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This is an electronic version of an article published in:

Husberg, M., Bernfort, L., Hallert, E., (2018), Costs and disease activity in early rheumatoid arthritis in 1996-2000 and 2006-2011, improved outcome and shift in distribution of costs: a two-year follow-up, *Scandinavian Journal of Rheumatology*, 47(5), 378-383.

<https://doi.org/10.1080/03009742.2017.1420224>

Original publication available at:

<https://doi.org/10.1080/03009742.2017.1420224>

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Costs and disease activity in early rheumatoid arthritis in 1996-2000 and 2006-2011, improved outcome and shift in distribution of costs: a 2-year follow-up.

Short title: Costs and disease activity in early RA

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ABSTRACT:

Objective: To evaluate changes in healthcare utilization, costs and disease activity from 1996 to 2011 for patients with early rheumatoid arthritis (RA).

Methods: Two cohorts of patients with early RA, included 1996-1998 (T1) and 2006-2009 (T2) were followed regularly and healthcare utilization, costs and disease activity was compared between the cohorts during 2 years after diagnosis.

Results: Disease activity was significantly improved in T2 vs T1. Drug costs increased in T2, €911 vs €535 in T1 ($p=0.017$) and costs for RA-related hospitalization decreased. More than 90% in T2 were prescribed DMARDs at inclusion compared to 50% in T1. At 2-year follow-up, levels were still >90% in T2, while corresponding values in T1 were just above 70%. Total direct costs were slightly higher in T2, €3941 vs €3364 in T1 (ns). Sick leave decreased in T2, €3511 vs €5672 in T1 ($p=0.025$) while disability pension increased slightly, €4889 in T2 vs €4244 in T1 (ns), but total indirect costs remained unchanged, €8400 in T2 vs €9916 in T1 (ns). Total direct and indirect costs did not differ between the cohorts, €12342 in T2 vs €13280 in T1 (ns) and loss of productivity still represented the largest component of total costs.

Conclusion: T2-patients were prescribed DMARDs earlier and more aggressively than T1-patients and a stable and better improvement in disease activity, function and quality-of-life was achieved in T2 compared to T1. There was a shift within the components in direct costs and indirect costs, but total costs remained essentially unchanged.

Key words:

early rheumatoid arthritis, disease activity, cost-of-illness, DMARDs, cohort studies

Rheumatoid arthritis (RA) imposes substantial burden to patient and to society (1-3). We have followed a cohort (Swedish acronym TIRA1, T1) with early (≤ 1 year) RA, enrolled 1996-1998 and evaluated disease activity and costs (2). A new cohort (T2) was established 2006-2009 and followed similarly. During year one, both cohorts improved, but T2 to a larger extent (4). Given the paradigm shift in RA-treatment, comprising not only biological drugs, but also early, aggressive treatment with traditional DMARDs in double and triple combinations, our intention was to calculate costs and evaluate consequences in real life over two years, for patients included during two periods with different treatment regimes.

Method

Patients

T1-cohort (320 patients) was recruited 1996-98 and T2-cohort (463 patients), 2006-09. Patients fulfilled $\geq 4/7$ of 1987 ACR-criteria *or* morning stiffness ≥ 60 minutes, symmetrical arthritis and small joint arthritis.

Clinical assessments

Clinical data was collected regularly, described elsewhere (2). Briefly, tender and swollen joint counts, erythrocyte sedimentation rate (ESR) and patient's global assessment were assessed and 28-joint count disease activity score (DAS28) calculated. C-reactive protein (CRP) was analyzed and patients reported pain and completed Health Assessment Questionnaire (HAQ).

Health economic questionnaire

Patients reported outpatient visits, hospital admissions, surgery and medication. Days with sick leave or disability benefits were reported and EuroQol-5D (EQ5D) and EQ-VAS was completed.

Costs

Costs for outpatient visits and surgery were calculated using official tariffs (www.skl.se) (www.socialstyrelsen.se) and drugs, market wholesale prices (www.fass.se). Indirect costs were calculated, using average productivity cost of full-time workers (www.scb.se). A societal perspective was applied, including all costs, regardless payer. Costs were inflation-adjusted to 2016, using Swedish Consumer Price Index (CPI), converted to €2016, €1=9.47 SEK (www.riksbank.se).

Statistics

Results are presented as means or numbers and proportions. Differences were analyzed by Student's t-test or chi-square test. Mean values were used, as relevant measure for cost data (13). As some cost distributions were skewed, bootstrapping with 5 000 replications with 95% CI (confidence interval from bootstrapped samples) was performed.

Ethical considerations

Patients gave written informed consent and the study protocol was approved by ethics committee, Dnr 96035, Liu 262/96-14, M168-05.

Results

Patients

At month 12, 276/320 (86%) patients remained in T1 and month 24, 254/320 (79%) and in T2, 340/463 (73%) and 286/463 (62%) respectively. Patients were lost for having difficulties with transportation, moving etc. Some remained in the clinical study, but declined to participate in the health economic part because of "too many questionnaires". Clinical characteristics at baseline were similar in patients with and without health economic data and there were no differences in education, marital status, sick leave and disability pension

between patients in the study and patients lost to follow-up. Except for age and education, socioeconomic variables were similar (table 1).

Table 1. Baseline characteristics of patients in T1 and T2 remaining in the study at 2-year follow-up and p-value for differences between the cohorts, mean (sd) unless otherwise stated. Significant p-values in bold.

	T1 n=254	T2 n=286	p
Sex (female %)	70.5	71.0	0.897
Age (yrs)	55.6 (15)	59.6 (13)	0.001
cohabiting (%)	75	74	0.799
education (yrs)	10.5 (2.0)	11.0 (2.3)	0.022
SL (%)*	46.2	40.1	0.272
DP (%)	9.3	14.8	0.126
SL and/or DP (%)	51.9	50.9	0.858
DAS28	5.3 (1.2)	5.1 (1.3)	0.176
pain (VAS)	47 (25)	52 (24)	0.041
CRP	30 (28)	26 (28)	0.073
HAQ (0-3)	0.9 (0.6)	1.0 (0.6)	0.027
EQ5D (0-1)	0.61 (0.24)	0.55 (0.27)	0.019
EQ-VAS(0-100)	59 (19)	57 (20)	0.261

*including part-time sick leave and part-time DP. 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);

Disease

At inclusion, T2-patients reported worse pain, HAQ and EQ5D, but DAS28, CRP and EQ-VAS were similar. At 3-month follow-up, there was a reversal from baseline pain scores in T2 compared to T1. A similar reversal was seen in EQ5D at month 6, with 0.74 in T2, compared to 0.69 in T1 (p=0.014). All variables improved in both cohorts at 1-year follow-up, but more pronounced in T2 and this was maintained at 2-year follow-up (fig 1).

Figure1. Clinical characteristics of T1 and T2 cohorts at inclusion, at 1- and 2-year follow-up. Lower values represent improvements, except for EQ5D and EQ-VAS where higher values represent improvements. DAS28=28 joint-count disease activity score, HAQ=Health Assessment Questionnaire, CRP=C-reactive protein, EQ5D=EuroQol-5D, EQ-VAS=EuroQol visual analogue scale.

Direct costs

Outpatient visits were similar year 2. In T2, 20 patients (7%) had inpatient care, 2 RA-related and 18 non-RA-related. Corresponding values for T1 were 18 patients (7.1%), 8 RA-related and 10 non-RA-related. In T2, 11 patients (3.9%) had 13 surgeries, 4 total joint replacements (TJR) and 9 hand/feet surgeries, and in T1, 14 patients (5.5%) had 16 surgeries, 1 TJR and 15 hand/feet surgeries. Drug costs year 2 were higher in T2, €911 vs €535 in T1. Two T1-patients (0.7%) had biologics and 39 (9.8%) in T2. Accordingly, biologics contributed to higher drug costs in T2, but costs for steroids, anti-osteoporosis drugs, folic acid and cardiovascular disease drugs were also higher in T2 compared to T1 (table 2).

Table 2. Direct and indirect costs (€) over two years in T1 and T2, mean (sd) and p-value for differences between bootstrapped 95% confidence intervals (95%CI). Significant p-values in bold.

	Year 1				Year 2			
	T1 n=276	T2 n=340	diff (95% CI)	p	T1 n=254	T2 n=286	diff (95% CI)	p
Direct costs								
physician	1260 (803)	1418 (880)	159 (24:295)	.021	913 (772)	998 (1016)	85 (-67:237)	.278
nurse	817 (373)	985 (862)	168 (67:272)	.001	587 (438)	597 (1228)	9 (-129:173)	.908
PT, OT	1250 (1214)	1879 (2890)	629 (300:971)	.002	870 (1212)	1013 (2031)	143 (-132:419)	.319
all visits	3327 (1736)	4282 (3658)	955 (526:1398)	.000	2371 (1662)	2608 (3158)	237 (-182:658)	.271
drugs								
DMARDs	144 (326)	129 (191)	-15 (-60:24)	.507	193 (412)	189 (304)	-4 (-68:56)	.898
bDMARDs	0 (0)	217 (1419)	217 (83:378)	.033	44 (556)	404 (2050)	360 (132:618)	.017
analgesics	18 (64)	13 (51)	-5 (-15:4)	.283	22 (84)	16 (42)	-5 (-18:5)	.369
steroids	15 (22)	27 (26)	12 (8:16)	.000	15 (23)	23 (25)	8 (4:12)	.000
NSAID	111 (127)	35 (80)	-76 (-94:-59)	.000	103 (114)	24 (62)	-79 (-95:-63)	.000
osteoporosis	14 (69)	49 (113)	36 (21:50)	.000	13 (35)	50 (106)	37 (25:50)	.000
folic acid	6 (16)	23 (17)	17 (14:19)	.000	6 (17)	23 (18)	17 (14:19)	.000
CVD	23 (78)	61 (151)	38 (20:57)	.000	42 (132)	80 (170)	38 (14:64)	.003
gastroprotect	44 (140)	11 (41)	-33 (-51:-16)	.002	51 (154)	20 (75)	-30 (-52:-10)	.008
other	26 (74)	70 (231)	44 (19:71)	.009	47 (108)	81 (257)	34 (3:69)	.053
all drugs	400 (456)	634 (1510)	234 (80:409)	.023	535 (805)	911 (2143)	376 (121:658)	.017
CAM								
surgey	37 (139)	15 (63)	-21 (-40:-4)	.041	30 (118)	17 (74)	-13 (-31:3)	.131
inpat RA	89 (676)	137 (918)	49 (-75:176)	.460	164 (865)	232 (1518)	68 (-125:293)	.532
inpat non-RA	352 (1820)	45 (490)	-307 (-547:-104)	.024	192 (1317)	19 (301)	-173 (-359:-28)	.085
tot dir costs	97 (868)	146 (800)	49 (-94:174)	.502	72 (506)	155 (826)	84 (-27:200)	.166
	4301 (3328)	5260 (4337)	959 (337:1560)	.002	3364 (3271)	3941 (4771)	577 (-108:1251)	.098
Indir costs								
SL	8332(14503)	5052(11928)	-3281(-5468:-1225)	.003	5672(11904)	3511(10510)	-2161(-4077:-282)	.025
DP	1969(7934)	3821(12606)	1852(197:3522)	.031	4244(11352)	4889(14197)	645(-1535:2811)	.558
tot indir cost	10301(16194)	8872(16643)	-1428(-4092:1180)	.282	9916(16441)	8400(17553)	-1516(-4449:1289)	.294
Total costs								
tot dir+indir	14602(17260)	14133(18187)	-469(-3377:2333)	.741	13280(17158)	12342(19032)	-939(-3977:2076)	.543
Indir costs <65								
SL <65	12727 (16092)	8530 (14496)	-4196 (-7596:-815)	.016	9188 (14139)	5835 (13031)	-3353 (-6292:-298)	.030
DP <65	2429 (8824)	6056 (15657)	3628 (902:6498)	.014	6655 (13632)	8403 (17748)	1748 (-1713:5287)	.329
tot indir<65	15155 (17477)	14587 (19536)	-568 (-4654:3482)	.782	15843 (18472)	14238 (20997)	-1605 (-5925:2825)	.469

PT/OT=physiotherapist and occupational therapist, all visits=total costs for outpatient care visits (physician, nurse, PT,OT), DMARD=disease-modifying anti-rheumatic drug, bDMARD=biological DMARD, NSAID=non-steroidal anti-inflammatory drug, osteoporosis=anti-osteoporosis drugs, CVD=cardiovascular disease, gastroprotect=gastroprotective drugs, CAM=complementary medicine, in-pat RA=inpatient care RA-related, in-pat non-RA=inpatient care non-RA-related, SL=sick leave, DP=disability pension, indir=indirect costs, dir+indir=direct and indirect costs, <65=patients below 65 years of age.

Prescription of disease-modifying anti-rheumatic drugs (DMARDs) differed substantially. At inclusion, 92.8% of T2 were prescribed DMARDs compared to only 49.5% in T1. Gradually, T2-patients were provided with DMARDs in double and triple combinations while this was

uncommon in T1. DMARD-prescription in T2 remained consistently >90%. At 3-month follow-up, prescription in T1 was almost 75%, but never reached T2-levels. In fact, DMARD-prescription in T1 even decreased slightly and amounted to 72.5% year 2.

Indirect costs

Sick leave was lower year 2 in T2 compared to T1, while disability pension was slightly higher resulting in lower, but non-significant, loss of productivity in T2.

Discussion

The improvements year one were more pronounced in T2 and were maintained in year two. Improvements in T1 remained basically unchanged and accordingly, T2-patients achieved better health status. Some T2-patients had biological drugs, but maybe more important was the fact that DMARD-treatment in T2 was initiated earlier and more aggressively. At inclusion, >90% of T2-patients were prescribed DMARDs compared to 50% in T1. DMARD-prescription increased in T1, but never reached T2-levels. The results are in line with a study, comparing cohorts from 1990s and 2000s, where 26% in the 1990s were prescribed DMARDs and 65% in the 2000s (6).

Previous studies have shown that early DMARD-treatment has improved outcome and working capacity compared to later treatment (7,8). Hence, the early aggressive use of traditional DMARDs in T2 might be of similar importance as the availability of biological drugs (9,10). Drug costs were higher in T2, due to biologic drugs but also due to increased prescription of other drugs. Kirchhoff et al reported similar results with increasing costs for biologics but also for steroids and anti-osteoporosis drugs, comparing 1997-98 with 2002 (11). They reported higher costs for NSAIDs, analgesics and gastroprotectors, while those costs were lower in our study. Our prices for gastroprotectors were lowered in 2009-10 and NSAIDs were also more expensive earlier due to use of the selective COX-2 inhibitors, which later on were replaced by cheaper non-selective NSAIDs (www.fass.se). Prescription of cyclosporine and gold was common in T1, while MTX was more common in T2 and this lowered average DMARD costs.

The decrease in hospitalization is not surprising since there has been shift from hospitalization to outpatient care. For instance, hospital days in Sweden due to RA were almost 103 000 in 1996 and approximately 35 000 one decade later (12). The decrease in hospitalization for all diagnoses was lower, approximately 13% and this may explain why RA-related hospitalization decreased in T2 while non-RA-related hospitalization was still high. (www.socialstyrelsen.se).

Surgery was more extensive in T2. Previous studies have presented similar results with decreasing hand and foot surgery, while TJR remain unchanged (13). Some TJR could be due to osteoarthritis but improved outcome of the disease may encourage patients to demand TJR, in order to achieve improved function.

There was shift within distribution of costs in T2 compared to T1. Drug costs increased, counterbalanced by reduced hospitalization, but total direct costs remained comparable. Birnbaum et al report similar changes 1997-2006 with increased drug costs, reduced hospitalization and unchanged total direct costs (14).

A shift was also observed within distribution of indirect costs. Sick leave decreased in T2 compared to T1, while disability pension increased slightly, but total indirect costs remained comparable. Simultaneously, sick leave decreased in the general population (www.forsakringskassan.se), suggesting that sick leave also is dependent on changes in labor market and levels of reimbursement (12,15).

Disability pension also decreased in the general population (www.forsakringskassan.se). Since T2-patients had better health status, decreasing disability pension might be expected, but by contrast, disability pension in fact increased slightly. One reason could be that T2-patients were somewhat older and hence less likely to return to the workforce after sick leave. Sweden has a generous welfare system, granting disability pension if sick leave persists more than a year, especially in older patients.

Direct and indirect costs are inflation-adjusted with CPI, and this is relevant since it will measure what the resources spent on RA, could be spent on in any other sector in society (12). However, over recent years, costs in the healthcare sector have increased more than CPI, explaining why some healthcare has become more expensive despite lower volumes.

The strength of the present study is our unique possibility to compare clinical and patient-derived data in two similar cohorts of patients, included from basically the same catchment area, 10 years apart. The overall structures of health care systems differ between countries and this may limit some comparisons. A further limitation is the loss of patients with health economic data at 2-year follow-up. There were, however, no differences at baseline between patients with and without health economic data. Furthermore, all costs were based upon self-reported data and although the questionnaires were kept as diaries, recall bias cannot be ruled out.

To conclude, T2-patients were prescribed DMARDs earlier and more aggressively than T1-patients and a better improvement in disease activity, function and quality-of-life was achieved in T2. There was a shift within components in direct and indirect costs, but total costs remained essentially unchanged and loss of productivity still represented the largest component of total costs.

Key messages:

1. Prescription of DMARDs was earlier and more aggressive in 2006-09 vs 1996-08
2. Health status was significantly improved in the 2006-09 cohort vs the 1996-08 cohort
3. There was a shift within cost components, but total costs remained unchanged.

Acknowledgements:

We thank all patients and co-workers in Eskilstuna, Falun, Jönköping, Kalmar, Lindesberg, Linköping, Motala, Norrköping, Oskarshamn, Västervik, and Örebro. We also thank Ms Ylva Billing for excellent co-operation.

Funding:

This work was supported by The County Council in Östergötland, Sweden and The Medical Research County Council of South-East Sweden (FORSS).

Disclosure statement:

The authors declare no conflicts of interest.

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