two trials showed that the chance of developing RA could be reduced if people with anti-citrullinated protein antibody (ACPA)-positive arthralgia were treated with abatacept [7,8]. Hence, secondary prevention of RA and/or its burden, defined as early detection to improve health outcomes within the at-risk stage, has become possible.

There is an ongoing debate about whether people at risk for RA should be treated with DMARDs, for instance since not everyone at-risk will eventually develop RA and treatment does not completely prevent RA [7–9]. On the other hand, for methotrexate also patients who did not develop RA demonstrated sustained benefits [9]. It is important to map the economic effects within the healthcare sector and beyond in this discussion. However, the economic effects of an intervention in the arthralgia at risk phase are unknown. Methotrexate is the first-line treatment for RA, and has low costs (~€60 per year per patient). It is relevant to investigate whether this is a cost-effective investment in the arthralgia phase. Therefore, we conducted an economic evaluation of the TREAT EARLIER trial, investigating the cost-effectiveness of an intervention with methotrexate in patients with CSA with subclinical joint inflammation.

METHODS

Study design

The TREAT EARLIER was a randomised, double-blind, placebo-controlled, proof-of-concept trial conducted between April 2015 and September 2019 at the Leiden University Medical Center (LUMC), the Netherlands (previously described elsewhere) (online supplemental file 2) [9]. Eligible patients were adults with arthralgia at risk for RA who were referred from 13 rheumatology outpatient clinics in the southwestern part of the Netherlands to the LUMC. Patients had to have recent onset arthralgia of small joints (<1 year of problems), suspicious for developing RA according to the rheumatologist, so-called CSA. Per definition, patients with clinically apparent inflammatory arthritis or another more plausible explanation for the problems were excluded. Compliance with the European Alliance of Associations for Rheumatology definition of arthralgia suspicious for progression to RA was not mandatory, as it was not yet developed at the design and start of the trial [4]. Besides arthralgia, patients also had to have subclinical inflammation. Prior to inclusion, patients underwent MRI at the LUMC, to assess the presence of subclinical joint inflammation. This was defined as having at least one joint tissue (synovitis, tenosynovitis, osteitis) with inflammation on MRI, scored by two independent blinded readers, present in <5% of the age-matched, symptom-free healthy population at the same location [10].

After inclusion in the trial (n = 236), patients were randomised (1:1) to one dose of intramuscular glucocorticoids and 1-year of treatment with methotrexate or placebo, followed by a second year without treatment. This second year was important to determine whether treatment effects persisted after stopping treatment, which is crucial in the context of prevention. The primary endpoint of the trial was the development of persistent clinically apparent inflammatory arthritis. This was defined as joint swelling confirmed by two rheumatologists, which needed to be confirmed after 2 weeks to determine persistent inflammatory arthritis. When the primary endpoint was reached, patients exited the study.

During the trial, other DMARD treatments were not allowed, unless the endpoint was reached. During the 2 years of follow-up, patients had visits to the outpatient clinic every 4 months, which included assessment of the primary endpoint and collection of clinical data as well as patient-reported outcomes. Additional visits were scheduled in between in case of an increase in

symptoms. In total, 3% of patients in the treatment arm and 4% of patients in the placebo arm were lost to follow-up [9].

Economic assessment

We performed cost-utility analyses to determine the incremental cost per quality adjusted life-year (QALY) ratio of treatment versus placebo. This incremental cost-effectiveness ratio is the difference in costs between the treatment and placebo arm, divided by the difference in QALYs, calculated with the following formula:

$$ICER = \frac{(costs\ \ treatment\ \ arm - costs\ \ placebo\ \ arm)}{(QALYs\ \ treatment\ \ arm - QALYs\ \ placebo\ \ arm)}$$

For the economic evaluation, we used the societal perspective, that includes both healthcare costs and productivity costs, as recommended by Zorginstituut Nederland [11]. We also used a healthcare perspective, that includes only healthcare costs to be able to compare results internationally, and to investigate the influence of productivity costs on the outcome. In both perspectives, we discounted costs at 3% and QALYs at 1.5% in the second year to value future benefits properly [11].

Quality adjusted life years

QALYs express the impact of the disease on patients' health over time by combining the quantity of life years with the quality of life during these life years. Living in perfect health for 1 year and living for 2 years with a quality of life of 0.5 both correspond to 1 QALY. The quality of life was measured with the European Quality of Life 5-Dimensions 5-Level questionnaire (EQ-5D-5L) and valued using the Dutch tariff [12,13]. From the EQ-5D-5L, QALYs were calculated over a 2-year period by taking the area under the curve.

Healthcare costs

Healthcare costs included medication costs and costs due to medical consumption. Medication costs included only the costs of the treatment used as intervention (one dose of intramuscular glucocorticoids and 1-year course of methotrexate), and were calculated from doses reported by patients. Medical consumption, such as visits to the general practitioner, visits to the outpatient clinic (which included laboratory testing and monitoring), hospitalisations and care at home were self-reported every 4 months with the institute of medical technology assessment (iMTA) medical consumption questionnaire [14]. Medication and medical consumption were valued at Dutch standard prices for the year 2024 (online supplemental table S1) [11,15].

Productivity costs

Productivity costs included absenteeism, defined as not being at work because of sick leave and presenteeism, which indicates reduced productivity while being at work. Productivity loss due to absenteeism and presenteeism were measured using the Work Productivity and Activity Impairment questionnaire [16]. The costs were estimated with the friction cost method, which assumes the replaceability of every employee in time. Therefore, only productivity costs from the start of long-term sick leave to the end of the friction period are taken into account [11]. The duration of this friction period is estimated using the time it takes to fill in vacancies plus 4 weeks, which is currently 16.4 weeks in the Netherlands [11]. Productivity losses were valued at standard hourly costs for the year 2024 (online supplemental table S1) [11].

Statistical analyses

The cost-effectiveness analysis was trial-based and followed the statistical analysis plan of the trial [9].

Upper and lower limit analyses to handle missingness

Patients who developed the endpoint of clinically apparent inflammatory arthritis exited the study and proceeded to regular care, including the start of RA treatment (whereby methotrexate is the first choice according to treatment recommendations for RA) [1]. Ideally, we would have gathered the data from these patients after development of clinically apparent arthritis (figure 1). This design creates a challenge because the time to the endpoint differs between the treatment and placebo arms, with the placebo arm reaching the endpoint earlier compared with the treatment arm [9]. Therefore, two scenario analyses were performed. First, the lower limit analysis in which we analysed the data as available. In this analysis, we likely underestimate the intervention effect, because patients who will develop the endpoint probably have a higher disease burden, more medical consumption and productivity losses are expected to have a shorter follow-up in the placebo group and start regular treatment earlier. Second, the upper limit analysis, in which we assumed that after patients have developed inflammatory arthritis, their outcome measures remain stable over time until the end of the study (last observation carried forward). In this analysis, we likely overestimate the intervention-effect since we ignore a larger part of the possible impact of RA-treatment in the placebo group than in the intervention group. We hypothesised that these two scenario analyses would represent the upper and lower limits of the true intervention effect.

Costs and effects

Both costs and QALYs were calculated using linear mixed models. For productivity costs and quality of life, we used constrained linear mixed models with time in months and treatment as independent variables. Constrained longitudinal data analysis is a well-established unconditional technique that constrains means of baseline to be equal between groups. A random intercept per individual and a random slope for the time variable were used. For healthcare costs a constrained generalised linear mixed effect model was used with a log link and gamma distribution, to be able to best fit the skewed cost data. For all linear mixed models, the interaction between time and treatment was tested to examine if the difference between treatment and placebo changed over time. Model assumptions (constant variance, normality and independence of the errors) were checked graphically by inspection of residuals. Random effects were assumed to be normally distributed with mean 0 and unknown variance and to be independent of residuals. Both the average costs per patient over 2 years were reported, as well as the numbers needed to treat to save a certain amount of euros or improve workability with a certain amount of days.

Probabilistic sensitivity analysis

After arriving at the point estimates for costs and QALYs, a probabilistic sensitivity analysis was performed to assess the uncertainty in these estimates. A bootstrap sample was drawn 10 000 times. From the results, 95% CIs were obtained. The outcomes were visually plotted within a cost-effectiveness plane and a cost-effectiveness acceptability curve, explained in online supplemental figure S1.

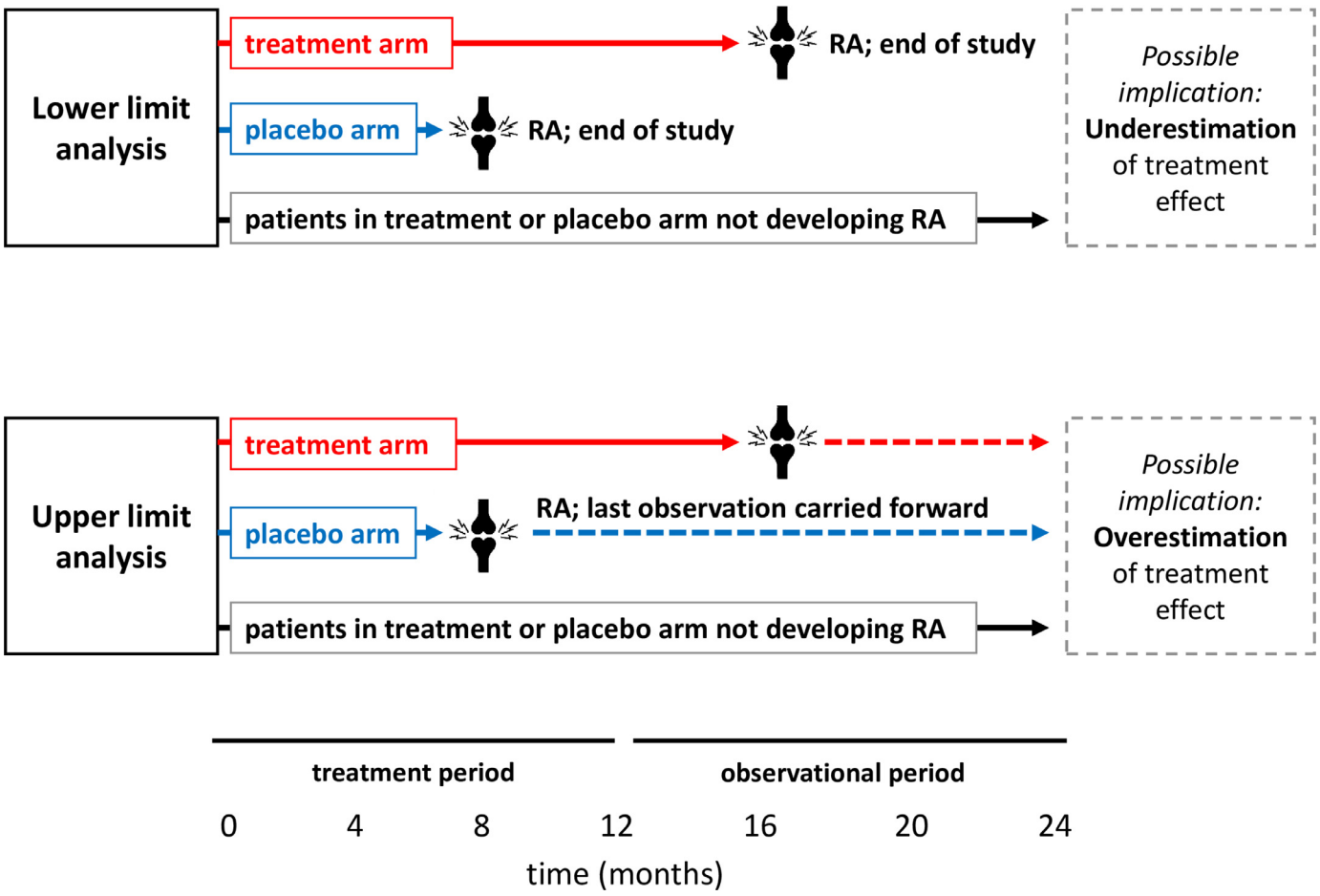

Figure 1. Overview of the upper and lower limit analyses that were used to arrive at the boundaries of the true effect of treatment. Patients who did not develop RA had complete data until the end of the trial. According to the trial protocol of the TREAT EARLIER study, patients who developed the endpoint exited the study. Because the time to the endpoint was different for patients within the treatment arm and the placebo arm, we had to handle the missingness of the data of these patients. Therefore, we conducted two analyses in which we approximated the true effect by setting an upper and a lower limit, as indicated in the figure. For the lower limit analysis, the data was analysed as it was, which probably results in an underestimation of the treatment effect, because patients who developed RA remained longer within the treatment arm compared with placebo, thereby having a larger impact of disease on a group level. For the upper limit analysis, the data of the patients with RA was carried forward to the end of the study after 2 years. In this way, the impact of the disease was larger and probably results in an overestimation of the treatment effect, since now in the placebo arm there is a longer impact of the disease due to extrapolation of the time point that the RA diagnosis was made. RA, rheumatoid arthritis.

Role of the funding source

This research was funded by the Dutch Research Council (NWO), the Dutch Arthritis Society and ZonMw. The funders of the study had no role in study design, data collection, data analysis, data interpretation or writing of the report.

Institutional review board approval

The protocol of the TREAT EARLIER trial was approved by the LUMC medical ethics committee (P14.296).

RESULTS

Patients

The baseline characteristics of the 236 patients are shown in table 1. On average, patients were aged 46 years at inclusion in the treatment group and 47 years in the placebo group, 62% and 68% were women, respectively. Median tender joint counts at baseline were four in the treatment group, and three in the placebo group. In both groups, 33% of patients were ACPA and/or rheumatoid factor positive. Functional limitations, measured with the Health Assessment Questionnaire, were similar in both groups (0.7).

Medical consumption

Medical consumption consisted of costs due to medication and healthcare use. Medication costs comprised of costs of methotrexate and one intramuscular glucocorticoid injection at baseline. On average, patients used 7.7 tablets per week, reflecting a weekly dose of 19 mg (table 2). Medication costs were estimated at €68 per treated patient in the intervention arm. Almost all patients went to the general practitioner, and all patients visited a specialist (table 2). The number of patients that had medical consumption was similar between the arms, though a number of visits/days was higher in the placebo arm compared with the treatment arm. This difference occurred at the level of visits to the physical therapist, visits to other primary care, hospital admissions and care at home (table 2). Medical consumption costs per patient over 2 years were estimated to be €2181 for the treatment arm and €2667 for the placebo arm. In other words, to save €10 000 on medical costs, it is necessary to treat at least 21 patients with CSA and subclinical joint inflammation detected with MRI compared with placebo.

Table 1
Baseline characteristics of the TREAT EARLIER trial

	Treatment group (n = 119)	Placebo group (n = 117)
Age	46 (13)	47 (11)
Aged above 67	8 (7)	2 (2)
Female sex	74 (62)	80 (68)
Symptom duration, weeks	28 (13–45)	27 (16–50)
68-TJC	4 (1–8)	3 (1–9)
ACPA and/or RF positive	39 (33)	38 (33)
Quality of life (EQ-5D-5L index)	0.64 (0.28)	0.66 (0.23)
Paid work	85 (74)	95 (83)
Working hours per week	32.8 (10.9)	31.1 (11.4)
Presenteeism	36% (28)	35% (29)
Absenteeism	7.8% (23)	7.2% (22)
HAQ-DI	0.71 (0.61)	0.70 (0.53)

Data are n (%), mean (SD) or median (IQR).
ACPA, anti-citrullinated protein antibody; EQ-5D-5L, EuroQol Quality of Life Questionnaire with 5 Dimensions measured with 5 Levels; HAQ-DI, Health Assessment Questionnaire Disability Index; RF, rheumatoid factor; 68-TJC, tender joint count including 68 joints.

Productivity losses

In total, 47% of patients in the treatment arm, and 49% in the placebo arm reported sick leave, with a mean duration of 32 and 57 days over 2 years after application of the friction cost method (table 2). Presenteeism was the highest contributor to productivity losses, and was reported by 79% of patients in the treatment arm and 87% of patients in the placebo group and occurred on average on 133 and 165 days (table 2). To improve the number of days without work productivity losses by 7 days per year, only two patients with CSA with subclinical joint inflammation detected with MRI needed to be treated compared with placebo. Average costs per patient over 2 years due to productivity losses were estimated to be €33 310 for the treatment arm, and €37 700 for the placebo arm. To be able to save €100 000 on productivity costs, it requires treatment of at least 23 patients with CSA and subclinical joint inflammation detected with MRI, compared with placebo.

Cost-effectiveness analysis

For the lower limit analysis, total costs (both healthcare and productivity costs) were estimated to be €35 559 for the treatment arm and €40 368 for the placebo arm, a difference of €4809 (95% CI −12 382 to 2726). Corresponding QALYs were 1.40 and 1.36, with a difference of 0.0408 (95% CI −0.0499 to 0.0906), indicating that treatment was the dominant strategy, because it was less costly and more effective (table 3). The main cost driver were the productivity costs, accountable for 97% of difference in costs.

For the upper limit analysis, the cost difference between treatment and placebo was estimated at €−7420 (95% CI −15 484 to 771), and the difference in QALYs were 0.0440 (95% CI −0.0499 to 0.0906) (table 3). This indicates that, as expected, differences between treatment and placebo were larger within the upper limit analysis (table 3).

Probabilistic scenario analyses

The probabilistic scenario analyses, visualised in figure 2, showed for the lower limit analysis that 67.3% out of 10 000 bootstrapped iterations were less costly and more effective, indicating that treatment was acceptable (for explanation; online supplemental figure S1). For the upper limit analysis, treatment was less costly and more effective for 70.9% out of 10 000 bootstrapped iterations (figure 2).

In online supplemental figure S2 the likelihood that treatment was cost-effective compared with placebo was shown across a range of cost-effectiveness thresholds. For every threshold

Table 2
Average productivity losses and healthcare usage indicated for both treatment arms over 2 years

	Treatment			Placebo		
Productivity	**n of patients (%)**	**Mean n of days among those with productivity loss (SD)**	**Mean n of days across all patients (SD)**	**n of patients (%)**	**Mean n of days among those with productivity loss (SD)**	**Mean n of days across all patients (SD)**
Absenteeism	56 (47)	32 (60)	14 (43)	57 (49)	46 (69)	22 (53)
Presenteeism	67 (79)	133 (104)	75 (102)	83 (87)	165 (129)	117 (132)
Medication in first year	**n of patients (%)**		**Mean dosage (SD)**	**n of patients (%)**		**Mean dosage (SD)**
Methotrexate	119 (100)		19.1 (7.4) mg	0		–
Intramuscular methylprednisolone injection	118 (99)		120 mg	0		–
Medical consumption	**n of patients (%)**	**Mean visits/days among the users (SD)**	**Mean across all patients (SD)**	**n of patients (%)**	**Mean visits/days among the users (SD)**	**Mean across all patients (SD)**
Visit to the general practitioner	114 (96)	10.3 (9)	9.8 (9)	113 (97)	8.2 (7)	7.9 (7)
Visit to the physical therapist	63 (53)	22.8 (32)	12.1 (26)	62 (53)	24.9 (31)	13.2 (25)
Visit to other primary care*	54 (45)	16.6 (18)	7.6 (15)	51 (44)	19.1 (23)	8.3 (18)
Visit to a specialist	119 (100)	7.0 (8)	7.0 (8)	117 (100)	7.1 (8)	7.1 (8)
Day treatments	26 (22)	10.6 (8)	6.3 (8)	27 (23)	10.7 (8)	6.6 (8)
Hospital or other admissions†, days	12 (10)	5.2 (4)	0.5 (2)	11 (9)	8.6 (9)	0.8 (4)
Care at home, hours	6 (5)	182 (259)	9.2 (67)	2 (2)	407 (502)	7.0 (71)

* Other includes psychologist, dietician, occupational physician, social worker, speech therapist and complementary medicine.
† Other admissions include psychiatric, revalidation or other centres.
n, number.

Table 3
Data from the lower and upper limit analyses based on the societal perspective, including both productivity costs and healthcare costs and the healthcare perspective, including only healthcare costs. All analyses resulted in less costs in the treatment arm, and more QALYs

	Treatment	Placebo	Difference (95% CI)
Lower limit analysis			
Costs from a societal perspective	€35 559	€40 368	€−4809 (−12 382 to 2726)
Costs from a healthcare perspective	€2249	€2667	€−418 (−1198 to 225)
QALYs	1.400	1.359	0.0408 (−0.0499 to 0.0906)
Upper limit analysis			
Costs from a societal perspective	€35 585	€43 005	€−7420 (−15 484 to 771)
Costs from a healthcare perspective	€2125	€2642	€−517 (−1269 to 103)
QALYs	1.384	1.340	0.0440 (−0.0499 to 0.0906)

Costs are indicated as average per patient over 2 years, QALYs were measured over 2 years.
QALY, quality adjusted life-year.

indicated at the x-axis, the proportion of bootstrapped iterations having a cost-effectiveness ratio at or below that threshold is plotted. At a threshold level of €50 000 per QALY, 88.1% of bootstrapped iterations indicated cost-effectiveness for treatment for the lower limit analysis (online supplemental figure S2A). For the upper limit analysis, 98.1% of bootstrapped iterations indicated cost-effectiveness for treatment (online supplemental figure S2B). Since the probability remained relatively stable when the threshold changed for both analyses, treatment was the preferred option over placebo across all levels of the threshold.

Healthcare perspective only

When using a healthcare perspective, including only healthcare-related costs and no productivity costs, corresponding total costs were estimated at €2249 for the treatment arm and €2667 for the placebo arm for the lower limit analysis, resulting in a cost difference of €−418 (95% CI 1198 to 225). Using the upper limit analysis the difference was €−517 (95% CI 1269 to 103) (table 3). This indicates again less costs in the treatment arm compared with placebo. Probabilistic scenario analyses, indicated in figure 3, show the same as the societal analysis. When using a willingness-to-pay threshold of €50 000, in total 78.0% of the lower limit analysis and 82.2% of the upper limit analysis indicated that treatment was cost-effective over placebo (online supplemental figure S3).

DISCUSSION

In this randomised, double-blind, placebo-controlled trial, we showed that an intramuscular injection with glucocorticoids followed by a 1-year course of methotrexate in patients with arthralgia at-risk for RA and subclinical inflammation detected with MRI is cost-effective over the course of 2 years. Treatment

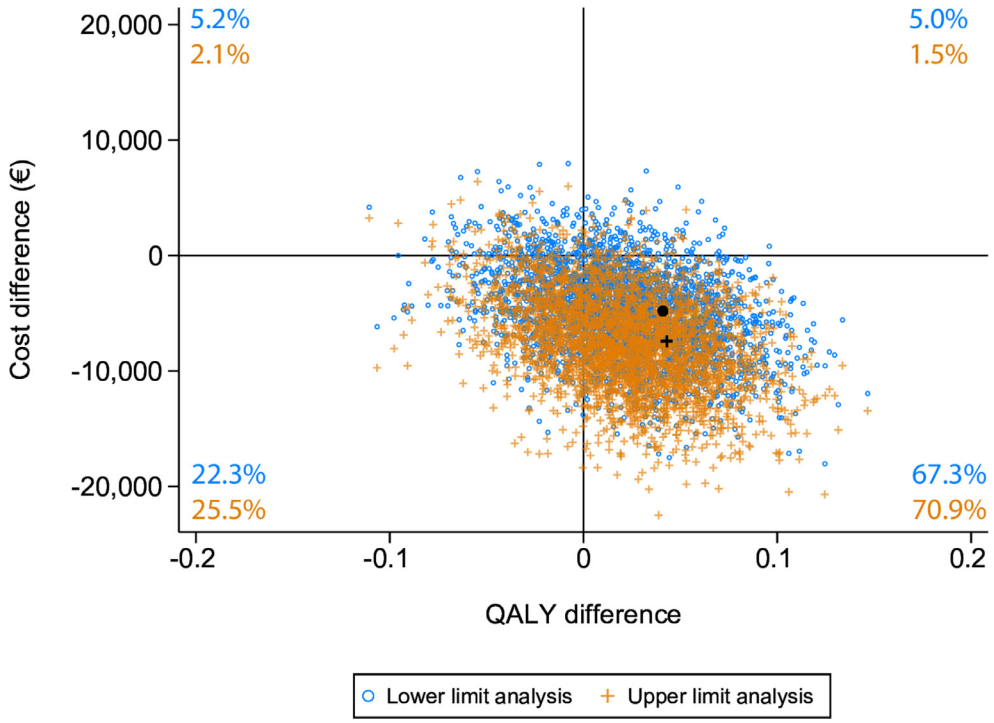

Figure 2. Results from the probabilistic uncertainty analyses shown in a cost-effectiveness plane of the lower and upper limit analysis from a societal perspective. The cost-effectiveness plane visually shows the differences in costs (y-axis) and effects (x-axis) between treatment and placebo shown from a societal perspective, that includes healthcare and productivity costs. The point estimate (black circle and cross) indicate that less costs, but better effects (QALYs) were seen in the treatment arm. The bootstrapped results (10 000 replications, blue circles and orange crosses) show the uncertainty of the estimate, in every corner of the graphs the percentage of bootstrap iterations in that quadrant is indicated. For more explanation, see online supplemental figure S1. QALY, quality adjusted life-year.

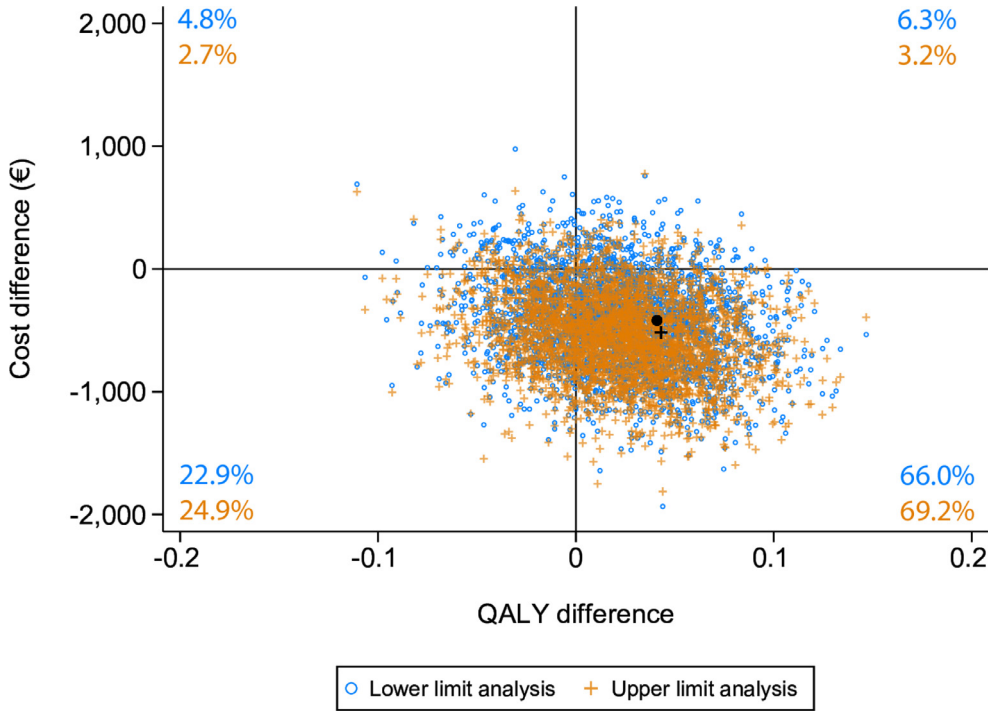

Figure 3. Results from the probabilistic uncertainty analyses shown in a cost-effectiveness plane of the lower and upper limit analysis from a healthcare perspective. The cost-effectiveness plane visually shows the differences in costs (y-axis) and effects (x-axis) between treatment and placebo shown from a societal perspective, that includes healthcare and productivity costs. The point-estimate (black circle and cross) indicate that less costs, but better effects (QALYs) were seen in the treatment arm. The bootstrapped results (10 000 replications, blue circles and orange crosses) show the uncertainty of the estimate, in every corner of the graphs the percentage of bootstrap iterations in that quadrant is indicated. For more explanation, see online supplemental figure S1. QALY, quality adjusted life-year.

during the TREAT EARLIER trial resulted in less costs, and a small improvement in quality of life. To our knowledge, this is the first study to assess the cost-effectiveness of a fixed-term treatment of people with arthralgia at-risk for RA.

The clinical report of the total patient population studied in the TREAT EARLIER trial showed no prevention of RA, but did demonstrate sustained improvements in subclinical joint inflammation, physical function, pain, morning stiffness of joints and work productivity due to treatment [9]. Importantly, these beneficial effects were obtained in both patients who progressed to RA as in patient who did not develop RA [9]. The outcomes relevant to cost-effectiveness analyses, that is, quality of life, healthcare usage and work productivity showed beneficial effects in line with those reported in the initial clinical report with 2 years follow-up [9]. Because of these improvements, and the affordability of the treatment, treatment with methotrexate was found to be cost-effective.

Total costs were predominantly determined by productivity losses. This has been previously described in established RA; in these patients, productivity costs represented ~70% of the total costs [17]. The fact that this is ~90% in patients with CSA might be due to the fact that patients were not diagnosed yet, and medical costs, that is, RA-related treatment costs, are therefore lower.

The average age of our population was 46 years. This indicates that the average patient is in the middle of his or her workable life, and most patients with CSA still have about 20 years of labour to contribute to society. The presence of symptoms or impairments that reduce productivity, therefore, has not only a great impact on the lives of individual persons, but also on society. Previously, it was shown that work productivity at RA diagnosis was the most important predictor of sick leave and disability pension over the course of 3 years [6]. From this, it may be presumed that when work productivity can already be improved in the at-risk phase of RA, this might exert its effect on the longer-term of those that develop RA. The current data on the cost-effectiveness of treatment in a risk stage of RA may fuel further studies aiming to achieve interception or prevention of developing RA, aiming to lower the impact of RA on society.

Discussions on secondary prevention also include the risk of overtreatment. The TREAT EARLIER trial showed that the beneficial effects of early treatment, that is, improvements in subclinical inflammation, symptoms and physical functioning, were not restricted to individuals who progressed to RA, but were also present in those who did not develop RA [9]. Treatment in these patients could even reduce joint inflammation and symptoms to almost normal levels, in contrast to the placebo group [9]. The effectiveness in both patients who did or who did not develop RA may contribute to the current finding of cost-effectiveness in the total trial population.

Despite the overall effect of an improvement in quality of life and less costs due to treatment, the question arises whether there are certain groups that will benefit more than others. Ideally, those who will benefit most from treatment should be targeted. Future studies are needed to be able to further narrow down the subgroups at risk, to arrive at stratified secondary prevention. Then cost-effectiveness analyses could be performed in the most relevant patient groups.

Generalisability of costs from the current study might be difficult, since every country has its own social security and healthcare system. In the Netherlands, the societal perspective is mandatory in cost-effectiveness analyses while in other countries the healthcare perspective is advocated. In the Netherlands, willingness to pay is considered to be €50 000 per QALY gained for RA, but this threshold differs across countries [18]. Cost-effectiveness was shown via different perspectives and different

levels of willingness to pay, indicating that the conclusions drawn are robust and probably also apply to other situations and healthcare systems.

Of note, costs for screening the patients before inclusion in the trial, including costs of MRI scans to assess subclinical joint inflammations, were not taken into account. This, however, should not have an influence on the cost-effectiveness outcomes for this trial as these were similar in treatment and placebo arms. Nonetheless, such costs might be worthwhile to include in other cost-effectiveness analyses in screening and/or real-world settings. A limitation is that there was no economic data collected after patients developed persistent clinically apparent inflammatory arthritis. Since patients with the endpoint probably had a higher burden of disease compared with those without the endpoint, and since the time to the endpoint was longer in the treatment arm compared with the placebo arm, there was more data collected on patients progressing to RA in the treatment arm. This could lead to an underestimation of the treatment effect. To overcome this, we designed upper and lower limit analyses in which we assumed for the upper limit analysis that patients developing clinical arthritis would remain in the study but kept the same level of all measurements throughout the remainder of the study (ie, last observation carried forward). In reality, those patients would receive antirheumatic treatment and their burden of disease would improve. We believe that by applying this approach, we have provided an underestimation (lower limit analysis) and an overestimation (upper limit analysis) of the true effect. Reflecting on the results, in all provided analyses we showed that treatment resulted in less costs and better QALYs, which emphasises the strength of our results.

Strengths of the current study include the randomised design which causes good internal validity. Also, validated outcome measures were used for calculations of QALYs and costs. Furthermore, questionnaires were collected every 4 months, and overall loss to follow-up was limited (<5%). Finally, the TREAT EARLIER trial is the first randomised controlled trial reporting on the cost utility of treatment with methotrexate in the at-risk phase of RA.

Future studies should focus on the longer-term outcomes of the initiation of methotrexate in the arthralgia phase at risk for RA. The current study had a 2-year follow-up period that started at the at-risk stage of arthralgia. Second, since the pathophysiology of ACPA-positive RA and ACPA-negative RA is different, future research could evaluate differences in cost-effectiveness in ACPA-positive and ACPA-negative at-risk states. Such future analyses should also address the heterogeneity in risk for RA that is present in the patient population of the TREAT EARLIER trial, and in the ACPA-negative risk group in particular. Lastly, since RA is a chronic disease for which part of the patients require expensive biologicals, future cost-effectiveness analyses should also consider a lifetime horizon. This requires health economic modelling to extrapolate short-term trial-based data.

In conclusion, we showed that treatment of people with arthralgia at-risk for RA and subclinical joint inflammation detected with MRI resulted in better work productivity, lower healthcare costs and improved quality of life. These data provide the first evidence that first-line treatment aiming at secondary prevention in arthralgia at-risk for RA is cost-effective.

Trial registration

EudraCT, 2014-004472-35, and the Netherlands Trial Register, NTR4853-trialNL4599.

X Elise van Mulligen @elisevmulligen

Acknowledgments

We thank all participating patients and rheumatologists for their invaluable contributions. This work has been previously presented at EULAR2024 congress [19].

Contributors

All authors made substantial contributions to the design of the work, acquisition of data or their interpretation. EvM and AvdH-vM had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Concept and design of the study: AvdH-vM and EvM. Acquisition, analysis or interpretation of data: All authors. Drafting of the manuscript: EvM. Critical revision of the manuscript for important intellectual content: All authors. Statistical analysis: EvM, SSB and LMAG. Obtained funding: AvdH-vM. Administrative, technical or material support: AvdH-vM, SSB and EvM. Supervision: AvdH-vM. EvM is the guarantor.

Funding

The TREAT EARLIER trial was funded by the Dutch Research Council (NWO) and the Dutch Arthritis Society. This work was funded by ZonMW, Efficiency grant number 10390012110002 and the Dutch Arthritis Society.

Competing interests

None declared.

Patient and public involvement

Patient partners were involved in the design of the TREAT EARLIER trial.

Patient consent for publication

Consent obtained directly from patient(s).

Ethics approval

Approval was received from ‘Commisie Medische Ethiek’ of the Leiden University Medical Centre (B19.008). Consent for publication was not applicable.

Data availability statement

Data are available upon reasonable request. The data are available upon reasonable request via the corresponding author.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1136/ard-2024-226286.

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