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EPIDEMIOLOGICAL SCIENCE

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ABSTRACT

Objective Early diagnosis and treatment-start is key for rheumatoid arthritis (RA), but the economic effect of an early versus a later diagnosis has never been investigated. We aimed to investigate whether early diagnosis of RA is associated with lower treatment-related costs compared with later diagnosis.

Methods Patients with RA consecutively included in the Leiden Early Arthritis Clinic between 2011 and 2017 were studied (n=431). Symptom duration was defined as the time between symptom onset and first presentation at the outpatient clinic; early treatment start was defined as symptom duration <12 weeks. Information on disease-modifying anti-rheumatic drug use per patient over 5 years was obtained from prescription data from patient records. Prices were used from 2022 and 2012 (proxy of time of prescription) to study the impact of changes in drug costs. Autoantibody-positive and autoantibody-negative RA were studied separately because differences in disease severity may influence costs.

Results Within autoantibody-negative RA, costs were 316% higher in the late compared with the early group (β=4.16 (95% CI 1.57 to 11.1); €4856 vs €1159). When using 2012 prices, results were similar. For autoantibody-positive RA, costs were 19% higher in the late group (€9418 vs €7934, β=1.19, 0.57 to 2.47). This effect was present but smaller when using 2012 prices. Within patients with autoantibody-positive RA using biologicals, late treatment start was associated with 46% higher costs (β=1.46 (0.91 to 2.33)); higher costs were also seen when using 2012 prices.

Conclusion When RA is detected within 12 weeks after symptom onset, treatment-related costs were lower in both autoantibody-negative and autoantibody-positive RA. This study is the first to report how early diagnosis and treatment start impact treatment-related costs.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Early diagnosis and subsequent treatment of rheumatoid arthritis (RA) is recommended because it prevents joint destruction and maintains functional capabilities and work productivity.
⇒ The economic effects of early versus later recognition of RA have not been studied yet.

WHAT THIS STUDY ADDS

⇒ Treatment-related costs and frequency of biological use were lower in both patients with autoantibody-negative and autoantibody-positive RA who had a symptom duration <12 weeks compared with those with a symptom duration >12 weeks.
⇒ Within autoantibody-positive RA, treatment initiation >12 weeks resulted in more intensive biological use with overall higher costs within the subgroup requiring biologicals.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Further cost-effectiveness studies are required to evaluate the cost-effectiveness of diagnostic interventions to promote early diagnosis of RA.

INTRODUCTION

Early detection and treatment of rheumatoid arthritis (RA) is a key European Alliance of Associations for Rheumatology (EULAR) and American College of Rheumatology recommendation to induce a milder disease course.[1 2] It has been shown that early detection and treatment (eg, <12 weeks after symptom onset) prevents joint destruction and helps maintain functional capabilities and increases the chances of sustained disease-modifying anti-rheumatic drug (DMARD)-free remission.[3–9] Patients with RA who were early treated were also more likely to stay in the workforce, thereby reducing productivity loss.[10 11]

Thus it is evident that early diagnosis and treatment increases the chance of a less severe burden of RA.[3] Resulting from that, one could expect that early detection and treatment also result in a reduction in the intensity and duration of treatment and a reduction in related treatment costs. Since currently, treatment-related costs are responsible for approximately 80% of all healthcare costs in RA, this indicates that the majority of the healthcare costs are taken into account when studying treatment-related costs.[12] Surprisingly, however, the economic effects of early recognition of RA in terms of treatment costs have not been studied. Consequently, the effects of early diagnosis and treatment on treatment-related costs are unknown. This data is relevant because if efforts are made to detect RA earlier, it is valuable to know how much is being saved. In this way, it can be determined how much additional healthcare costs can be made to promote early identification of RA in order for this strategy to be cost-effective. In light of the current rising healthcare costs, this is relevant for society to keep rheumatological care affordable.

This prompted us to investigate whether early identification and treatment of RA (within 12 weeks after symptom onset; as recommended by EULAR[13]) results in a reduction of treatment-related costs when compared with a patient group that was seen after 12 weeks of symptom onset. We aimed to study this separately in autoantibody-positive and autoantibody-negative RA, because it is known that the severity of the disease course is different.

We took advantage of a large inception cohort. Ideally, data from randomised controlled trials with a sufficiently long duration of follow-up would have been analysed for this study question, because observed differences can then be attributed to early (intervention) versus delayed (placebo) treatment. However, no such placebo-controlled trials with DMARDs in early RA exist. Large longitudinal observational cohort data are also valuable. Since early diagnosis is then probably not only related to time effects, but also to patients and disease-related factors, we made efforts to control for this confounding by applying inverse probability weighting.

METHODS

Study population

Patients were enrolled in the Leiden Early Arthritis Clinic (EAC), which is a population-based inception cohort consisting of patients presenting with recent onset arthritis with a symptom duration ≤2 years.[14] All consecutive patients with RA fulfilling the 1987 and/or 2010 criteria, and who started a DMARD, included between May 2011 (the time when electronic prescriptions became available) and December 2017 were evaluated. The latter end date allowed a 5-year follow-up period of patients. A detailed overview of patient selection can be found in online supplemental figure S1. Of note, the rheumatology outpatient clinic of the Leiden University Medical Center (LUMC) is the only referral centre in a healthcare region of >400 000 inhabitants and has made many efforts to reduce the referral time for patients with suspected arthritis. This includes continuous education and communication with general practitioners and with prioritised routes for early access of patients suspected of arthritis. The latter includes, among others, since 2011, the implementation of the early arthritis recognition clinic; which is a 1.5 lines screening clinic where in case of doubt, general practitioners can send patients for evaluation of the presence of inflammatory arthritis. This screening clinic has no waiting list and the introduction has increased the early identification of RA.[15–18] In addition, patients with a suspicion of arthritis or RA who are referred to the hospital outpatient clinic directly by the general practicioner (GP) and not via the 1.5 lines screening clinic were usually seen within 2 weeks at the outpatient clinic.

Immediately after entering the EAC, all patients were treated in routine care according to national and international treatment guidelines and, in the case of biologicals, according to local protocols with respect to biological choice.[13 19] Conventional synthetic (cs)DMARDs were promptly started after diagnosis, with methotrexate as the first choice. Treat-to-target treatment adjustments were made based on the Disease Activity Score (DAS). When patients failed on their initial treatment, another csDMARD was started or added. A biological was only allowed when patients with RA failed at least two csDMARDs. Within the LUMC, the policy is to evaluate every indication for biological start within a weekly meeting at the department in order to arrive at careful biological use. A tumour necrosis factor (TNF) inhibitor is the first choice biological; for the second biological the local preference was less strict but frequently concerned a second TNF inhibitor. This procedure may result in a lower frequency of biological use compared that in other settings or centres. All consecutively included patients with RA were studied except for patients who participated in a clinical trial or with missing information on symptom duration (online supplemental figure S1).

At baseline, when patients with RA entered the study, swollen and tender joint counts and laboratory procedures were performed for routine diagnostic laboratory screening, including: anti-citrullunated protein antibody (ACPA, EliA CPP (anti-cyclic citrullinated peptides (CCP) 2), Phadia, considered elevated if ≥7 U/mL), IgM rheumatoid factor (RF) (in-house ELISA, considered elevated if ≥3.5 IU/mL), C-reactive protein (CRP) (elevated if ≥10 mg/L) and erythrocyte sedimentation rate (ESR). Autoantibody-positivity was defined as an elevated ACPA titre and/or an elevated RF titre.

Definition of symptom duration

At baseline, patients were asked about the date their joint symptoms started. The symptom duration was defined as the time between this date and their first visit to the outpatient clinic in weeks. Thus, symptom duration includes both patient delay (ie, the time between symptom onset and the first visit to the general practitioner) and referral delay, which is the time between visiting the general practitioner and the rheumatologist.[20]

Based on the symptom duration, early treatment start was defined as within 12 weeks after symptom onset and late treatment start as later than 12 weeks after symptom onset. The 12-week period was chosen in line with EULAR guidelines.[1]

Outcomes

The main outcome was the total cost of DMARDs per patient within 5 years after the baseline visit, comparing patients who received early treatment to patients who received late treatment. To improve generalisability to other settings, within the first part of the results outcomes were not expressed in costs.

Information on DMARD use was obtained from prescription data from electronic patient records which were available for all included patients, indicating that we had no missingness in medication data. Of note, in the Netherlands, only rheumatologists can prescribe DMARDs and general practitioners are not allowed to start or repeat prescriptions of DMARDs. Moreover, the Department of Rheumatology of the LUMC is the only referral centre in our healthcare region. In case a patient deceased or when a patient was discharged because of DMARD-free remission (after 5 years~25% of patients), after that time point no medication prescriptions in the electronic medical files were recorded and costs were then zero. Prescriptions were valued using Dutch prices from 2022 to match the time of data extraction, and also using Dutch prices from 2012 as a proxy for the prices at the time of prescription (online supplemental table S1). When DMARDs were not yet on the market in 2012, the average percentual price difference of available DMARDs in 2012 and 2022 was estimated and applied to estimate a 2012 price (online supplemental table S1). Using 2012 prices was done to evaluate the impact of price changes over time that may result from loss of market exclusivity, launch of new medicines and price policies, which is especially relevant for biologicals.[21] Price levels and availability of DMARDs are dependent on time and country and may be considered difficult to generalise. Therefore, we also report intermediate outcomes that are less susceptible to differences in settings and regulations; these are the number and types of biologicals used since biologicals are the main cost

drivers in treatment-related costs. The number of biologicals used was indicated yearly, both the proportion of patients using a biological as well as the cumulative proportion. Janus kinase inhibitors were categorised as biologicals throughout this manuscript. In patients in DMARD-free remission, the treatment costs were zero.

To evaluate whether treat-to-target was achieved, the course of the DAS based on 44 joints over 5 years was studied.

Statistical analyses

Autoantibody-positive (defined as positivity for ACPA and/or RF) and autoantibody-negative RA were studied separately because of the known differences in severity of the disease course.[14] For the comparison of costs between early and late treatment groups, we corrected for baseline imbalances. This was done because of the observational nature of this study, and the concomitant risk of confounding by indication due to more severely ill patients being referred and treated earlier. Correction was performed by using inverse probability weighting based on propensity scores.[22 23] In this study, propensity scores were defined as the conditional probability of being in the early or late group given a set of observed baseline variables. This method is suited to balance between two (treatment) groups in observational studies.[24] To overcome the missingness of baseline variables for constructing propensity scores, multiple imputations with chained equations with 40 imputations, were used.[25] Details concerning the missingness of baseline variables are provided in online supplemental table S2 and were generally below 10%.

Variable selection was based on previous knowledge, combined with an assessment of baseline differences between the early and late groups. Since autoantibody-negative and autoantibody-positive RA were studied separately and also showed differences in baseline differences in variables, we calculated the propensity scores separately for these two groups. Furthermore, for a secondary analysis of patients that used biologicals, propensity scores were separately determined. We used the variables age, sex, body mass index, presence of morning stiffness, (sub)acute onset of disease, current smoking, swollen joint count, tender joint count, upper extremity involvement, small joint involvement, symmetrical problems at onset, ESR, CRP, DAS44, Visual Analogue Scale pain and Health Assessment Questionnaire. Stratified for autoantibody status, weighting was optimised. Assessment of the overlap of the distributions of the propensity scores (area of common support) showed 10 autoantibody-negative and 7 autoantibody-positive patients who did not have a probability of being in the early or late group and were therefore disregarded from further analyses (online supplemental figure S2).[24]

To assess whether the inverse probability weighting improved the comparability of the early and late treatment groups, three matching statistics were calculated: Rubin's B (the standardised difference of the means of the linear index of the propensity score in the early and late treatment group), Rubin's R (the ratio of early to late variances of the linear index of the propensity score) and the median absolute standardised bias (which is the median of the ratios of the difference of the sample means in the early and late groups over the square root of the average of the variances in both groups). In case groups are not balanced, additional corrections will be done based on the remaining differences in variables after weighting (double robust method).[23 26]

Differences in medication costs were analysed with generalised linear models using medication costs as the dependent variable, and the early or late group as the independent variable. We set the weights for each individual in the late group to 1 and for each individual in the early group to $p/(1-p)$, with p being the estimated probability that an individual is in the late group. In this way, we estimated the average reduction of costs in the late group when they would have been seen earlier (average treatment effect of the treated). The generalised linear model was used with a log link and gamma distribution to handle the skewed distribution of the cost data.[27]

The course of the disease activity over time was analysed using mixed effects logistic or linear mixed models, with DAS remission, DAS low disease activity or DAS44 as the dependent variable and time and early or late treatment as independent variables.

All data was analysed using Stata Software V.16 (StataCorp).

Patient and public involvement

Patients and the public were involved in the design of the Leiden EAC, and subsequently informed on study results and follow-up investigations.

RESULTS

Patient population

From the total population of 431 patients with RA, 165 patients were autoantibody-negative and 266 patients were autoantibody-positive. Median (IQR) symptom duration in autoantibody-positive RA was 5.6 (3.3–8.7) weeks in the early group, and 28.1 (18–53) weeks in the late group. In autoantibody-negative RA the symptom duration was 6.3 (4–8.4) weeks and 26.9 (17–50) weeks in the early and late group, respectively. At diagnosis, the early group had more severe inflammation and more issues (ie, higher DAS and components, more morning stiffness) compared with the late group (table 1) in both autoantibody-negative and autoantibody-positive RA.

After 5 years of follow-up, 24 patients died and 13 patients moved to another hospital; these patients were fairly equally distributed between ACPA-positive and ACPA-negative RA and early and late treatment groups (online supplemental table S3).

Course of disease activity

Despite a slightly higher DAS at baseline (when patients entered the study with arthritis) in the early groups, the percentages of patients having DAS remission or low disease activity over 5 years, were similar in the early and late groups (figure 1). This similar course of DAS was present in both autoantibody-positive as in autoantibody-negative RA, and also when studying DAS continuously (online supplemental figure S3). This shows that, over time, treat-to-target was achieved, irrespective of early or later treatment start or autoantibody status.

Biological use over time

Comparing the percentage of biological use per time point revealed that biological use increased gradually within autoantibody-negative RA after the first year. Within the early group, there was overall similar biological use in the early and late group. For autoantibody-positive RA, the proportion of patients using a biological showed a faster increase within the early group, which slightly decreased in year 4 (figure 2A). When comparing the cumulative percentages of biological use over time, a similar trend was seen that early groups needed less biologicals within autoantibody-negative RA and for autoantibody-positive RA the percentage increased faster within the early group (figure 2B).

These results of more biological use in the early group (especially within autoantibody-positive RA) together with the

Table 1 Baseline characteristics stratified for autoantibody status, indicated for early (<12 weeks after symptom onset) and later treatment start (>12 weeks after symptom onset)

	Autoantibody-positive RA		Autoantibody-negative RA	
	<12 weeks (n=121)	>12 weeks (n=145)	<12 weeks (n=83)	>12 weeks (n=82)
Age at inclusion, mean (SD)	60.7 (13)	56.5 (14)	63.0 (13)	60.3 (14)
Female sex, n (%)	76 (63)	93 (64)	57 (69)	54 (66)
BMI, mean (SD)	26.0 (4.9)	25.5 (3.8)	27.5 (5)	28.2 (6)
Symptom duration (weeks), median (IQR)	5.6 (3.3–8.7)	28.1 (18–53)	6.3 (4–8.4)	26.9 (17–50)
Morning stiffness >60 min, n (%)	59 (56)	58 (49)	48 (63)	37 (54)
(Sub)acute onset*, n (%)	72 (64)	32 (24)	38 (51)	14 (18)
Smoking (current), n (%)	31 (27)	44 (31)	15 (19)	11 (14)
Upper extremity involvement, n (%)	92 (85)	116 (85)	68 (87)	70 (90)
Small joint involvement, n (%)	96 (83)	124 (88)	73 (88)	71 (89)
Start symptoms symmetrical, n (%)	75 (69)	96 (71)	62 (79)	57 (73)
Swollen joint count (68-joints), median (IQR)	6 (2–11)	4 (2–8)	9 (4–12)	5 (2–12)
Tender joint count (71-joints), median (IQR)	7 (3–13)	7 (3–11)	9 (5–15)	12 (6–18)
ESR, median (IQR)	34 (19–50)	28 (14–38)	33.1 (17-46)	17 (6–38)
CRP, median (IQR)	11.2 (4.6–28)	8.3 (3–21)	15.4 (7.4–41)	5.4 (3–23.6)
DAS44, mean (SD)	2.96 (0.89)	2.70 (0.79)	3.21 (0.75)	3.02 (0.94)
Patient global assessment, mean (SD)	44 (27)	43 (24)	48 (24)	50 (25)
VAS pain, mean (SD)	58 (24)	55 (27)	65 (24)	64 (21)
HAQ-DI, mean (SD)	1.03 (0.7)	0.93 (0.7)	1.21 (0.6)	1.00 (0.6)

*Compared with gradual or intermittent onset of symptoms.
BMI, body mass index; CRP, C-reactive protein; DAS44, Disease Activity Score with 44 joints; ESR, erythrocyte sedimentation rate; HAQ-DI, Health Assessment Questionnaire Disability Index; RA, rheumatoid arthritis; RF, rheumatoid factor; VAS, Visual Analogue Scale.

differences in baseline characteristics between the early and late group suggest that patients with RA who came early, had more inflammation and also required biologicals more often during their treat-to-target treatment. Thus this suggests that patients with RA who came early were different from those that came later.

Types of biologicals used

Comparing autoantibody-positive and autoantibody-negative RA during follow-up revealed that more patients in the autoantibody-positive group used biologicals (n=43, 16%) than patients in the autoantibody-negative group (n=10, 6%). On a group level, also a broader variety of biologicals was used (n=16 vs n=7, p=0.002) (figure 3). Within the patients with autoantibody-negative RA that used at least one biological, the

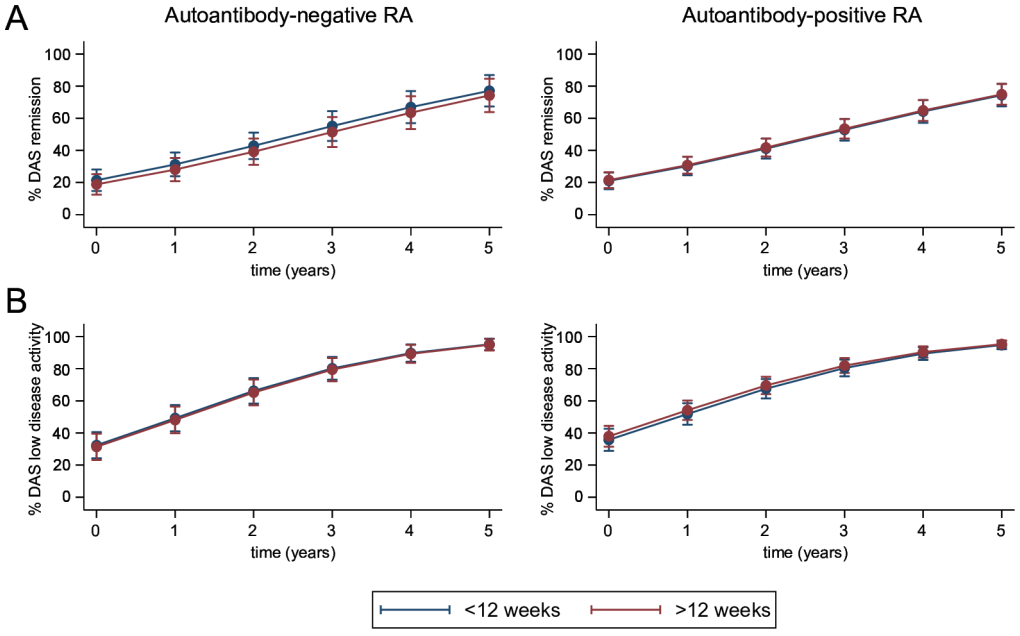

Figure 1 Percentages of (A) remission (DAS44<1.6) and (B) low disease activity (DAS44<2.4) indicated over time for early treatment start (within 12 weeks) and late treatment start (>12 weeks), separately for autoantibody-negative RA and autoantibody-positive RA. Raw data is shown without inverse probability weighting. DAS44, Disease Activity Score based on 44 joints; RA, rheumatoid arthritis.

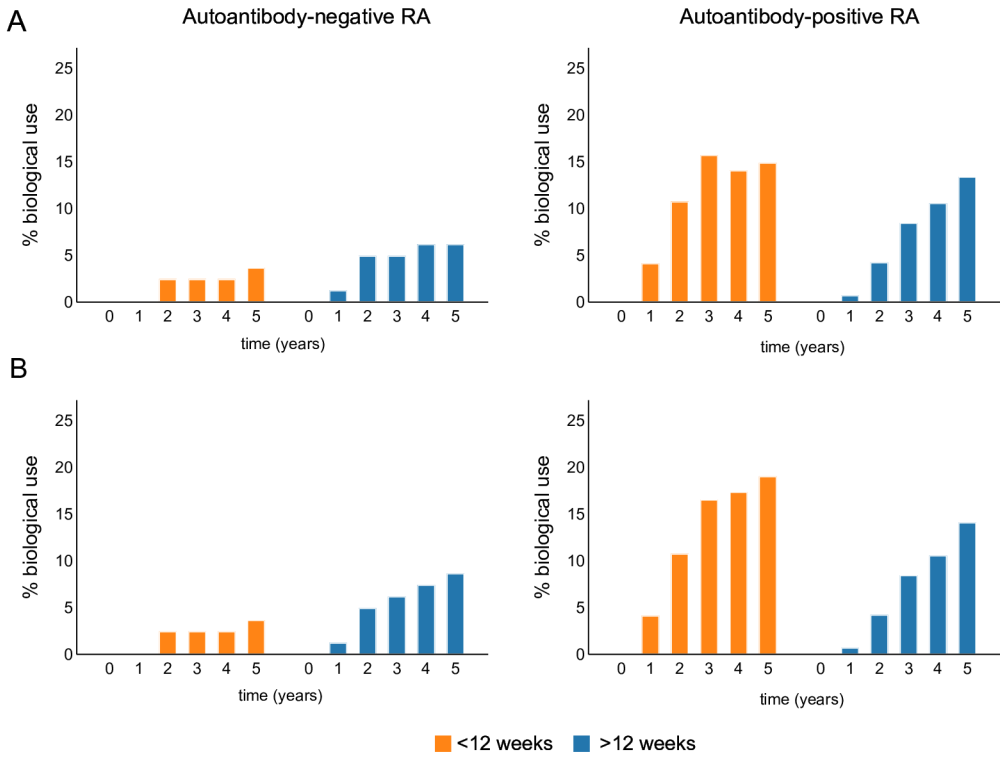

Figure 2 Biological use over time indicated for autoantibody-negative RA (left), and autoantibody-positive RA (right). (A) Percentage of patients using biologicals, indicated per year, for early (<12 weeks) and later (>12 weeks) treatment start. (B) Cumulative percentage of biological use, indicated per year, for early (<12 weeks) and later (>12 weeks) treatment start. Raw data is shown without inverse probability weighting. RA, rheumatoid arthritis.

average number of biologicals used per patient was 1.0 in the early group and 1.3 in the late group. In total, three different types of biologicals were used among all patients in the early group versus four in the late group (figure 3). Within the patients with autoantibody-positive RA that used biologicals, the average number of biologicals used per patient was 1.8 in both the early and late groups. Also, the number of different types of biologicals used was the same within the early and late group (both n=8) (figure 3).

Cost of DMARD treatment

First, prescriptions were valued using 2022 price levels (online supplemental table S1).[21 28] Mean (standard deviation (SD)) total costs of treatment over 5 years for autoantibody-negative RA were €3822 (SD €12 475). When 2012 prices were used, costs were in general higher because the biologicals were more expensive: €5540 (SD €19 023). The main driver of the prices was the biological costs, which accounted for an average of €2352 (61%). The average total treatment costs among biological users was €43 320 (SD €27 672) within this group. The other part comprised of costs of csDMARDs and glucocorticoids. The average treatment cost for patients who never used a biological was €1274 (SD €3625). Hospitalisation costs for intravenous admission of treatment were included in the mentioned treatment costs and comprised~7% of the total treatment-related costs.

For patients with autoantibody-positive RA, the average total cost of treatment over 5 years was €9077 (SD €23 024) using 2022 prices and €12 654 (SD €29 701) when 2012 prices were used. Of the €9077, €6825 (75%) was due to biological costs. Within this group, average total treatment costs were €45 219 (SD €38 572) for biological users only. The average total treatment costs for patients who never used a biological was €1881 (SD €5665).

Together these data show that treatment-related costs are higher for autoantibody-positive RA than autoantibody-negative RA and that within both sets of RA a small group of patients, those using biological, are responsible for the majority of treatment-related costs.

Treatment costs: early versus late treatment start

We then continued with comparing treatment costs of patients with early and late treatment start, within autoantibody-negative and autoantibody positive RA separately. As we have seen that the early and late groups were different at diagnoses and over time, we addressed confounding by indication using inverse probability weighting without and with applying a double robust method (for details see online supplemental table S4,S5).[23]

Within autoantibody-negative RA, costs were €4856 in the late group compared with €1159 in the early group over 5 years, with a β=4.16 (95% CI 1.57 to 11.1), indicating 316% higher costs in the late group (figure 4). With the double robust method, the difference was larger (β=4.36, 95% CI 1.92 to 9.87, indicating 336% higher costs in the late group). Comparing late and early groups using 2012 prices provided a smaller difference (β=3.60, 95% CI 1.32 to 9.79), indicating 260% higher costs in the late group (figure 4). Using the double robust method, the costs were estimated to be 298% higher (β=3.98, 95% CI 1.71 to 9.24).

For patients with autoantibody-positive RA, costs were €9418 in the late group and €7934 in the early group (β=1.19, 95% CI 0.57 to 2.47, indicating 19% more costs in the late group) (figure 4). With the double robust method, there were 35% more costs in the late group (β=1.35, 95% CI 0.63 to 2.90). This was also observed when using 2012 prices (β=1.08, 95%

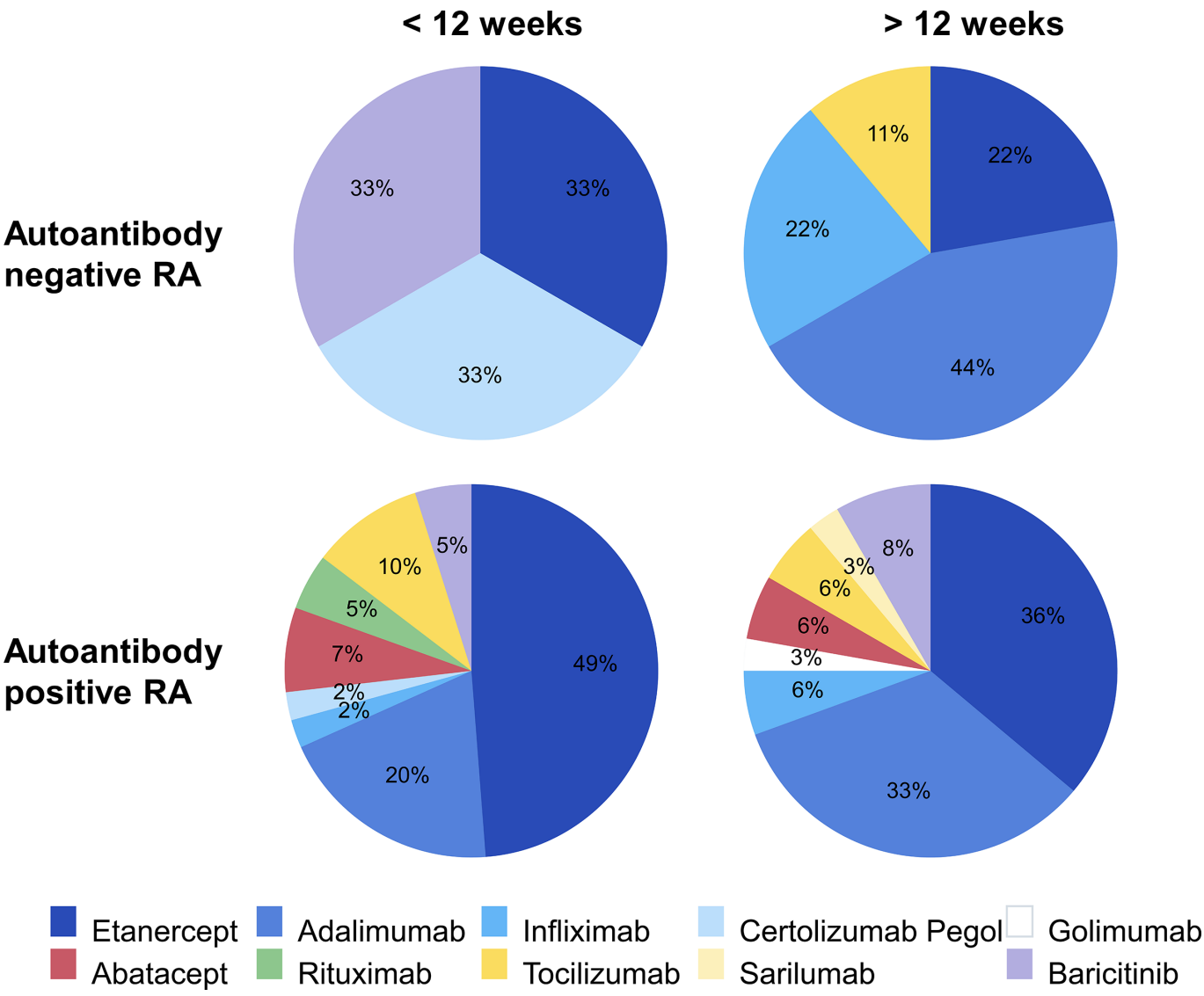

Figure 3 Types of biologicals prescribed to patients over the course of 5 years, indicated for autoantibody-negative and autoantibody-positive RA, and for early (<12 weeks after symptom onset) and later treatment start (>12 weeks after symptom onset) separately. Raw data is shown without inverse probability weighting. RA, rheumatoid arthritis.

CI 0.54 to 2.18) (figure 4). Using the double robust method the difference was 14% (β=1.14, 95% CI 0.54 to 2.40).

Treatment-related costs over time showed that differences between early and late groups occurred already within the first year in autoantibody-negative disease, while in autoantibody-positive disease the difference occurred later (figure 5).

When only patients were studied who used a biological, the difference between early and late became much larger: €17 184 with a corresponding β of 1.46 (95% CI 0.91 to 2.33), indicating 46% higher costs in the late group. Using 2012 prices resulted in a difference of €17 865, with a β of 1.33 (95% CI 0.85 to 2.07), which indicates 33% higher costs in the late group (figure 6, online supplemental table S6). This latter analysis was exploratory, and could not be done for autoantibody-negative RA, due to a low number of autoantibody-negative patients using biologicals.

DISCUSSION

Although early treatment is generally recommended, evaluations of the effects of early treatment on costs are surprisingly absent. This study is the first to investigate the effect of an early diagnosis and early initiation of treatment on treatment-related costs in autoantibody-positive and autoantibody-negative RA. Both in autoantibody-negative RA, patients that were treated early (within 12 weeks after symptom onset) had less treatment-related costs. Relatively seen, the difference between early and late treatment was the largest within autoantibody-negative RA, though the absolute differences were comparable in autoantibody-negative and autoantibody-positive RA. When focusing on biological users among the autoantibody-positive patients, there was a larger absolute difference in treatment costs between early and later detected RA. Overall, the effect of early start of treatment seems to have an impact on reducing treatment-related costs in both autoantibody-positive and autoantibody-negative RA.

The finding that treatment-related costs of autoantibody-positive RA were higher compared with autoantibody-negative RA, confirms previous research on the economic burden of ACPA positive and negative RA.[29] This finding can be explained by the observation that less biologicals were needed within a treat-to-target strategy compared with autoantibody-positive RA. This is in line with the general knowledge that autoantibody-negative

Figure 4 Treatment-related costs for autoantibody-negative (left) and autoantibody-positive RA (right), comparing early (<12 weeks after symptom onset) with later diagnosis (>12 weeks after symptom onset). The cost of treatment was based on (A) 2022 prices, or (B) 2012 prices. Prices that were used for the calculation of medication costs are listed in online supplemental table S1. Data is shown with inverse probability weighting. Error bars indicate SEM. RA, rheumatoid arthritis.

RA is the less severe phenotype compared with autoantibody-positive RA.

We observed that in autoantibody-negative RA, later detection and subsequent treatment resulted in more biological use and more treatment-related costs, indicating that the treatment burden is higher due to the later treatment start. The fact that seeing autoantibody-negative patients earlier could possibly lead to reduced treatment-related costs, is an important incentive to promote early identification of autoantibody-negative RA.

Previous studies showed that though autoantibody-positive RA traditionally had more structural joint damage and subsequently suffered from greater disability compared with autoantibody-negative RA, the disease burden has become equally severe for both RA subtypes, considering the current

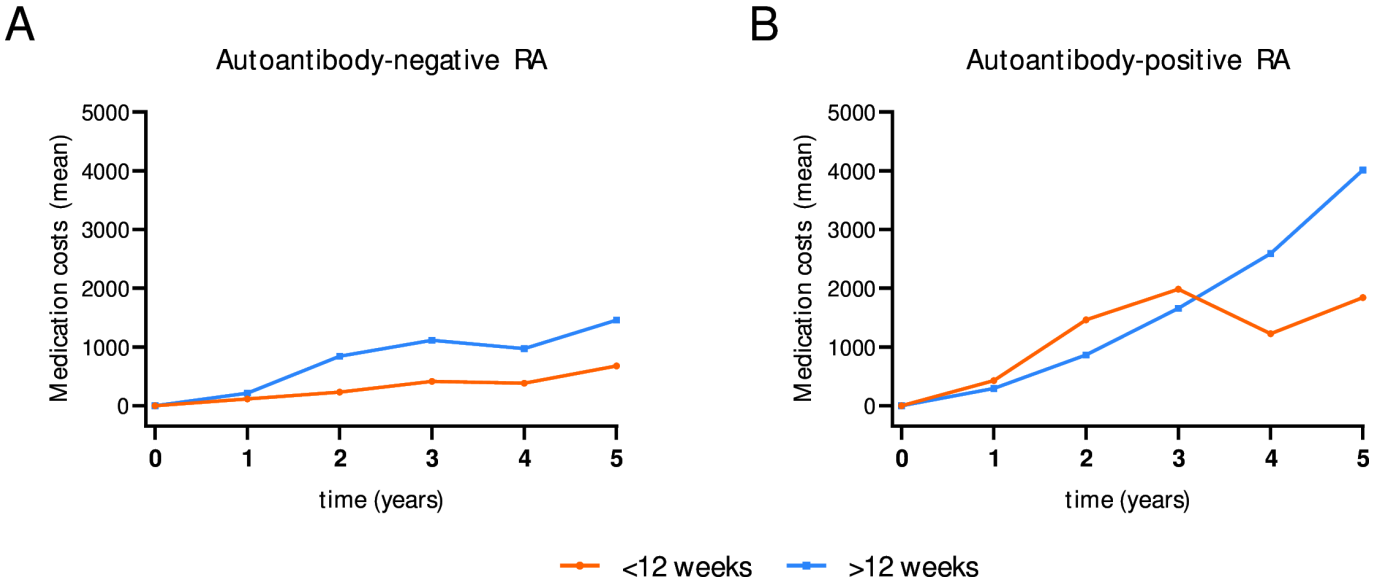

Figure 5 Treatment-related costs over time for (A) autoantibody-negative and (B) autoantibody-positive RA (right), comparing early (<12 weeks after symptom onset) with later diagnosis (>12 weeks after symptom onset) indicated for each year. The cost of treatment was based on 2022 prices. Treatment-related costs shown are weighted but not modelled to illustrate where the difference between groups occurs over time. Prices that were used for the calculation of medication costs are listed in online supplemental table S1. RA, rheumatoid arthritis.

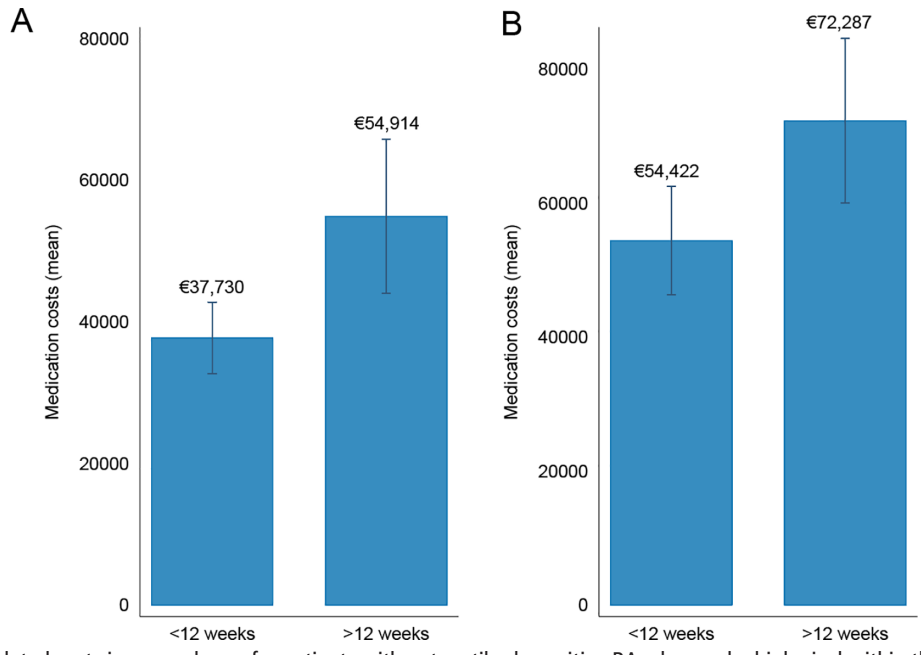

Figure 6 Treatment-related costs in euros shown for patients with autoantibody-positive RA who used a biological within the 5 years of follow-up, comparing early (<12 weeks after symptom onset) with later referral (>12 weeks after symptom onset). (A) Treatment-related costs based on 2022 prices, and (B) treatment-related costs based on 2012 prices. Prices that were used for the calculation of medication costs are listed in online supplemental table S1. Data is shown with inverse probability weighting. Error bars indicate SEM. RA, rheumatoid arthritis.

treat-to-target strategies.[30] However, this means that in order to achieve the target, more intensive treatment is needed within autoantibody-positive RA. Underlining this, patients with autoantibody-positive RA in this study more often needed a biological, resulting in higher treatment-related costs. Interestingly, within our study, we noticed differences in the need for treatment within autoantibody-positive RA. This suggests that, although autoantibody-negative RA is sometimes considered to be heterogeneous in nature, also autoantibody-positive RA is heterogeneous in nature; also here the early group differed from the remaining autoantibody-positive group. Nonetheless, the overall relative difference between the early and late groups in treatment-related costs for patients with autoantibody-positive RA seemed to be lower than in autoantibody-negative RA, still cost savings were seen. Independent of the treatment-related costs, we know that early detection is beneficial for improving long-term outcomes for autoantibody-positive RA, which emphasises the importance of early detection and subsequent treatment for other reasons than treatment-related costs.[14]

Among the patients with autoantibody-positive RA who required biological, treatment-related costs were higher within the patients with a longer symptom duration at treatment start. Despite the fact that on a group level early detection of autoantibody-positive RA did not reduce the frequency of starting of biologicals, it might be beneficial in reducing biological cycling and switching. This possibly explains the observed difference between the early and late groups in the biological users group.

Data used for this study have been collected within a particular setting, namely within the LUMC where early referral has been optimised both at the level of educating general practitioners and at the level of providing early access for patients suspected of arthritis and minimising 'rheumatologists delay' in access. Overall, 50% of patients were diagnosed within 12 weeks after symptom start, which is quite unique compared with other settings, as other inflammatory arthritis cohorts showed lower frequencies, for example, in ESPOIR~22% of patients had a symptom duration <12 weeks at first visit.[8] Because of this optimisation in early recognition, the symptom duration in our delayed group is therefore presumably shorter than that in other centres in patients with symptom onset for >12 weeks. This early recognition contributed to a relatively low number of inflamed joints at diagnosis and a relatively low prescription of biologics. For these reasons, the differences between early and late treatment as observed here could be underestimated compared with settings where early referral was less optimised. This implies that when this study was performed in a more general rheumatology outpatient clinic an even larger benefit of early diagnosis could have been observed. Another important effect of optimisation of early recognition is that most likely the amount of prescribed biologicals was lower in our setting compared with others, which is seen in the overall low percentage of patients using a biological.

This study focused on treatment-related costs (costs of drugs). These costs are only part of total healthcare costs, in which also costs from comorbidities or disease-related hospitalisation play a role. Nonetheless, of all healthcare costs, within RA 80% is due to treatment.[12] However, the total economic burden of RA consists, besides healthcare costs, also of costs due to work productivity losses which actually is the main cost component. These productivity losses have an even higher impact on society, since these costs are for RA high: up to 80% of the total economic burden is due to productivity losses.[12] Therefore, by not incorporating costs due to work productivity losses most likely the full economic impact of RA is underestimated.[12] Furthermore, it was also shown that in patients with newly diagnosed ACPA-positive RA the economic burden was driven mainly by treatment-related cost, which indicates that our approach covered at least the most relevant direct costs for early RA.[31] Costs of productivity losses were not taken into account, previous research showed that work impairments are as severe for ACPA-positive as for ACPA-negative RA.[30] The effect of an early diagnosis on work-related

outcomes and costs could be a topic for further research. Also, subsequent cost-effectiveness analysis could combine all these outcomes and investigate the effect of early diagnosis and treatment from a societal perspective, also using a longer time horizon.

This study has limitations. First, the division of symptom duration in early (<12 weeks) and late (>12 weeks) may be arbitrary. The EULAR guidelines for early arthritis even advise a cut-off of 6 weeks, though for this study we chose to use 12 weeks, since achieving treatment start within 6 weeks after symptom onset is often not feasible.[1]

Second, we did our utmost best to correct for possible confounding by applying inverse probability weighting, and even added double robust analyses in which we corrected for the variables that were not similar after weighting in the groups. However, this approach is always inferior to a randomised controlled trial (RCT) for early versus late treatment. Despite our efforts to minimise confounding, we noticed that although baseline characteristics became more similar they still showed differences in, for example, inflammatory markers (ESR, CRP) and acute onset for both autoantibody-positive and autoantibody-negative RA. Especially within autoantibody-positive RA, there seemed to be a subgroup that was seen early, had more inflamed joints at diagnosis, and was escalated quickly to a biological, which is the major driver of the treatment-related costs. Hence, we cannot exclude that there was still residual (unmeasured) confounding that may have diluted the effect of early treatment start.

Medication data in this study was derived from electronic patient files. A strength of this is that these data were quite complete. However, there were also 37 patients lost to follow-up because of death or moving. This could induce attrition bias,[32] especially when these patients are not equally distributed among the groups. Fortunately, however, the percentage of patients lost to follow-up in the early and late groups were almost similar (online supplemental table S3), which makes relevant attrition bias less likely.

Cost data is subjective to differences in healthcare systems between countries and differences over time. We included price levels from 2022 for prices at the time of data extraction, and from 2012 as a proxy for at the time of prescription to overcome this time-effect. The Dutch prices and setting might not be comparable to all countries. Therefore, within the first part of the results outcomes were not expressed in costs to improve generalisability of results to other settings. For instance, we presented the percentage of patients using biologicals, which is not related to price differences between countries.

In conclusion, this is the first study showing the effect of early diagnosis and treatment on treatment-related costs. When RA is detected within 12 weeks after symptom onset, treatment-related costs seem to be lower.

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Patient consent for publication Not applicable.

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