Rheumatoid arthritis is still expensive in the new decade: a comparison between two early RA cohorts, diagnosed 1996-98 and 2006-09

Eva Hallert, Magnus Husberg, Almina Kalkan and Lars Bernfort

This is an electronic version of an article published in:

Eva Hallert, Magnus Husberg, Almina Kalkan and Lars Bernfort, Rheumatoid arthritis is still expensive in the new decade: a comparison between two early RA cohorts, diagnosed 1996-98 and 2006-09, 2016, Scandinavian Journal of Rheumatology, 1-8.

Scandinavian Journal of Rheumatology is available online at informaworldTM:
http://dx.doi.org/10.3109/03009742.2015.1126344

Rheumatoid arthritis is still expensive in the new decade: a comparison between two early RA cohorts, diagnosed 1996-98 and 2006-09.

Hallert E, Husberg M, Kalkan A, Bernfort L

Center for Medical Technology Assessment, Division of Health Care Analysis, Linköping University, Linköping, Sweden.

Abstract

Objectives: To calculate total costs during the first year after diagnosis in 463 patients with early rheumatoid arthritis included 2006-09 (T2) and compare results with a similar cohort included 1996-98 (T1).
Method: Clinical/laboratory data were collected regularly in both cohorts and patients completed biannual questionnaires reporting healthcare utilization and number of days lost from work.
Results: Disease activity was similar in both cohorts at inclusion. Significant improvements were seen during the first year in both cohorts, but were more pronounced in T2. Out-patient care increased and hospitalization decreased in T2 vs T1. Almost 3% had surgery in both cohorts, but in T2, only women. Drug costs were higher in T2, €689 vs €435 in T1, and comprised 12% of direct costs and 4% of total costs. Corresponding values for T1 were 9% and 3%. In T1, 50% were prescribed DMARDs at inclusion, compared to T2, where prescription was >90%. Direct costs were €5716 in T2 and €4674 in T1. Costs for sick leave were lower in T2, €5490 vs €9055 in T1, but disability pensions were higher, €4152 vs €2139, resulting in unchanged total costs. In T1, direct costs comprised 29% and indirect costs 71% of total costs. Corresponding values for T2 were 37% and 63%.
Conclusions: The earlier and more aggressive treatment with traditional DMARDs in T2 resulted in better outcome compared to T1. Direct costs were higher in T2, partly offset by decreased sick leave, but total costs remained unchanged.

Key words:
early rheumatoid arthritis, direct costs, indirect costs, DMARDs, cohort studies

Rheumatoid arthritis (RA) is a chronic inflammatory disease, associated with pain, joint destruction and progressive disability. The economic consequences are substantial with high costs for healthcare utilization and loss of productivity (1,2). The introduction of biological drugs during the last decade has led to improved management of the disease but has also substantially increased total costs, which are now predominantly driven by drug costs (3-5). Reports from clinical trials have implied that reduced health care utilization and increased work ability may offset the increasing drug costs (6-8). Results from real life studies do however not appear to be quite as good as those reported in clinical trials (9-11). Given this development, a challenging question is, whether the increasing costs to some extent have been offset by savings in other areas of health care or by a decrease in loss of productivity, i.e. sick leave and disability pension. In the present study, costs for healthcare utilization and sick leave and disability pension have been compared between two cohorts of patients with early RA, enrolled 10 years apart from basically the same catchment area. The development of disease activity and disability in the first cohort (TIRA1), has previously been described (2,5). Direct and indirect costs have been analysed and predictors for high costs have been calculated (2,5,12). The aim of the present study was to calculate total costs during the first year after diagnosis in a cohort of patients with early RA, enrolled in the 21st century (TIRA2), and compare with costs from TIRA1, enrolled one decade earlier.

METHOD

Patients
During 1996-98, 320 patients with early (≤1 year) RA were recruited from 10 rheumatology units in Sweden, corresponding to a catchment area of >1 million inhabitants (TIRA1, T1, Swedish acronym for 'early intervention in RA'). The patients fulfilled at least 4/7 of 1987 ACR criteria (13) *or* suffered from morning stiffness ≥60 minutes, symmetrical arthritis, and small-joint engagement (metacarpo-phalangeal or proximal inter-phalangeal joints of hands, or metatarso-phalangeal joints). A second cohort, TIRA2 (T2), was launched 10 years later from basically the same catchment area and 463 patients with early RA (≤1 year) were enrolled 2006-09.

Clinical assessments
Clinical and laboratory data were collected at inclusion, after 3, 6, 12, 18 and 24 months, and then annually, using similar instruments and questionnaires in both cohorts. Details of the T1-study are described previously (2). Briefly, tender and swollen joint counts were registered, erythrocyte sedimentation rate (ESR) was analysed, 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 (14). Patients reported pain on a VAS-scale and completed the Health Assessment Questionnaire (HAQ) (15). On-going, instituted, and withdrawn medication was registered at all visits.

Health economic questionnaire
Extensive cost data was collected regularly in both cohorts. Besides the baseline questionnaire with sociodemographic data including age, sex, marital status, educational level and employment status, the patients were provided with health economic questionnaires every 6 months. The questionnaires were kept as diaries and patients reported continuously all outpatient visits, admissions to hospital and surgical procedures. Dosage and frequency of all prescribed drugs was reported as well as drugs bought over the counter. In case complementary medicine, such as herbal medication and chiropractic therapy, was used, this was also reported. Number of days with sick leave or days with disability benefits during the period was reported and the patients also completed the health related quality-of-life instrument EuroQol-5D (EQ5D) with 5 questions covering mobility, self-care, usual activities, pain/discomfort and anxiety/depression, with 3 levels of answers; no problems, some problems or severe problems. The EQ5D 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, equal to full health (16). In addition, EQ-VAS (0-100) was completed, 0 corresponding to worst imaginable health and 100 to best imaginable health. Costs in the first cohort were calculated, using unit costs from 2001, inflation-adjusted to 2013, using the Swedish Consumer Price Index (CPI) and in the second cohort, unit costs from 2009, inflation-adjusted to 2013 with CPI. All costs were converted to 2013 euros, using the average exchange rate in 2013, €1=8.6494 SEK (http://www.riksbank.se)

Costs
Costs were calculated using the official Swedish County Council tariffs for outpatient visits, including all overhead costs involved in the patient visit, such as administration costs, laboratory analyses, radiographs and salaries of relevant staff involved in the visit (http://www.skl.se). Costs for surgery, including costs for surgical interventions and a standardized number of hospital days were calculated according to the diagnostic-related coding system (http://www.socialstyrelsen.se). Additional hospitalization, besides standard care, was calculated as additional days in hospital. Drug costs were calculated using dosage and duration multiplied by unit costs using market wholesale prices (http://www.fass.se). Indirect costs were calculated, using the human capital approach, estimating the value of lost production during the entire period of absence, similarly for sick leave and for disability pension, using the average productivity cost of all gainfully employed Swedish full-time

workers (http://www.scb.se). In order to describe loss of productivity similarly for the patients, all days were recalculated to full-time days, for instance 1 full-time day is equal to 2 days with 50% or 4 days with 25%. Health-care in Sweden is tax financed and except for a minor annual co-payment of 2200 SEK (€254), all prescription medications, including biologic drugs, are free of charge during the rest of the year. In the present study, a societal perspective is applied, including all costs, regardless payer.

Statistics
Continuous variables are reported as means with standard deviations (SD) and categorical variables as numbers and proportions and differences were analyzed by Student's t-test or by chi-square test or Fishers exact test. Although some cost distributions were skewed, mean values were used, as an informative measure for cost and resource use data (17). Results are presented for the total group and for women and men separately. Level of significance was set at $p<0.05$. For clarification, costs are also presented as median values with interquartile range (IQR) in an appendix. All analyses were performed using IBM SPSS 22.0.

Ethical considerations
All patients gave written informed consent to participation. The study protocol was approved by the local ethics committee in Linkoping.

RESULTS

Patients
The T1-cohort comprised 320 patients (67% women) and the T2-cohort comprised 463 patients (67% women). At 1-year follow-up, data was available in 276/320 (86%) patients, 68% women in T1 and in 340/463 (73.4%) patients, 70% women in T2. Patients were lost to follow-up for reasons such as having moved from the area, declining further participation because of "too many tests", having difficulties with transportation to the hospital, etc. Some patients remained in the clinical part of the study, but did not want to participate in the health economic part, "too many questionnaires". A larger proportion of men were lost to follow-up in both cohorts, but there were no differences in age, educational level, marital status, levels of sick leave and disability pension between patients with health economic data and patients with missing data. Levels of DAS28, HAQ, pain, EQ5D and EQ-VAS were also similar in patients with and without health economic data. Baseline characteristics of patients in T1 and T2 are presented in table 1.

Table 1. Baseline characteristics of patients in T1 (1996-98) and T2 (2006-09) and p-value for differences between the two cohorts and differences between women in T1 and T2 and differences between men in T1 and T2.

	total			women			men		
	T1	T2	p	T1	T2	p	T1	T2	p
	n=276	n=340		n=187	n=239		n=89	n=101	
age (yrs)	56 (15)	59 (14)	**0.019**	54 (15)	58 (13)	**0.013**	60 (13)	62 (14)	0.481
cohabiting (%)	73	73	0.978	70	71	0.961	78	78	0.979
education (yrs)	10.6 (2.1)	11.0 (2.3)	**0.025**	10.7(2.1)	11.2 (2.3)	**0.050**	10.3(2.0)	10.6(2.1)	0.351
SL (%)*	49.1	39.6	0.067	45.9	34.5	0.056	57.4	55.1	0.817
DP (%)	10.5	13.9	0.309	8.9	15.6	0.094	14.3	8.9	0.389
SL and/or DP (%)	54.4	50.2	0.423	50.8	46.8	0.501	63.8	60.8	0.756
DAS28	5.3 (1.2)	5.1 (1.3)	0.102	5.3 (1.2)	5.2 (1.2)	0.305	5.3 (1.0)	5.0 (1.4)	0.154
pain (VAS)	48 (25)	53 (25)	**0.017**	48 (24)	54 (24)	**0.030**	47 (26)	51 (26)	0.310
HAQ (0-3)	0.9 (0.6)	1.0 (0.6)	0.094	0.9 (0.6)	1.0 (0.6)	0.090	0.8 (0.5)	0.8 (0.6)	0.715
EQ5D (0-1)	0.59 (0.26)	0.55 (0.27)	0.107	0.60 (0.25)	0.55 (0.27)	0.**044**	0.57 (0.27)	0.57 (0.28)	0.966
EQ-VAS(0-100)	58 (19)	57 (21)	0.478	59 (20)	56 (21)	0.176	58 (19)	60 (20)	0.397

SL=sick leave; DP=disability pension; DAS28=28 joint-count disease activity score; HAQ=Health Assessment Questionnaire; EQ5D=EuroQol-5D, VAS= visual analogue scale (0-100);
Values given as % or mean (sd)
*including part-time sick leave and part-time DP
Significant p values are indicated in bold.

Women in T2 were older, 58 (13) years vs 54 (15) in T1 and their level of education was slightly higher. They reported more pain and lower EQ5D, but marital status, sick leave and disability pension, HAQ, DAS28 and EQ-VAS were similar in both cohorts. There were no significant differences between men in T1 and T2.

At the 1-year follow-up, there were significant improvements in both cohorts compared to baseline values (Table 2).

Table 2. Clinical characteristics of the T1-cohort and the T2 cohort at inclusion (M0=month 0) and at 1 year (M12=month 12) follow-ups and p-value for differences between inclusion and follow-up for the total group and for women and men respectively in the two cohorts.

T1-cohort	Total T1			Women T1			Men T1		
	M0	M12		M0	M12		M0	M12	
	n=276		p	n=187		p	n=89		p
DAS28	5.3 (1.2)	3.8 (1.4)	**<0.000**	5.3 (1.2)	3.9 (1.5)	**<0.000**	5.3 (1.0)	3.5 (1.3)	**<0.000**
HAQ	0.9 (0.6)	0.6 (0.5)	**<0.000**	0.9 (0.6)	0.7 (0.6)	**<0.000**	0.8 (0.5)	0.4 (0.4)	**<0.000**
Pain	48 (25)	39 (27)	**<0.000**	48 (24)	41 (27)	**0.001**	47 (26)	35 (27)	**<0.000**
EQ5D	0.59 (0.26)	0.70 (0.21)	**<0.000**	0.60 (0.25)	0.69 (0.21)	**0.002**	0.57 (0.27)	0.71 (0.23)	**<0.000**
EQ-VAS	58 (19)	65 (19)	**<0.000**	59 (20)	65 (20)	**0.006**	58 (19)	60 (20)	**<0.000**

T2-cohort	Total T2			Women T2			Men T2		
	M0	M12		M0	M12		M0	M12	
	n=340		p	n=239		p	n=101		p
DAS28	5.1 (1.3)	2.7 (1.2)	**<0.000**	5.2 (1.2)	2.9 (1.3)	**<0.000**	5.0 (1.4)	2.3 (1.0)	**<0.000**
HAQ	1.0 (0.6)	0.4 (0.5)	**<0.000**	1.0 (0.6)	0.5 (0.5)	**<0.000**	0.8 (0.6)	0.3 (0.4)	**<0.000**
Pain	53 (25)	27 (23)	**<0.000**	54 (24)	28 (23)	**<0.000**	51 (26)	24 (22)	**<0.000**
EQ5D	0.55 (0.27)	0.74 (0.19)	**<0.000**	0.55 (0.27)	0.73 (0.19)	**<0.000**	0.57 (0.28)	0.77 (0.19)	**<0.000**
EQ-VAS	57 (21)	73 (19)	**<0.000**	56 (21)	73 (19)	**<0.000**	60 (20)	75 (18)	**<0.000**

DAS28=28 joint disease activity score (0-10), HAQ=Health Assessment Questionnaire (0-3), Pain=pain VAS, visual analogue scale (0-100), EQ5D (0-1). EQ-VAS=general health, visual analogue scale (0-100).
Values given as mean (sd)
Significant p values are indicated in bold.

The improvement at the 1-year follow-up was, however, more pronounced in T2 compared to T1, with significantly better outcome in all variables except for the EQ5D, which did not reach significance, when comparing women and men separately. Biological drugs were available for patients in T2, but very few (n=9) were prescribed these drugs during the first year. Data were also calculated excluding the 9 patients who were prescribed biologics during the first year (data not shown).This did however not affect the results and data were similar to results presented for the total group (Table 3).

Table 3. Differences between the two cohorts at the 1-year follow-up with differences between the groups and between women and men respectively.

	Total			Women			Men		
	T1	T2		T1	T2		T1	T2	
	n=276	n=340	p	n=187	n=239	p	n=89	n=101	p
DAS28	3.8 (1.4)	2.7 (1.2)	**<0.000**	3.9 (1.5)	2.9 (1.3)	**<0.000**	3.5 (1.3)	2.3 (1.0)	**<0.000**
HAQ	0.6 (0.5)	0.4 (0.5)	**<0.000**	0.7 (0.6)	0.5 (0.5)	**<0.000**	0.4 (0.4)	0.3 (0.4)	**0.041**
Pain	39 (27)	27 (23)	**<0.000**	41 (27)	28 (23)	**<0.000**	35 (27)	24 (22)	**0.004**
EQ5D	0.70 (0.21)	0.74 (0.19)	**0.016**	0.69 (0.21)	0.73 (0.19)	0.091	0.71 (0.23)	0.77 (0.19)	0.058
EQ-VAS	65 (19)	73 (19)	**<0.000**	65 (20)	73 (19)	**<0.000**	67 (17)	75 (18)	**0.005**

DAS28=28 joint disease activity score (0-10), HAQ=Health Assessment Questionnaire (0-3), Pain=pain VAS, visual analogue scale (0-100), EQ-5D (0-1). EQ-VAS=general health, visual analogue scale (0-100).
Values given as mean (sd)
Significant p values are indicated in bold.

Outpatient care and hospitalization

Costs for outpatient care increased from €3615 in T1 to € 4654 in T2 ($p<0.0001$), while hospitalization due to RA, decreased from €382 in T1 to €49 in T2 ($p=0.007$). All costs are presented in Table 4.

Table 4. Direct and indirect costs (€) during the first year in the two cohorts and p-value for differences between the cohorts and for differences between women and men respectively in the two cohorts.

	total			women			men		
	TIRA1 n=276	TIRA2 n=340	p	TIRA1 n=187	TIRA2 n=239	p	TIRA1 n=89	TIRA2 n=101	p
physician	1369 (873)	1541 (956)	**.021**	1468 (961)	1624 (1010)	.107	1162 (605)	1347 (786)	.069
nurse	888 (405)	1070 (936)	**.001**	888 (390)	1160 (958)	**.000**	886 (437)	856 (849)	.751
PT. OT	1359 (1319)	2042 (3141)	**.000**	1421 (1244)	2270 (3147)	**.000**	1228 (1463)	1503 (3073)	.442
all visits	3615 (1886)	4654 (3976)	**.000**	3777 (1906)	5054 (4074)	**.000**	3276 (1807)	3706 (3576)	.289
DMARDs	156 (354)	140 (207)	.485	163 (384)	142 (200)	.458	142 (284)	137 (225)	.891
bDMARDs	0	235 (1542)	**.005**	0	174 (1365)	**.049**	0	380 (1896)	**.047**
analgesics	20 (70)	14 (55)	.257	17 (58)	17 (65)	.999	25 (90)	6 (16)	.059
steroids	16 (24)	29 (28)	**.000**	14 (18)	27 (25)	**.000**	20 (32)	34 (32)	**.003**
NSAID	120 (138)	37 (87)	**.000**	128 (142)	39 (86)	**.000**	104 (128)	35 (88)	**.000**
anti-osteo	15 (75)	54 (123)	**.000**	21 (91)	62 (132)	**.000**	2 (12)	33 (96)	**.001**
folic acid	7 (17)	25 (18)	**.000**	6 (14)	25 (18)	**.000**	8 (23)	25 (20)	**.000**
cardiovasc	25 (85)	66 (164)	**.000**	20 (69)	63 (167)	**.000**	36 (112)	73 (158)	.064
gastroprot	48 (152)	12 (44)	**.000**	56 (167)	14 (50)	**.001**	30 (114)	8 (24)	.076
other drugs	28 (81)	76 (251)	**.001**	33 (90)	69 (177)	**.008**	17 (56)	94 (371)	**.042**
all drugs	435 (495)	689 (1641)	**.007**	459 (534)	632 (1508)	.136	384 (399)	825 (1920)	**.026**
CAM	40 (151)	17 (68)	**.020**	53 (179)	22 (79)	**.030**	12 (47)	3 (24)	.138
surgery	96 (734)	149 (997)	.462	115 (849)	213 (1184)	.343	57 (398)	0	.181
in-pat RA	382 (1978)	49 (533)	**.007**	529 (2343)	60 (618)	**.008**	73 (688)	23 (229)	.491
in-pat	105 (943)	158 (869)	.468	127 (1114)	142 (871)	.869	60 (390)	196 (867)	.158
total dir	4674 (3616)	5716 (4713)	**.002**	5060 (4072)	6123 (4754)	**.013**	3862 (2200)	4753 (4491)	.079
SL	9055 (15760)	5490 (12963)	**.003**	8797 (14888)	5360 (12899)	**.013**	9596 (17529)	5797 (13172)	.097
DP	2139 (8622)	4152 (13700)	**.027**	2233 (8977)	4609 (14374)	**.037**	1944 (7870)	3070 (11949)	.451
tot indir	11194 (17598)	9642 (18087)	.284	11030(17120)	9970(18425)	.544	11539(18658)	8866 (17326)	.307
total costs	15868 (18757)	15358(19764)	.745	16090(18198)	16093(20051)	.999	15401(19977)	13619(19050)	.530
SL < 65	14040 (17763)	8601 (15388)	**.001**	12655(16444)	8057 (15125)	**.015**	17792(20649)	10091(16129)	**.038**
DP< 65	3317 (10563)	6505 (16707)	**.022**	3211 (10631)	6929 (17178)	**.025**	3604 (10482)	5343 (15427)	.508
indir<65	17357 (19328)	15106(20745)	.269	15866(18582)	14986(20874)	.708	21396(20891)	15434(20564)	.143

PT/OT = physiotherapist and occupational therapist, all visits = total costs for outpatient care visits (physician, nurse, PT,OT), DMARDs = non-biologic DMARDs, bDMARDs = biological DMARDs, NSAID = nonsteroidal anti-inflammatory drugs, anti-osteo = anti-osteoporosis drugs, cardiovasc = cardiovascular disease drugs, gastroprot = gastroprotective drugs, CAM = complementary medicine, in-pat RA = inpatient care, RA-related, in-pat = inpatient care, non-RA-related, total dir = total direct costs, SL = sick leave, DP = disability pension, indir<65 = total indirect costs for patients <65.
Values given as mean (sd)
Significant p values are indicated in bold.

Surgery

There was a small, but non-significant increase in surgery in T2, €149 vs €96 in T1. In T1, 8 patients (2.9%), 5 women and 3 men, had 10 surgeries, 1 total knee replacement and nine various hand and foot surgeries. Two patients had two surgeries each during the first year. In T2, 9 patients (2.7%) had 10 surgeries, with one patient having 2 surgeries. There were 2 total joint replacements in knees, 4 hand surgeries including arthrodesis, carpal tunnel

releases and tenosynovectomies of wrist and fingers and 4 extensive foot surgeries in T2. Notably, all surgery in the T2-cohort was performed in women.

Drugs

Total costs for drugs were significantly higher in T2, €689 vs €435 in T1 (p=0.004), partly because biologic drugs were not available in T1, but also due to increasing costs for a number of other drugs. With the exception of costs for gastro protectors and nonsteroidal anti-inflammatory drugs (NSAIDs) which decreased, costs for traditional disease-modifying antirheumatic drugs (DMARDs) and analgesics remained unchanged and there was a significant increase in steroids, anti-osteoporosis drugs, folic acid and cardiovascular disease drugs (p<0.0001) (table 2). At inclusion, approximately 50% of patients in T1 were prescribed DMARDs, in contrast to patients in T2, where more than 90% were provided with DMARDs, usually methotrexate (MTX) as monotherapy or in combinations with hydroxychloroquine and sulfasalazine. The prescription of DMARDs increased rapidly in T1, but was still at 1 year follow-up, lower than in the T2-cohort (Figure 1).

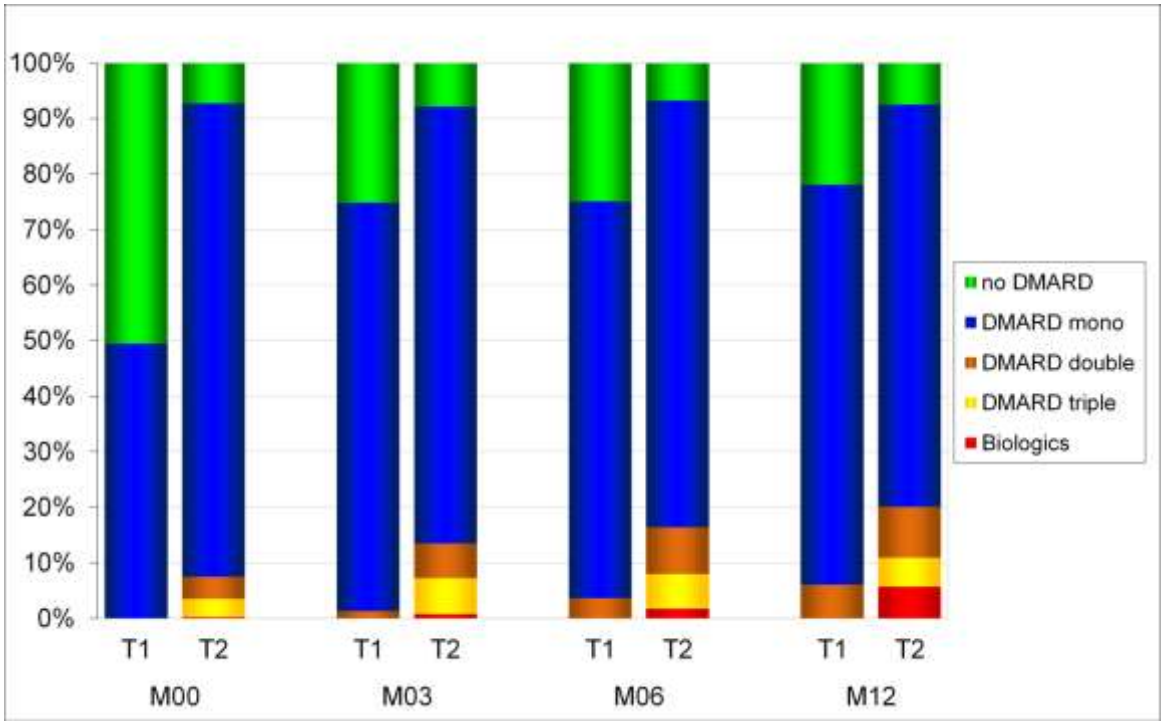

Figure 1. Prescription of DMARDs in the T1-cohort (included 1996-98) and the T2-cohort (included 2006-09) during the first year after diagnosis. M00 represents time point of inclusion, M03, the 3-month follow-up, M06, the 6-month follow-up and M12, the 12-month follow-up.

Costs for traditional DMARDs were similar in both cohorts, despite lower prescription levels in T1. This was due to frequent prescription of more expensive DMARDs in T1, such as cyclosporin A and gold. In the T1-cohort, costs for cyclosporin A made up for more than 1/3 of total costs for traditional DMARDs. In T2, basically all patients were prescribed MTX and this lowered the average costs, MTX being less expensive than gold and cyclosporine. Complementary alternative medicine was used by 23% of patients in T1 and 12% in T2 and average costs were low, €40 and €17 respectively.

Sick leave and disability pension
Sick leave was lower in T2 compared to T1, but disability pension was higher, resulting in basically unchanged total loss of productivity, €11194 in T1 vs €9642 in T2 (p=0.3). Results were similar, when calculating sick leave and disability pension separately for patients <65. Sick leave decreased and disability pension increased and total loss of productivity remained unchanged €17357 vs €15106 (p=0.3). Some patients in both cohorts were permanently work disabled at inclusion and since we in some cases do not know the reason for being granted disability pension, some pensions may be due to other diseases besides arthritis.

Total costs and composition of costs
Total direct costs increased from €4674 in T1 to €5716 in T2 (p=0.002) and with basically unchanged indirect costs, this resulted in unchanged total costs, €15868 in T1 vs €15358 in T2 (p=0.7) (table 2). There was a slight shift within the composition of costs in the 2 cohorts. Drug costs in T1 comprised 9% of direct costs and 3% of total costs during the first year, while drug costs in T2 comprised 12% of direct costs and 4% of total costs. In T1 direct costs made up for 29% of total costs and indirect costs 71%. The corresponding values for T2 were 37% and 63% respectively.

DISCUSSION

The present study analyzes two cohorts with early RA-patients recruited from basically the same catchment-area, 10 years apart, and followed in longitudinal prospective studies. Health care utilization and loss of productivity was analyzed in the recent cohort and comparisons were made with the previous cohort, included one decade earlier.

Measures of disease activity decreased significantly in both cohorts, but were more pronounced in T2. The improvement in T2 coincides with an earlier and more aggressive treatment with traditional DMARDs. Treatment strategies in RA patients have changed substantially over the past decades. From a step-up approach with NSAIDs and analgesics and eventually single DMARD therapy, treatment has become more aggressive and MTX, as monotherapy or in combinations, has been regarded the anchor drug, early in the disease course (18). In T1, less than 50% of the patients were prescribed DMARDs at inclusion compared to more than 90% of patients in T2. Biological drugs were introduced into the market around year 2000, hence available only for the T2 cohort. However, very few patients in T2 were prescribed biologics during the first year after diagnosis.

As expected, hospitalization decreased in frequency as well as in length of stay. During the recent decade, there have been substantial structural changes in most areas of health care in Sweden, with a reduction in number of hospital beds and increase in number of outpatient visits. A vast majority of patients, especially within the area of rheumatology, were transferred to outpatient care instead of, as was the case earlier, being hospitalized. Hence the decreasing costs for hospitalization and increasing costs for outpatient care are explained by the shift from inpatient care to outpatient care (19). This has also been shown from the Norfolk Arthritis Register, where direct costs were more than doubled over a period of ten years. Outpatient care increased and inpatient care decreased, but the large increase in costs was mainly due to the use of biologics (20).

The proportion of patients undergoing surgery was basically similar in the two cohorts. Some studies have reported decreasing surgery in recent years. Nikiphoro et al. reported declining rates of hand and foot surgery, while total joint replacements remained unchanged and a Swedish study reported decreasing total joint replacements in hips, but increasing replacements in knees (21,22). We had one total joint replacement in the first cohort and two in the second. Our study covers however only the first year after diagnosis and allows limited conclusions. Surgery is an important outcome, especially concerning total joint replacements, but must be evaluated over longer periods. It is also likely that the total joint

replacements during the first year in the two cohorts could be more associated with co-existent osteoarthritis rather than with rapid joint destruction from RA alone. It was, however, remarkable that all surgery in T2 was performed only in women.

Prescription of DMARDs differed between the cohorts and the time between diagnosis and initiation of DMARDs was substantially shorter in T2. Duration of symptoms prior to study entry was ≤1 year in both studies and at inclusion, no patients were on DMARDs. At the first clinical assessment, i.e. time point of inclusion, less than 50% of patients in T1 were prescribed DMARDs compared to more than 90% of patients in T2. Prescription levels increased during the first year in T1, but were still below 80% at one-year follow-up, while prescription in T2 was more than 90% during the whole period. Most studies emphasize that DMARDs should be started as soon as the diagnosis is set (23). In a recent Norwegian study, the time from diagnosis to DMARD start decreased from average 10 months in 2000 to 10 days in 2010, and this led to a substantial increase in remission rates (24). Besides the increased use of MTX, there has also been a gradual increase in average doses, from 7,5-15 mg/week up to 20-30 mg/week (25). Total costs for DMARDs were higher in T2, but costs were also higher for steroids, osteoporosis drugs, folic acid and drugs for cardiovascular diseases. Similar results are presented in a German study, reporting increased drug costs in 2002 compared to 1997-98 (26). Increased use of steroids was also shown in a recent Norwegian study (24), suggesting increased adherence to EULAR recommendations (27). The increased usage of folic acid could be associated with the increased prescription of MTX as supplementation, and has also been shown by others (24). By contrast, costs for gastroprotectors were lower in T2, mainly due to prices being lowered. Costs for NSAIDs were also lower, due to frequent prescription of selective NSAIDs, COX-2 inhibitors, in T1, while cheaper non-selective NSAIDs were more common in T2.

Sick leave decreased in T2, but was offset by higher disability pension resulting in unchanged loss of productivity. This is in line with a number of previous studies. Poulakka et al. reported decreasing sick leave and corresponding increases in disability pension during 4 years after diagnosis (28). A Swedish study reported a decrease in sick leave days from 118 to 35 while disability pension days increased from 29 to 81 during 4 years after diagnosis (29). Similar results were presented from France, where sick leave days decreased from 44 to 13 and disability pension days tripled from 10 to 33 (30).

Huscher et al. reported that direct costs increased from €4914 to €8206 for patients <65 and from €4100 to €6221 for patients >65. This is higher than our costs, basically due to a large use of biologics, with 25.2% of their patients being prescribed these drugs (31). Total indirect costs were however roughly unchanged over 10 years, as was also the case in our study. In a review, based on 26 studies until 2007, direct costs were on average €4170 and indirect costs €8452 (32). Direct costs are in line with costs in T1, but our indirect costs are higher. In a recent Swedish study, mean annual cost for patients <65 was €6090 for sick leave, which is lower than our €8601, while costs for disability pension, €6202, is comparable to ours, €6505 (33). In our first cohort, direct costs made up for 29% and indirect costs 71% of total costs and in the second cohort, 37% and 63% respectively. In the study by Eriksson et al. including only patients <65, the differences were larger. Despite increasing costs for biologics, indirect costs in their study still made up for almost 73% of total costs. However, restricting our indirect costs to patients <65, our average indirect costs increase with approximately €6000, and this makes our proportions almost identical, approximately 72% and 28% (33).

The patients in the two cohorts are enrolled from rheumatology units corresponding to a catchment area of one million inhabitants, with incidence and mortality rates of RA very close to average rates in Sweden, increasing the generalizability within the country (34). The possibility of extrapolating data elsewhere may however be limited by the various structures of health care systems in different countries, making plain comparisons between studies difficult. Disability rates may differ depending on availability, levels of remuneration and

access to health care. In Sweden, all persons are included in the national tax funded health insurance system with universal access to health care and except for minor annual co-payments, all prescription medications, including biologic drugs, are free of charge and there are no formal restrictions for drug prescriptions (35). The health insurance system allows all persons aged 16-64 sick leave benefits when they are unable to work due to illness or injury. If inability to work persists >1 year and is considered to be permanent, disability pension will be granted.

The strength of the present study is our unique possibility to compare two cohorts of patients included from basically the same catchment area, 10 years apart and analyze development of disease activity with respect to changes in cost components during the first year after diagnosis. A drawback is the loss of patients with complete health economic data at 1 year follow-up. There were, however, no significant differences at baseline between patients with and without health economic data.

To conclude, the present study reflects the development in Sweden over the recent decade and demonstrates a substantial improvement of the disease, with lower disease activity and better functional capacity. The increasing direct costs were partly offset by decreasing sick leave, but disability pension increased and total costs remained unchanged.

Funding:
This work was supported by grants from the Medical Research County Council of South-East Sweden (FORSS) and the County Council in Östergötland. The authors do not have any financial support from commercial sources or any other financial interests, which could create a potential conflict of interest with regard to the work.

REFERENCES

1.Lenssinck ML, Burdorf A, Boonen A, Gignac MA, Hazes JM, Luime JJ. Consequences of inflammatory arthritis for workplace productivity loss and sick leave: a systematic review. Ann Rheum Dis 2013;72:493-505.

2.Hallert E, Husberg M, Jonsson D, Skogh T. Rheumatoid arthritis is already expensive during the first year of the disease (the Swedish TIRA project). Rheumatology 2004;43:1374-82.

3.Kavanaugh A. Economic consequences of established rheumatoid arthritis and its treatment. Best Pract Res Clin Rheumatol 2007;21:929-42.

4.Gulfe A, Kristensen LE, Saxne T, Jacobsson LT, Petersson IF, Geborek P. Rapid and sustained health utility gain in anti-tumour necrosis factor-treated inflammatory arthritis: Observational data during 7 years in southern Sweden. Ann Rheum Dis 2010;69:352-7.

5.Hallert E, Husberg M, Kalkan A, Skogh T, Bernfort L. Early rheumatoid arthritis 6 years after diagnosis is still associated with high direct costs and increasing loss of productivity: the Swedish TIRA project. Scand J Rheumatol 2014;43:177-83.

6.Smolen JS, Han C, van der Heijde D, Emery P, Bathon JM, Keystone E et al. Infliximab treatment maintains employability in patients with early rheumatoid arthritis. Arthritis Rheum 2006;54:716-22.

7.Kimel M, Cifaldi M, Chen N, Revicki D. Adalimumab plus methotrexate improved SF-36 scores and reduced the effect of rheumatoid arthritis (RA) on work activity for patients with early RA. J Rheumatol 2008;35:206-15.

8.Kavanaugh A, Smolen JS, Emery P, Purcaru O, Keystone E, Richard L et al. Effect of certolizumab pegol with methotrexate on home and work place productivity and social activities in patients with active rheumatoid arthritis. Arthritis Rheum 2009;61:1592–600.

9.van Vollenhoven RF, Geborek P, Forslind K, Albertsson K, Ernestam S, Petersson IF et al. Conventional combination treatment versus biological treatment in methotrexate-refractory early rheumatoid arthritis: 2 year follow-up of the randomised, nonblinded, parallel-group Swefot trial. Lancet 2012;379:1712-20.

10.Kalkan A, Hallert E, Bernfort L, Husberg M, Carlsson P. Costs of rheumatoid arthritis during the period 1990-2010: a register-based cost-of-illness study in Sweden. Rheumatology 2014;53:153-60.

11.Rantalaiho V, Kautiainen H, Korpela M, Hannonen P, Kaipiainen-Seppänen O, Möttönen M et al. Targeted treatment with a combination of traditional DMARDs produces excellent clinical and radiographic long-term outcomes in early rheumatoid arthritis regardless of initial infliximab. The 5-year follow-up results of a randomised clinical trial, the NEO-RACo trial. Ann Rheum Dis 2014;73:1954-61.

12.Hallert E, Husberg M, Skogh T. Costs and course of disease and function in early rheumatoid arthritis: a 3-year follow-up (the Swedish TIRA project). Rheumatology 2006; 45:325-31.

13.Arnett FC, Edworthy SM, Bloch DA, McShane DJ, Fries JF, Cooper NS et al. The American rheumatism association 1987 revised criteria for the classification of rheumatoid arthritis. Arthritis Rheum 1988,31:315-324.

14.Prevoo MLL, van´t Hof MA, Kuper HH, van Leeuwen MA, van de Putte LBA, van Riel PL. Modified disease activity scores that include twenty-eight-joint counts. Arthritis Rheum 1995;38:44-8.

15.Ekdahl C, Eberhardt KB, Andersson SI, Svensson B. Assessing disability in patients with rheumatoid arthritis. Scand J Rheumatol 1998;17:263-71.

16.The EuroQol group. The EuroQol: a new facility for the measurement of health-related quality of life. Health Policy 1990;16:199-208.

17.Thompson SG, Barber JA. How should cost data in pragmatic randomised trials be analysed? BMJ 2000;320:1197–200.

18.Sokka T. Increases in use of methotrexate since the 1980s. Clin Exp Rheumatol 2010 (61):S13-20.

19.Petersson IF. Team care.Traditions and new trends. J Rheumatol 2006;33:1895-6.

20.Nikiphorou E, Davies C, Mugford M, Cooper N, Brooksby A, Bunn DK et al. Direct Health Costs of Inflammatory Polyarthritis 10 Years after Disease Onset: Results from the Norfolk Arthritis Register. J Rheumatol 2015;42:794-8.

21.Nikiphorou E, Carpenter L, Morris S, Macgregor AJ, Dixey J, Kiely P et al. Hand and foot surgery rates in rheumatoid arthritis have declined from 1986 to 2011, but large-joint replacement rates remain unchanged: results from two UK inception cohorts. Arthritis Rheumatol 2014;66:1081-9.

22.Hekmat K, Jacobsson L, Nilsson JA, Petersson IF, Robertsson O, Garellick G et al. Decrease in the incidence of total hip arthroplasties in patients with rheumatoid arthritis - results from a well-defined population in south Sweden. Arthritis Res Ther 2011;13:R67.

23.Singh JA, Furst DE, Bharat A, Curtis JR, Kavanaugh AF, Kremer JM et al. 2012 update of the 2008 American College of Rheumatology recommendations for the use of disease-modifying antirheumatic drugs and biologic agents in the treatment of rheumatoid arthritis. Arthritis Care Res 2012;64: 625-39.

24.Aga AB, Lie E, Uhlig T, Olsen IC, Wierød A, Kalstad S et al. Time trends in disease activity, response and remission rates in rheumatoid arthritis during the past decade: results from the NOR-DMARD study 2000-2010. Ann Rheum Dis 2015;74:381-8.

25.Visser K, van der Heijde D. Optimal dosage and route of administration of methotrexate in rheumatoid arthritis: a systematic review of the literature. Ann Rheum Dis 2009;68:1094-9.

26.Kirchhoff T, Ruof J, Mittendorf T, Rihl M, Bernateck M, Mau W et al. Cost of illness in rheumatoid arthritis in Germany in 1997-98 and 2002: cost drivers and cost savings. Rheumatology 2011;50:756-61.

27.Gorter SL, Bijlsma JW, Cutolo M, Gomez-Reino J, Kouloumas M, Smolen JS et al. Current evidence for the management of rheumatoid arthritis with glucocorticoids: a systematic literature review informing the EULAR recommendations for the management of rheumatoid arthritis. Ann Rheum Dis 2010;69:1010-4.

28.Puolakka K, Kautiainen H, Pekurinen M, Möttönen T, Hannonen P, Korpela M et al. Monetary value of lost productivity over a five year follow up in early rheumatoid arthritis estimated on the basis of official register data on patients' sickness absence and gross income: experience from the FIN-RACo trial. Ann Rheum Dis 2006; 65: 899-904.

29.Neovius M, Simard JF, Askling J; ARTIS Study Group. How large are the productivity losses in contemporary patients with RA, and how soon in relation to diagnosis do they develop? Ann Rheum Dis 2011;70:1010-5.

30.Dadoun S, Guillemin F, Lucier S, Looten V, Saraux A, Berenbaum F et al. Work productivity loss in early arthritis during the first 3 years of disease: a study from a French National Multicenter Cohort. Arthritis Care Res 2014;66:1310-8.

31.Huscher D, Merkesdal S, Thiele K, Zeidler H, Schneider M, Zink A; German Collaborative Arthritis Centres. Cost of illness in rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis and systemic lupus erythematosus in Germany. Ann Rheum Dis 2006;65:1175-83.

32.Franke LC, Ament AJ, van de Laar MA, Boonen A, Severens JL. Cost-of-illness of rheumatoid arthritis and ankylosing spondylitis. Clin Exp Rheumatol 2009;27(4 Suppl 55):S118-23.

33.Eriksson JK, Johansson K, Askling J, Neovius M. Costs for hospital care, drugs and lost work days in incident and prevalent rheumatoid arthritis: how large, and how are they distributed? Ann Rheum Dis 2015;74:648-54.

34.Neovius M, Simard JF, Askling J; ARTIS study group. Nationwide prevalence of rheumatoid arthritis and penetration of disease-modifying drugs in Sweden. Ann Rheum Dis 2011;70:624-9.

35.Kalkan A, Roback K, Hallert E, Carlsson P. Factors influencing rheumatologists' prescription of biological treatment in rheumatoid arthritis: an interview study. Implement Sci 2014:11; 153-5.