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DAS28 at 3 months after diagnosis of early rheumatoid arthritis is strongly associated with direct and indirect costs over the following 4 years. The Swedish TIRA project.

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Short title
DAS28 \geq 3.2 is associated with high costs over 4 years

Abstract

Objective: to explore possible association between disease activity at 3-month follow-up after rheumatoid arthritis (RA) diagnosis and costs over following 4 years.

Methods: 320 patients with early (≤ 1 year) RA were assessed at regular intervals. Clinical and laboratory data were collected and patients reported health care utilisation and number of days lost from work. At 3-month follow-up, patients were divided into 2 groups according to disease activity, using DAS28 with a cut-off level at 3.2. Direct and indirect costs and EQ-5D over following 4 years were compared between the groups. Multivariate regression models were used to control for possible covariates.

Results: A DAS28 level of ≥ 3.2 , 3 months after diagnosis was associated with high direct and indirect costs over following 4 years. Patients with $\text{DAS28} \geq 3.2$ at 3-month follow-up had more visits to physician, physiotherapist, occupational therapist and nurse, higher drug costs, more days in hospital and more extensive surgery compared to patients with 3-month $\text{DAS28} < 3.2$. Number of days lost from work due to sick-leave and permanent work disability was also higher in this group. The effect of disease activity on health-related quality-of-life was highly significant. In regression models, DAS28 at 3-month follow-up was significantly associated with costs over the following years.

Conclusions: DAS28 3 months after diagnosis is an important prognostic marker regarding healthcare utilisation and costs. Achieving remission or low disease activity 3 months after diagnosis is likely to decrease morbidity, increase quality of life and save costs for the patient and for the society over the following years.

Introduction

Rheumatoid arthritis (RA) is a chronic progressive disease associated with tissue destruction and functional disability [1]. The economic consequences are substantial for the patients, their families and for the society [2,3]. The utilisation of health care resources and the number of days lost from work increase dramatically already during the first year of disease [4,5]. A number of studies have shown that costs increase with deteriorating functional ability [6-10]. It has also been shown that disease activity is associated with functional capacity and that disease activity is the most important determinant of loss of function [11-14]. Disease severity has also been associated with costs, mainly for sick leave and permanent work disability [6,15,16]. Work disability occurs early in the disease and represents major costs. Indirect costs have typically been 2-3 times higher than direct costs. In a recent Swedish study, 30% of patients below 65 years of age had become permanently work disabled within 3 years after diagnosis [17]. The introduction of biological agents has substantially increased total costs and direct costs are now predominantly driven by drug costs [7]. From the Swedish TIRA cohort we previously reported that average disease activity in patients with early RA was significantly improved 3 months after diagnosis and thereafter remained rather unchanged over the following years. There was a significant association between DAS28 at the 3 month follow-up and DAS28 values over the following 3 years for men and for women and for all age groups. DAS28 was also associated with functional capacity over the following years [17]. The present study was done to explore a possible association between disease activity as measured by DAS28 at the 3-month follow-up after diagnosis and costs over the following 4 years.

Patients and methods

Patients

All patients participated in a prospective cohort of early (≤ 12 months after arthritis onset) RA, i.e. 'the Swedish TIRA' study [18]. TIRA is the Swedish acronym for 'early intervention in rheumatoid arthritis', where the involvement of physiotherapists, occupational therapists and nurses are considered in addition to the interventions administered by physicians. From January 1996 through April 1998, 320 patients were enrolled from 10 rheumatology units in southeast Sweden corresponding to a catchment area of 1 million inhabitants. To be included, the patients should fulfil at least 4 of 7 criteria according to the 1987 revised ACR criteria (19) or had suffered from morning stiffness (60 minutes or more as judged by the patients), symmetrical joint affection and arthritis in small joints (fingers/toes). Ninety-five per cent of the patients fulfilled the 1987 ACR criteria. The patients were assessed at inclusion, after 3, 6, 12, 18 and 24 months, and then annually.

Clinical assessments

Clinical and laboratory data were collected at all visits. Details of the study have been described previously [5]. Briefly, tender and swollen joint counts were registered by the physician on a 28-joint score, erythrocyte sedimentation rate (ESR) was analysed and the patient's global assessment of disease activity was estimated on a 100-mm visual analogue scale (VAS) and the 28-joint count disease activity score (DAS28) was calculated (20). Serum levels of C-reactive protein (CRP) were analysed as well as isotype-specific (IgM and IgA) rheumatoid factors (RF) and antibodies to cyclic citrullinated peptide (anti-CCP, 2nd generation CCP2 test from EuroDiagnostica, Arnhem, NL). Patients reported pain on a 100-mm visual analogue scale and completed the Swedish version of the Stanford Health Assessment Questionnaire (HAQ) [21].

Medication

Ongoing, instituted, and withdrawn medication with disease modifying anti-rheumatic drugs (DMARDs), non-steroidal anti-inflammatory drugs (NSAIDs), corticosteroids, and analgesics

were registered at all visits. Drug treatment decisions were made by the physician's preference.

Health care questionnaire

Demographic and socio-economic data, including age, sex, marital status, educational level and employment status were collected at study start. Educational level was rated as low, having primary school level, medium with secondary school level and high with college or university level. During the first 2 years, patients received questionnaires every 6 months and reported all health care utilisation and days lost from work over the following 6 months. Over the following years, patients received questionnaires once a year. The questionnaires were kept as diaries and patients reported prospectively all visits to health professionals as well as admissions to hospital, surgical procedures, and dosage and frequency of all prescribed drugs as well as drugs bought over the counter. In case complementary medicine was used, this was also reported. A distinction was made between disease-specific and non-disease-related resource use and analyses were limited to care for treatment of the arthritis. Number of days with sick-leave or days with disability benefits during the period was reported and they were recalculated to equal full-time days. In each questionnaire, patients also completed the health related quality-of-life instrument EuroQol-5D (EQ-5D). EQ-5D is a self-administered instrument with five questions covering five different domains; mobility, self-care, usual activities, pain/discomfort and anxiety/depression with 3 levels of answers, no problems, some problems or severe problems. The EQ-5D score is defined as the preference of patients for a given state of health and expressed as a utility value between 0 which is equal to death and 1 which is equal to full health [22].

Direct costs

Costs were rated using tariffs from the Swedish Federation of County Councils and the unit cost for outpatient visit to physician was SEK 2 100 (€227) and outpatient visit to physiotherapist, occupational therapist or nurse was SEK 700 (€76) [23]. Costs for surgery, including total costs for surgical interventions and a standardised number of hospital days were calculated according to the NordDRG system [24]. The cost for total joint replacement of hip or knee was SEK 76 862 (€8 309), foot surgery SEK 33 151 (€3 584), major hand/elbow surgery SEK 19 141 (€2 069) and minor hand surgery SEK 12 365 (€1 337). Additional hospitalisation, besides standard care, was calculated as additional days, estimating a day in hospital to 2 800 SEK (€ 302 or \$ 269). For comparison with previous data, costs are expressed in 2001 Euro. The annual average currency 2001 was SEK 10 = € 1.08 = \$ 0.96.

Indirect costs

Indirect costs were calculated, using the human capital approach, estimating the value of lost production during the entire period of work absenteeism, assuming full productivity. Loss of productivity also comprises the value of lost production due to premature death caused by the disease. This has not been taken into account in the present study. The cost applied to 1 day was SEK 1 000 (€ 108 or \$ 96) and was estimated similarly for sick-leave and for early retirement. It was calculated using the average of the gross income of all gainfully employed Swedish full-time workers, corresponding to SEK 30 000 (including taxes and other fees) (€ 3 243 or \$ 2 886) [25]. Loss of productivity was calculated using the number of days with sick-leave or disability benefits (including non-working days), as reported by the patients. For patients working part time, sick leave days were recalculated to equal full time days. The same was done if a full time employee was on sick leave part time of the day. A societal perspective was applied calculating costs regardless payer.

Ethics considerations

All patients gave written informed consent to participate. The study protocol was approved by the regional ethics committee in Linköping.

Statistics

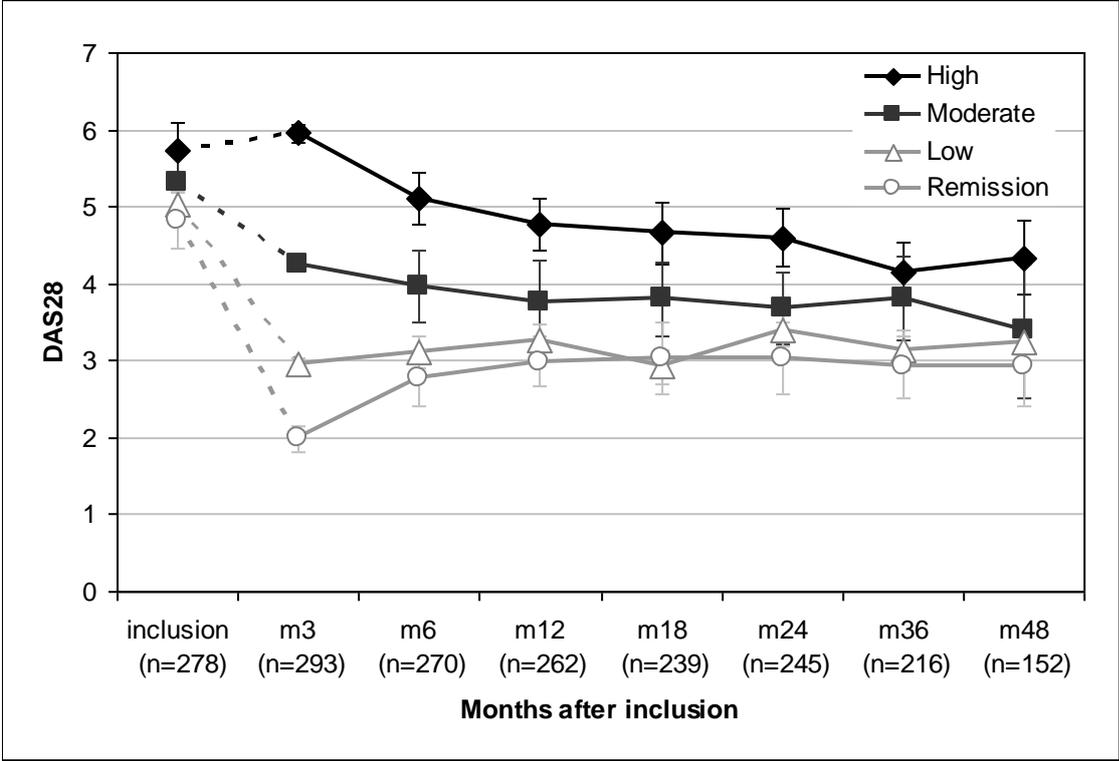
Data are presented as mean with standard deviation (SD) and with 95% confidence interval (95% CI) and as median with interquartile range (IQR) or proportions. Comparisons were made by Student's t-test or Mann-Whitney U-test for continuous data and Chi-square tests or Fisher's exact test for categorical data. The patients were divided into 4 groups according to treatment response at the 3-month follow-up using DAS28 levels, remission, low, moderate and high disease activity, and then into 2 groups using DAS28 with a cut-off level at 3.2. Direct and indirect costs were compared between the 2 groups over the following 4 years. Linear regression models with direct and indirect costs as dependent variables were performed, controlling for possible confounding effects of age and gender. Analyses were also performed with log-transformed data. Only complete observations were used, no missing values were replaced in the analyses. The level of significance was set at 0.05. All analyses were performed using PASW 18.0 (SPSS Inc., Chicago, Ill, USA).

Results

Two rheumatology units left the study after the 3 year follow-up, leaving 8 units, with 257 patients at baseline, still participating in the study. At the 4 year follow up, 195 patients were still in the study. Sixty-two patients had been lost to follow up; 15 died, 9 moved from the area, 9 patients had become well and did not want to participate further and 29 patients declined further participation for various reasons such as "too many tests", "difficulties with transportation to the hospital" etc. The dropouts were older compared to the study group (65 vs 54 years at inclusion) but their average level of anti-CCP antibodies was significantly lower compared to patients in the study group (246 U/L vs 435 U/L). Of the remaining 195 patients at 4 year follow up, complete health economic data were available in 118 patients (61%). There were no differences in clinical or demographic data between patients with health economic data (n=118) and patients with missing data (n=77).

At inclusion, the patients had active arthritis with an average DAS28 of 5.3. At the 3-month follow-up, significant improvements were seen regarding all clinical and laboratory data, but a majority of patients still had a DAS28 level above 3.2. The patients were divided into 4 groups according to the DAS28 level at the 3-month follow up. A DAS28 level <2.6 corresponds to remission, 2.6-3.1 to low disease activity, 3.2-5.1 to moderate disease activity and DAS28 ≥5.1 corresponds to high disease activity. Figure 1 shows the average DAS-scores for these groups at inclusion and at follow up during the first 4 years. There was no significant difference between the 4 groups at baseline, demonstrating that the subgroups formed at month 3 were not established already from the beginning and in addition, there was a "carry on" effect with the DAS28-scores over time. Patients with good response at month 3 had lower average DAS28-scores over the following years and the average scores the 2 lower groups followed each other quite closely (Figure 1).

Fig. 1 Patients divided into 4 groups according to the DAS28 level at the 3-month follow-up and their respective DAS28 levels at inclusion and at follow ups over 4 years.



Patients in remission and patients with low disease activity at month 3 were grouped together and constituted a group with a DAS28-score <3.2 and patients with moderate and high disease activity at month 3 constituted a group with a DAS28-score ≥3.2. Demographic and clinical data for patients with DAS28<3.2 and DAS28≥3.2 at 3-month follow-up are shown in table 1.

Table 1 Characteristics for patients with DAS28<3.2 and DAS28≥3.2 at 3-month follow-up, mean (SD) or n (%).

	DAS28<3.2 at month 3 n=86	DAS28≥3.2 at month 3 n=207	p-value
age	53 (16)	58 (14)	0.015
women n (%)	53 (62%)	144 (69%)	0.255
education >12 yrs n (%)	36 (46%)	56 (29%)	0.007
living with partner n (%)	64 (80%)	143 (72%)	0.178
swollen joints (0-28)	1.9 (2.5)	6.1 (5.2)	<0.001
tender joints (0-28)	0.9 (1.6)	6.3 (5.4)	<0.001
ESR (mm/h)	11 (7)	31 (21)	<0.001
global VAS (0-100)	19 (15)	43 (24)	<0.001
DAS28 (0-10)	2.3 (0.6)	4.7 (1.0)	<0.001
CRP (mg/l)	8 (9)	20 (23)	<0.001
pain VAS (0-100)	21 (17)	43 (23)	<0.001
IgM-RF+ n (%)	49 (73%)	127 (74%)	0.858
IgA-RF+ n (%)	48 (71%)	125 (72%)	0.796
anti-CCP+ n (%)	42 (66%)	100 (63%)	0.701

IgM-RF, IgA-RF and anti-CCP are baseline data and were available in 260, 263 and 242 patients.

Patients in the high DAS-group were older and they also had a significantly lower level of education. There was a difference between the 2 groups concerning DAS28 and all the components constituting the DAS28 score, with significantly higher levels in high DAS group. HAQ was assessed only once a year and thus no HAQ-data were available at 3-month follow-up. IgM-RF, IgA-RF and anti-CCP were available in 260, 263 and 242 patients respectively, and did not differ between DAS28<3.2 group and DAS28≥3.2 group.

There was no difference in DMARD prescription between the 2 groups from time point of inclusion and month 3. DMARDs were prescribed according to the preference of the physician and 72% of all patients received DMARDs during the first 3 months. In the DAS28 <3.2 group, 69% of the patients were prescribed DMARDs compared to 73 % of patients in the DAS28 ≥3.2 group (ns).

Direct and indirect costs during the 4 first years after inclusion were compared between the 2 groups. Because of non-Gaussian distribution of some cost data, data are presented with means (SD) as well as with medians (IQR). The arithmetic mean is more relevant regarding resource consumption since it reflects total costs, whereas median values better reflect costs in the typical patient (table 2).

Table 2 Costs (€) over 4 years for patients with DAS28<3.2 and DAS28≥3.2 at 3-month follow-up.

	mean (SD)			median (IQR)		
	DAS28<3.2 at month 3	DAS28≥3.2 at month 3	p	DAS28<3.2 at month 3	DAS28≥3.2 at month 3	p
Year 1 (n=73/189)						
direct costs	2 760 (1 272)	4 147 (3 264)	<0.001	2 289 (1 070)	3 175 (2 519)	<0.001
amb care*	2 400 (1 121)	3 099 (1 600)	<0.001	2 041 (713)	2 462 (1 731)	<0.001
drugs	250 (194)	384 (450)	0.001	198 (230)	261 (267)	0.023
hospitalisation	50 (276)	544 (2 054)	0.001	0 (0)	0 (0)	0.128
surgery	37 (313)	86 (659)	0.537	0 (0)	0 (0)	0.423
indirect costs	3 918 (10 069)	11 200 (15 007)	<0.001	0 (567)	0 (23 856)	0.001
total costs	6 678 (10 754)	15 347 (15 831)	<0.001	2 429 (2 770)	5 359 (26 350)	<0.001
indir costs <65**	5 500 (11 587)	17 938 (15 491)	<0.001	0 (3 279)	17 878 (33 272)	<0.001
Year 2 (n=71/172)						
direct costs	2 447 (1 738)	3 173 (3 206)	0.019	1 856 (1 532)	2 227 (2 135)	0.033
amb care	1 920 (1 448)	2 120 (1 451)	0.293	1 283 (990)	1 663 (1 345)	0.070
drugs	323 (334)	524 (804)	0.005	213 (337)	339 (419)	0.010
hospitalisation	112 (767)	319 (1 432)	0.140	0 (0)	0 (0)	0.230
surgery	68 (330)	180 (875)	0.141	0 (0)	0 (0)	0.508
indirect costs	5 732 (11 748)	10 066 (15 120)	0.014	0 (1 356)	0 (19 981)	0.080
total costs	8 178 (12 350)	13 239 (15 796)	0.006	2 383 (6 251)	3 659 (23 203)	0.005
indir costs <65	8 188 (13 337)	15 831 (16 390)	0.002	0 (15 678)	8 967 (34 026)	0.007
Year 3 (n=59/131)						
direct costs	1 693 (1 408)	3 085 (3 706)	<0.001	1 102 (988)	1 749 (2 510)	<0.001
amb care	1 171 (916)	1 494 (1 211)	0.045	832 (378)	1 058 (907)	0.007
drugs	303 (466)	1 005 (2 400)	0.002	142 (372)	314 (536)	0.001
hospitalisation	123 (672)	147 (790)	0.842	0 (0)	0 (0)	0.703
surgery	70 (377)	415 (1 856)	0.044	0 (0)	0 (0)	0.124
indirect costs	7 123 (13 828)	9 913 (15 227)	0.215	0 (5 424)	0 (19 981)	0.267
total costs	8 816 (13 998)	12 998 (16 402)	0.074	1 532 (7 273)	3 395 (22 005)	0.017
indir costs <65	10 006 (15 523)	15 100 (16 595)	0.098	0 (19 926)	9 631 (34 400)	0.092
Year 4 (n=32/79)						
direct costs	2 073 (3 384)	3 666 (5 417)	0.065	1 083 (903)	2 035 (2 962)	0.064
amb care	1 007 (807)	1 191 (1 068)	0.382	680 (680)	832 (1 210)	0.528
drugs	881 (2 792)	1 704 (3 721)	0.207	289 (399)	448 (883)	0.055
hospitalisation	0 (0)	191 (1 161)	0.147	0 (0)	0 (0)	0.266
surgery	148 (588)	525 (1 871)	0.113	0 (0)	0 (0)	0.488
indirect costs	5 825 (11 560)	11 197 (17 007)	0.058	0 (7 728)	0 (24 243)	0.405
total costs	7 899 (11 699)	14 863 (18 626)	0.020	1 641 (9 881)	3 557 (32 382)	0.079
indir costs <65	7 456 (12 647)	17 344 (18 506)	0.008	0 (11 416)	8 524 (40 406)	0.062

* ambulatory care visits to physician, physiotherapist, occupational therapist and nurse.

** indirect costs calculated for patients <65 years of age

Direct costs were higher over the following years for the group with DAS28 ≥3.2 at month 3 compared to the group with DAS28 <3.2. Mean indirect costs were also higher in the DAS28 ≥3.2 group. The median indirect costs, however, were 0 in both groups all years, reflecting that almost 35% of the patients were above 65 years of age and accordingly did not incur any indirect costs.

Costs for outpatient visits to physician, physiotherapist, occupational therapist and nurse were significantly higher year 1 and 3 in the high DAS group and drug costs were significantly higher all years except year 4 in high DAS group compared to low DAS group.

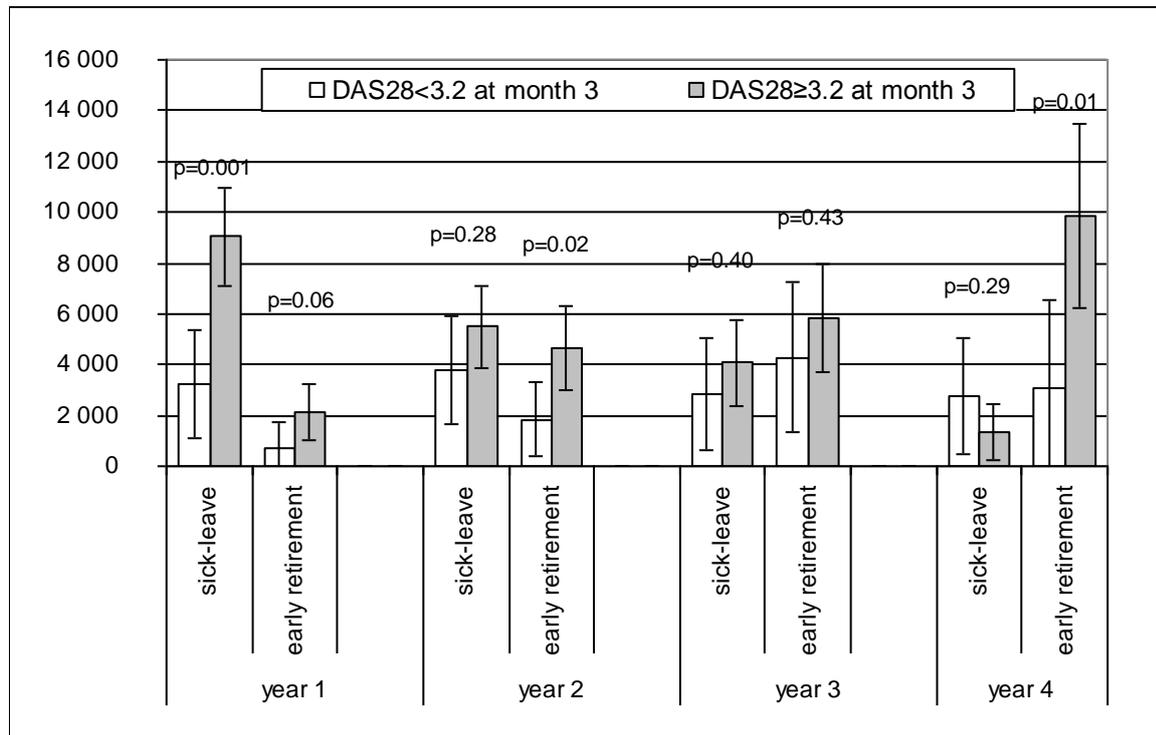
Between month 0 and 3, DMARD medication was similar in the 2 groups, but after month 3, it increased to 80% in the high DAS-group, while it remained unchanged, 69%, in the low DAS-group. After 6 months, 4% of patients in the high DAS-group were on combination treatment compared to 1% in low DAS-group and at 1 year follow up, 8% in the high DAS-group were on combination treatment compared to 4% in the low DAS-group. Patients in the high DAS-group also switched more frequently between different DMARDs. The high DAS group had a significantly higher consumption of analgesics but prescription of steroids was similar in both groups over the years. Approximately 40% of patients in both groups were on steroids at all follow ups during the first 4 years after diagnosis.

Costs for hospitalisation decreased in both groups over the years and during year 4, no patients in the DAS28 <3.2 group had days in hospital. Median values for hospitalisation and surgery were 0 all years. The proportion of patients admitted to hospital during year 1 was 10% in the high DAS-group vs 4% in the low DAS-group. The corresponding values were 9% vs 4% during year 2, 5% vs 3% during year 3 and 4% vs 0% during year 4. Costs for complementary medicine were rather low and did not differ between the 2 groups (data not shown).

Twelve surgeries (corresponding to 0.14 per patient) were performed in the DAS<3.2 group and all of them were hand surgery. There were 2 thumb arthrodeses and the remaining 10 were carpal tunnel releases and tenosynovectomies of palm and finger. In the DAS≥3.2 group there were in total 44 surgeries (corresponding to 0.21 per patient). Five extensive foot surgeries and 10 total joint replacements of hip and knee were performed. There were also 29 hand and elbow surgeries with synovectomies, arthrodeses, carpal tunnel releases, wrist and finger tenosynovectomies and extensive wrist and digital surgery due to tendon ruptures.

Indirect costs were analysed separately for sick leave and early retirement and were higher in the DAS28 ≥3.2 group, compared to the DAS28 <3.2 group. The costs for sick leave during year 1 were € 9 055 vs € 3 202 and costs for early retirement were € 2 145 vs € 716. The corresponding values year 2 were € 5 490 vs € 3 815 and € 4 634 vs € 1 835. The costs year 3 were € 4 081 vs € 2 833 and € 9 913 vs € 7 123. During year 4 the costs for sick leave were € 1 368 vs € 2 755 and for early retirement € 9 829 vs € 3 069. In the DAS28≥3.2 group, sick leave gradually decreased over the years and was replaced by increasing early retirement. At 4 year follow up, very few patients in the high DAS group were still on sick leave because the vast majority of DAS28≥3.2 patients had become permanently work disabled. This substantial transition from sick leave to early retirement was not seen in the low DAS group (Figure 2).

Fig. 2 Costs (€) for sick leave and early retirement over 4 years for patients with DAS28<3.2 and DAS28≥3.2 at 3-month follow-up, mean (95%CI.) P-values for difference between low and high DAS28 group.



Costs were log-transformed for the regression analysis and linear regression models were performed with direct and indirect costs as dependent variables, controlling for possible confounding effects of age and gender during year 1-4. The association between DAS28 at month 3 and future costs remained when age and gender were entered in the model. There was an association between educational level and indirect costs, but since education was highly correlated to both age and gender, this association weakened when age and gender were entered into the regression. Regression models were performed, taking advantage of all DAS values, using DAS28 as a continuous variable. Regression models were also performed using DAS as a categorical variable. The results were rather similar, but the statistical strength was slightly weakened when DAS was categorized, while losing information as not all DAS values were used. Only patients with complete cost data all 4 years were included in the model. Both regression models with categorized and continuous DAS 28 and with log-transformed and non log-transformed data are presented in table 3.

Table 3 Linear regression models for influences on direct and indirect costs.

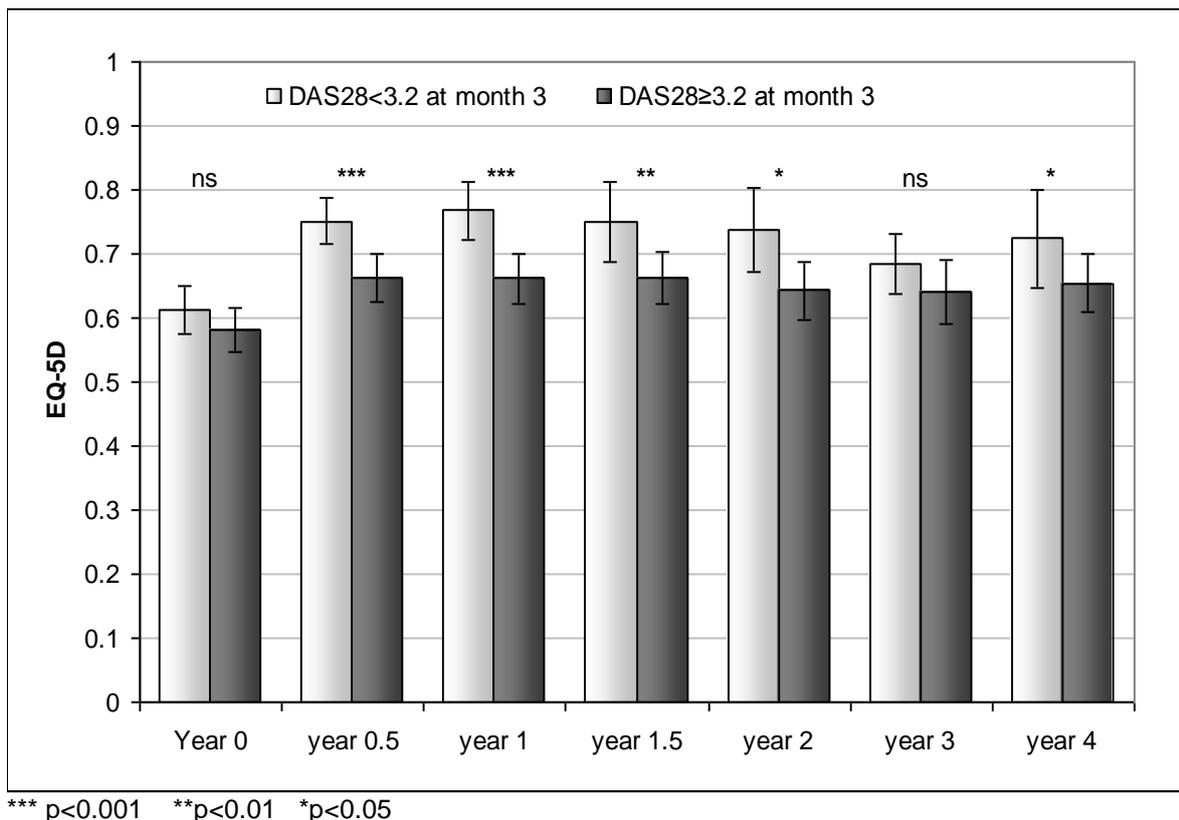
	Non log-transformed			Log-transformed		
	B*	adj R ² =0.03 95% CI for B	p	B	adj R ² =0.06 95% CI for B	p
direct costs (n=87)						
constant	16 849	4 816 - 28 881	0.007	4.120	3.891 - 4.349	0.000
DAS≥3.2, month 3	6 924	-169 - 14 018	0.056	0.155	0.020 - 0.290	0.025
age (year)	-128	-356 - 101	0.269	-0.003	-0.008 - 0.001	0.123
sex (male)	-3 244	-10 287 - 3 798	0.362	-0.075	-0.209 - 0.059	0.271
indirect costs (n=59)						
	B*	adj R ² =0.14 95% CI for B	p	B	adj R ² =0.06 95% CI for B	p
constant	-20 478	-78 921 - 37 965	0.486	1.627	-0.554 - 3.807	0.141
DAS≥3.2, month 3	39 805	7 926 - 71 685	0.015	1.205	0.016 - 2.395	0.047
age (year)	867	-437 - 2 170	0.188	0.017	-0.032 - 0.066	0.488
sex (male)	13 257	-20 490 - 47 004	0.435	0.359	-0.900 - 1.618	0.570
direct costs (n=87)						
	B*	adj R ² =0.11 95% CI for B	p	B	adj R ² =0.16 95% CI for B	p
constant	6 940	-6 194 - 20 074	0.296	3.907	3.659 - 4.154	0.000
DAS28, month 3**	3 733	1 573 - 5 892	0.001	0.081	0.040 - 0.121	0.000
age (year)	-134	-345 - 78	0.214	-0.003	-0.007 - 0.001	0.087
sex (male)	-2 623	-9 361 - 4 116	0.441	-0.062	-0.189 - 0.065	0.333
indirect costs (n=59)						
	B*	adj R ² =0.17 95% CI for B	p	B	adj R ² =0.08 95% CI for B	p
constant	-51 299	-112 402 - 9 804	0.098	0.698	-1.595 - 2.991	0.544
DAS28, month 3**	13 792	4 179 - 23 404	0.006	0.415	0.055 - 0.776	0.025
age (year)	900	-356 - 2 156	0.157	0.018	-0.029 - 0.065	0.446
sex (male)	14 436	-18 822 - 47 694	0.388	0.393	-0.855 - 1.641	0.530

* unstandardised coefficients

** continuous DAS

Disease activity at month 3 was highly related to quality-of-life as measured by EQ-5D. At inclusion there was no difference between the DAS-groups but at all following time points, except year 3, patients with DAS28≥3 at the 3-month follow-up had significantly lower EQ-5D scores compared to the high DAS-group (Figure 3).

Fig. 3 EQ5D over 4 years in patients with DAS28<3.2 and DAS28≥3.2 at 3-month follow-up.



Discussion

We have previously reported that the level of disease activity after 3 months of treatment in early RA was related to disease activity over the following 3 years [17]. In the present study the relationship between the level of disease activity at 3-month follow-up and costs over the following years was analysed. Direct and indirect costs increased with increased disease activity as measured by DAS28. Patients with low DAS levels incurred low costs and patients with high DAS levels incurred high costs independent of age and gender. There were no big differences between the patients at inclusion according to disease activity and prescription of DMARDs was similar in both groups during the first 3 months. Sixty-nine per cent of the patients in the low DAS-group were prescribed DMARDs, compared to 73% in the high DAS-group, suggesting that only low-DAS group responded to treatment. The patients in the TIRA project were recruited during a period just before the anti-TNF biologics became available on the market, and anti-rheumatic medication was not instituted according to a study protocol but as judged appropriate by the rheumatologists. At the 3-year follow up, 5.1% of the patients were prescribed biologics. After 4 years, the proportion had risen to 12.3%. As most of them belonged to the 3-month DAS≥3.2 group, this affected drug costs in this group year 4. These anti-TNF treated patients did, however, in fact incur higher costs even before the start of anti-TNF treatment, compared to the non-TNF patients [17].

All surgery in the low DAS group was hand and finger surgeries and most of them were minor operations. There was more surgery done in the DAS28≥3.2 group and, above all, more extensive surgery. All total joint replacements of hips and knees were performed in the high DAS group as well as all foot surgeries, most of them major surgery with correction of severe rheumatoid forefoot deformities. Surgical interventions in hands and upper limbs were

more extensive in the $DAS28 \geq 3.2$ group, for instance elbow surgery and reconstruction of ruptured tendons.

To a large extent, patients who achieved low disease activity 3 months after diagnosis maintained the low disease activity. This is in line with results from the BeSt study, where patients who achieved low disease activity had a high probability of maintaining a low DAS level over the following year [26]. Also Aletaha et al reported that the level of disease activity after 3 months of treatment was significantly related to the level of disease activity after 1 year [14]. A study from Belgium showed that good response to treatment at 4 month follow-up was predictive of remission later on [27].

Utility as measured with EQ-5D was significantly lower over 4 years in patients who were in the high DAS-group 3 months after diagnosis, confirming the effect of disease activity on health related quality-of-life. This is important because quality-of-life is connected with many aspects of life and is very meaningful to the patient when evaluating outcome of disease.

Several studies have concluded that HAQ is a strong predictor of costs [3,7,8,10]. In the present study, unfortunately, no HAQ scores were available at the 3-month follow-ups, since HAQ was assessed only once a year. The HAQ scores were, however, significantly higher in the $DAS \geq 3.2$ group at all time points over the following 4 years. At baseline, mean HAQ was 0.8 in the group with $DAS28 < 3.2$ at 3 months and 0.9 in the $DAS28 > 3.2$ group. At 1 year follow up, the corresponding values were 0.4 and 0.7 ($p < 0.0001$). Similar highly significant differences were seen after 2 and 3 years and at 4 year follow up, the HAQ scores were 0.6 vs 0.8 ($p = 0.025$).

A more rapid suppression of disease activity may very well have the potential to lower both direct and indirect costs [13,14]. From the FIN-RACo Trial, Puolakka et al reported that poor clinical improvement was related to substantial loss of productivity [28]. In our cohort, the disease activity of patients treated with biological agents, acquired decreased disease activity, but despite good disease control, this had very little effect on working capacity among the patients who already were on long-term sick-leave or had become early retired. Once work disability had occurred, there was limited success in returning to work [17]. This may suggest that early powerful treatment is necessary before patients leave the job market.

Different approaches can be made when calculating indirect costs. The most commonly used method is the human capital approach, which values the productivity of the individual as the gross income together with employer's contribution, estimating the value of lost productivity during the entire time of absenteeism. The human capital approach assumes full productivity and may favour persons with higher salaries, thus being more 'cost-effective' for expensive treatments, and giving no value to house-wives and students with no salary. In the present study, the same average income has been calculated for all patients, regardless gender or occupation, in order primarily not to focus on differences in salary. This average income was in fact also approximately the same as the average income of the general population, when adjusted for age and gender similar to that of the TIRA cohort. Women, in the present study, worked more part time, approximately 80%, compared to men, working almost 100%. This might give women as a group a potential lower loss of productivity, despite a rather similar full-time salary. Another method of calculating costs is the friction method which assumes that loss of productivity proceeds until the person returns to work or is replaced by someone unemployed, given that no society achieves full employment. Thus, the friction method yields accordingly lower costs compared to the human capital approach [29].

A limitation of the present study is the increasing number of patients with missing health economic data, with only 61% reporting data during year 4. Patients lost to follow up in the TIRA study were older than patients remaining in the study and this probably had effect on the outcome, but they also had significantly lower levels of anti-CCP, possibly in part

offsetting this effect. However, concerning the health economic questionnaires, there were no differences in any clinical or demographic data between the patients with complete health economic data and the patients with missing questionnaires. Non-medical costs, such as assistive devices, transportation costs, and adaptations were not included in the present study. This is also a drawback since these expenditures may be quite substantial from the very beginning of the disease. Furthermore, all costs were based upon self-reported data and recall bias cannot be ruled out. It has, however, previously been shown that patient-reported data are reliable and correlate well with data from payers' sources and social insurer registers [30].

The strength of the present study is the well-characterised patient material and the longitudinal prospective design with regular follow-ups, allowing analyses of long-term outcomes of patients with recent-onset RA. Many previous studies on costs have been performed cross-sectionally.

To conclude, our study implies the importance of early suppression of disease activity, primarily to maintain a good health but also to reduce future health care costs and loss of productivity for society.

Key messages

- DAS \geq 3.2 at month 3 is associated with high direct and indirect costs over 4 years.
- Patients with DAS \geq 3.2 have lower scores of EQ5D over 4 years.
- Very early suppression of disease activity is likely to save costs for patient and for society.

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Disclosure

The authors declare no conflicts of interest.

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