Direct and indirect healthcare costs of rheumatoid arthritis patients in Turkey

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Abstract

Objective

To estimate the annual cost of rheumatoid arthritis (RA) in Turkey by obtaining real-world data directly from patients.

Methods

In this cross-sectional study, RA patients from the rheumatology outpatient clinics of 10 university hospitals were interviewed with a standardised questionnaire on RA-related healthcare care costs.

Results

The study included 689 RA patients (565 females) with a mean age of 51.2±13.2 years and mean disease duration of 9.4±7.8 years. The mean scores of the Routine Assessment of Patient Index Data 3 and the Health Assessment Questionnaire-Disability Index (5.08±2.34 and 1.08±0.68, respectively) indicated moderate disease activity and severity for the whole group. One-third of the patients were on biologic agents and 12% had co-morbid conditions. The mean number of annual outpatient visits was 11.7±9.6 per patient. Of the patients, 15% required hospitalisation and 4% underwent surgery. The mean annual direct cost was €4,954 (median, €1,805), whereas the mean annual indirect cost was €2,802 (median, €608). Pharmacy costs accounted for the highest expenditure (mean, €2,777; median, €791), followed by the RA-related consultations and expenses (mean, €1,600; median, €696).

Conclusion

RA has a substantial economic burden in Turkey, direct costs being higher than indirect costs. Although both direct and indirect costs are lower in Turkey than in Europe with respect to nominal Euro terms, they are higher from the perspectives of purchasing power parity and gross domestic product. Early diagnosis and treatment of RA may positively affect the national economy considering the positive correlation between health care utilisations and increased cost with disease severity.

Key words

rheumatoid arthritis, healthcare cost, Turkey, economic burden of disease

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Introduction

Rheumatoid arthritis (RA) is an autoimmune chronic disease characterised by pain and swelling of the joints with eventual progress to joint damage. Restricted daily activities due to pain and disability, multiple co-morbidities, and requirements for continuous treatment have negative impact on the physical and mental functions of RA patients, and thus, RA is regarded as having one of the worst health-related quality of life scores among chronic diseases (1, 2).

Although RA is still an incurable disease, the introduction of biologic agents along with more effective treatment strategies have considerably improved the clinical expectations of the patients (3). On the other hand, the high cost of biologic agents, monitoring for adverse events, and frequent visits required for tight disease control lead to significant increases in health care utilisations and costs of RA patients (4).

Many published studies show the economic burden of RA. Societal costs of RA in the United States have been estimated to be between $19 billion and $39 billion in 2005 (5). Moreover, with approximately 3 million prevalent RA patients, the total economic impact of RA in Europe is estimated around 45 billion Euros (6, 7). The economic burden of RA will possibly increase in the future when the global shift towards an ageing population together with elevated prevalence rates of RA among the elderly is considered. Furthermore, the impact of ageing may become increasingly relevant to the burden of RA through increasing comorbidities, as they are associated with poor quality of life in RA patients (8).

To date, the economic burden of RA in Turkey has been the subject of only a few studies using the national healthcare system databases, hospital bills, price lists or expert assumptions for cost estimates (9-12). The present study aimed to estimate the annual cost of RA in Turkey by obtaining real-world data directly from the patients.

Materials and methods

The present cross-sectional study was conducted in RA patients from the rheumatology outpatient clinics of 10 tertiary care hospitals in Turkey. Patients aged ≥18 years old with a RA diagnosis according to the American College of Rheumatology (ACR) 1987 criteria (13) who were registered and treated in the rheumatology clinics in 2009 or 2010 with at least one follow-up visit.

Data were collected using a standard questionnaire between May 2011 and August 2012. The questionnaire included various questions on patient demographics (age, gender, disease duration), existing co-morbid conditions (*e.g.* cardiovascular diseases, diabetes mellitus), medication use, RA-related health care and community service utilisations, and expenditures for medical devices, home care needs, and work loss (sick leave days). This questionnaire was developed and used in Europe previously (14) and the questionnaire was tested in a sample of Turkish RA patients before the present study to assess its comprehensibility. Informed consent was obtained from all patients before the study.

For the assessment of disease activity, the Routine Assessment of Patient Index Data 3 (RAPID3), which is a solely patient-reported disease activity instrument consisting of a combination of measures for pain, function, and global assessment of disease activity, was used (15). The RAPID3 is scored on a scale of 0–10 and higher scores indicate higher disease activity. The Health Assessment Questionnaire-Disability Index (HAQ-DI) was also used for functioning (16). The HAQ-DI is scored on a scale of 0–3 and higher scores indicate worse functioning.

Direct costs consisted of inpatient and outpatient costs, costs of medications for RA, and costs for consultations by other medical specialties along with the expenses for complementary/alternative therapies (*e.g.* physiotherapy, massage, acupuncture, etc.). Indirect costs included other expenses such as for transfer to hospital, expenditures for accommodation and/or vehicle changes, purchase of special equipment like canes, shoes, utensils etc. due to RA, caregiver expenses, and costs for paid work loss (sick leave days).

Statistical analysis

Costs for outpatient care and pharmacy,

Table I. Demographic and clinical characteristics of the study participants.

All patients	n=689
Age, years, mean±SD	51.2 ± 13.2
≤65 years, n (%)	599 (87)
Females, n (%)	565 (82)
Disease duration, year, mean±SD	9.4 ± 7.8
Biologic use, n (%)	244 (35.4)
csDMARD use, n (%)	612 (88.8)
Diabetes mellitus, n (%)	81 (11.8)
Hypertension, n (%)	71 (10.3)
Allergy, n (%)	49 (7.1)
Respiratory disease, n (%)	48 (7)

csDMARDs: conventional synthetic disease-modifying drugs; SD: standard deviation.

Table II. Health care utilisations.

	n=689
Number of outpatient visits per patient, mean±SD	11.7 ± 9.6
Hospitalisation, n (%)	104 (15.1)
Hospitalisation days, mean±SD	11.7 ± 10.0
Hospitalisation >1 day, n (%)	23 (22.1)
Surgery, n (%)	28 (4.1)
Rehabilitation visits, n (%)	3 (0.4)
Joint prosthesis, n (%)	16 (2.3)
Direct graphy, n (%)	323 (46.9)
Scanning, n (%)	100 (14.5)
MRI, n (%)	44 (6.4)
Ultrasound, n (%)	81 (11.8)
EMG, n (%)	26 (3.8)
Blood test, n (%)	606 (88.0)

MRI: magnetic resonance imaging; EMG: electromyography; SD: standard deviation.

work loss, caregiver, and any other RA-related expenses (*e.g.* acupuncture, homeopathic, other) that are not covered by social insurance were collected for a 3-month period and the annual costs were calculated by multiplying these costs by 4. Additional RA-related investments were collected for a 1-year period. For work loss, current wages were taken into account and the human capital approach was used. All costs were expressed in Euros according to the exchange rate in 2011 (€1.00 = 2.3 Turkish Lira, without inflation adjustment). Pearson's correlation coefficient was used to examine the internal validity of the disease-specific measures. Spearman's rank test was used to evaluate the correlation among numerical variables.

Results

The majority (82%) of the 689 interviewed patients were female and 87% were younger than 65 years of age (Table I). The mean RAPID3 and HAQ-DI scores indicated moderate disease activity and severity for the whole group and the female patients had significantly higher RAPID3 and HAQ-DI scores than the male patients (5.17±2.32 *vs.* 4.64±2.39, p=0.0273 for RAPID3 and 1.15±0.68 *vs.* 0.77±0.63, p<0.0001 for HAQ-DI). Conventional synthetic disease-modifying drugs (csDMARDs) were the most frequently prescribed (89%) medications, followed by glucocorticoids (60%), gastroprotective agents (52%), non-steroidal anti-inflammatory drugs (NSAIDs; 43%), topical creams (12%), and analgesics (8%). One-third of the patients were on biologic agents. The use of biologic agents and csDMARDs was significantly higher among the patients ≤65 years of age than those >65 years of age (37% *vs.* 24%, p=0.0196 for biologic agents and 90% *vs.* 80%, p=0.0044 for csDMARDs). Of the patients, 12% had co-morbid conditions such as diabetes mellitus, cardiovascular diseases, allergy, and respiratory disorders.

Table II shows health care utilisations incurred by the patients such as outpatient clinic visits, hospitalisations, surgery, and various investigations. The mean number of annual outpatient visits per patient was 11.7±9.6. Hospitalisation was required for 15% of the patients during the same time period with an average hospital stay of 11.7 days. Of the patients, 4.1% underwent surgery, of which approximately 60% consisted of joint replacement operations. Blood tests (88%) were the most common laboratory investigation, followed by radiographic examinations.

Table III. Annual average direct and indirect costs of rheumatoid arthritis.

	Annual average costs Mean±SD	Median (IQR, 25th-75th percentile)
Direct costs (€)*		
Inpatient	195 ± 857	0 (0-71)
Outpatient	382 ± 428	299 (184-449)
Medications	2777 ± 3379	791 (384-5293)
RA-related consultations/expenses	1600 ± 2,836.96	696 (435-1565)
Indirect costs (€)*		
Additional RA-related cost	1677 ± 4180	87 (22-959)
Caregiver	640 ± 747	417 (174-835)
Workday loss	485 ± 1386	104 (0-290)

RA: rheumatoid arthritis; SD: standard deviation, *See text for the definition of costs.

Table III shows annual direct and indirect costs. The most significant expenditure accounted for medications (mean, €2,777), followed by other RA-related consultations (*e.g.* acupuncture, homeopathic, other) which affected 5.5% of the patients, bringing their average annual burden to €1,600. With the addition of outpatient cost (mean, €382) and inpatient cost (mean, €195), the mean total annual cost per patient was estimated as €4,954 (median, €1,805). For indirect RA costs, costs due to work loss, additional RA-related costs, and caregiver costs were evaluated. The additional RA-related costs, such as purchase of a new car, accommodation or special equipment, constituted the most significant percentage of indirect costs. This cost was spent by 6% of the patients accounting for €1,677 in 1 year. Of the patients, 14% were employed and 62% had employer permitted sick leave (annual average of 27 days) costing €485 annually. Finally, the mean annual out-of-pocket cost for caregivers was estimated as €640.

Direct and indirect costs according to the HAQ-DI scores (<0.6, 0.6–1.1, 1.1–1.6, 1.6–2.1, >2.1) are summarised in Table IV. There was a positive significant correlation between HAQ scores and total direct costs (Spearman's rho=0.076, p<0.05).

Discussion

Rheumatoid arthritis is a chronic, progressive disease that brings substantial medical and economic burden on patients, health services, and caregivers (17). According to various studies, the average annual cost per RA patient appears to be around €13,000 in Europe

Table IV. Direct and indirect costs according to the Health Assessment Questionnaire-Disability Index.

Parameters	HAQ-DI Scores				
	<0.6 n=192	0.6-<1.1 n=163	1.1-<1.6 n=171	1.6-<2.1 n=105	≥2.1 n=57
Direct costs (€)					
Inpatient	278 ± 1,197	178 ± 699	209 ± 796	69 ± 266	160 ± 780
Outpatient	411 ± 639	377 ± 401	354 ± 228	399 ± 290	358 ± 276
Medications	2,457 ± 3,147	2,480 ± 3,300	2,707 ± 3,336	3,668 ± 3,784	3,195 ± 3,462
RA-related consultations	1,017 ± 1,048	915 ± 981	2,799 ± 4,511	1,058 ± 1,390	817 ± 507
Total	3,194 ± 3,456	3,063 ± 3,452	3,483 ± 3,935	4,206 ± 3,958	3,770 ± 3,853
Indirect costs (€)					
Additional RA-related costs	2,895 ± 4,749	947 ± 1,314	392 ± 768	585 ± 982	3,695 ± 7,514
Caregiver	558 ± 463	393 ± 329	653 ± 670	665 ± 951	1,059 ± 1,188
Workday loss	170 ± 381	273 ± 358	1,135 ± 2,778	1,504 ± 1,842	2,389 ± 3,232
Total	549 ± 1,720	466 ± 714	921 ± 1,779	967 ± 1,604	2,809 ± 5,751

Data are presented as mean±standard deviation. HAQ-DI: Health Assessment Questionnaire-Disability Index

Table V. Rheumatoid arthritis-related costs in four Europe countries and in Turkey according to nominal Euros, 2011 Euros, purchasing power parity (Dollars), and ratio to gross domestic product per capita.

	Costs in nominal €s			Costs in 2011 €s			Costs in 2011 PPP$s			Costs / GDP per capita (%)		
	Direct	Indirect	Total	Direct	Indirect	Total	Direct	Indirect	Total	Direct	Indirect	Total
Germany	8.206	9.754	17.960	8.206	9.754	17.960	6.392	7.598	13.991	24%	29%	53%
Netherlands	5.058		-	6.404	-	-	5.328	-	-	17%	-	-
Belgium	3.463	6.483	9.946	4.397	8.232	12.630	3.689	6.907	10.596	13%	24%	37%
France	4.003	7.328	11.331	4.924	9.015	13.939	4.161	7.617	11.778	15%	28%	43%
Turkey	4.954	2.802	7.756	4.954	2.802	7.756	11.246	6.361	17.607	65%	37%	102%

Nominal Euros are as given in references. 2011 Euros are calculated with consumer price index, 2011 purchasing power parity (Dollars) is calculated with implied purchasing power parity conversion rates. Consumer price index, implied conversion rates and gross domestic product per capita obtained from International Monetary Fund, World Economic Outlook Database.

(6). Nearly one third of this cost is due to productivity loss and one fifth of this cost is due to inpatient and outpatient health care costs (6). On the other hand, the estimated costs vary even among European Union countries such as France (€13,939), the Netherlands (€6,404–only direct costs), and Belgium (€12,630), Germany (€17,960) which indicates that these data may not be easily adapted to other countries (18-21); note that cost figures are converted to 2011 Euros according to the consumer price index (CPI) for Belgium, Netherlands, and France. The CPI, purchasing power parity (PPP) conversion rates, and gross domestic product (GDP) per capita figures used in calculations are obtained from the International Monetary Fund, World Economic Outlook database (22).

Until now, four studies investigated the economic burden of RA in Turkey (9-12). In the first study, data were obtained from hospital bills and price lists and annual costs were estimated around €2,669 (9). In the second study, estimates were based on an expert panel and direct cost values were calculated as €2,917 (10). Although expert panels provide useful information, they are open to unavoidable biases and the consensus reached by the panel may reflect a compromise. The third study used the national health insurance database and direct health care costs for RA ranged between €1,425 and €3,276, depending on disease severity levels (11). The patients in that study apparently had higher RA severity levels with high biological usage. The fourth study used national claims database and found annual health care costs as €2,385 for established cases and €2,000 for new cases (12).

The estimated direct cost for RA in the present study was €4,954. Our estimate for annual indirect cost (€2,802) was lower than that of a previous study estimating the indirect cost as €7,059 (10). This may be explained by the fact that our study did not consider costs of early retirement or early death as the other study did. The average annual workday loss (€485) in our study slightly exceeded the estimate (€321.82) reported by Malhan *et al*. (10).

The main limitations of the present study were its cross-sectional design and inclusion of only patients being followed-up in tertiary health care centres. Furthermore, the wide variability between the means and medians of the costs indicated a non-homogeneous distribution of these costs among the patients. This might be related to the biologic agent use in one third of the patients. On the other hand, the present study used real-world data and assessed variables that were not previously examined in other studies, thereby allowed a thorough analysis of direct and indirect costs of RA in Turkey. The significant variability of individual patient costs indicates the need of prospective observational studies for highlighting the effect of modern therapies on direct and indirect costs. Impact of dose esca-

lation as discussed in literature may be one of the explanatory factors for the variance of the cost observed in real world setting (23). Moreover, the introduction of biosimilars into the market may further contribute to the variability in individual patient costs in future studies (24).

In conclusion, our results indicate the significant economic burden of RA in Turkey. Direct and indirect costs are lower in Turkey than in European countries. However, they are higher from the perspectives of PPP and GDP per capita (Table V). There was also a significant positive correlation between HAQ-DI scores and total direct costs, confirming that the costs increased as the disease worsened.

The positive correlation between health care utilisations and increased cost with disease severity warrants further studies aiming to reveal the effect of early diagnosis and treatment of RA on the national economy.

References

1. MATCHAM F, SCOTT IC, RAYNER L *et al*.: The impact of rheumatoid arthritis on quality of life assessed using the SF-36: a systematic review and meta-analysis. *Semin Arthritis Rheum* 2014; 44: 123-30.
2. KINGSLEY G, SCOTT IC, SCOTT DL: Quality of life and the outcome of established rheumatoid arthritis. *Best Pract Res Clin Rheumatol* 2011; 25: 585-606.
3. SMOLEN JS, ALETAHA D: Rheumatoid arthritis therapy reappraisal: strategies, opportunities and challenges. *Nat Rev Rheumatol* 2015; 11: 276-89.
4. JÖNSSON B, KOBELT G, SMOLEN J: The burden of rheumatoid arthritis and access to treatment: uptake of new therapies. *Eur J Health Econ* 2008; 8 (Suppl. 2): S61-86.
5. BIRNBAUM H, PIKE C, KAUFMAN R, MARYNCHENKO M, KIDOLEZI Y, CIFALDI M: Societal cost of rheumatoid arthritis patients in the US. *Curr Med Res Opin* 2010; 26: 77-90.
6. LUNDKVIST J, KASTÄNG F, KOBELT G: The burden of rheumatoid arthritis and access to treatment: health burden and costs. *Eur J Health Econ* 2008; 8 (Suppl. 2): S49-60.
7. RAT AC, BOISSIER MC: Rheumatoid arthritis: direct and indirect costs. *Joint Bone Spine* 2004; 71: 518-24.
8. GERYK LL, CARPENTER DM, BLALOCK SJ, DEVELLIS RF, JORDAN JM: The impact of co-morbidity on health-related quality of life in rheumatoid arthritis and osteoarthritis patients. *Clin Exp Rheumatol* 2015; 33: 366-74.
9. MALHAN S, AKBULUT LA, BODUR H, TULUNAY CF: Annual costs of rheumatoid arthritis in Turkey. *Rheumatoid Int* 2010; 30: 637-41.
10. MALHAN S, PAY S, ATAMAN S *et al*.: The cost of care of rheumatoid arthritis and ankylosing spondylitis patients in tertiary care rheumatology units in Turkey. *Clint Exp Rheumatol* 2012; 30: 202-7.
11. BASER O, BASER E, ALTINBAS A, BURKAN A: Severity index for rheumatoid arthritis and its association with health care costs and biologic therapy use in Turkey. *Health Econ Rev* 2013; 3: 5.
12. BASER O, BURKAN A, BASER E, KOSELERLI R, ERTUGAY E, ALTINBAS A: Direct medical costs associated with rheumatoid arthritis in Turkey: analysis from National Claims Database. *Rheumatoid Int* 2013; 33: 2577-84.
13. ARNETT FC, EDWORTHY SM, BLOCH DA *et al*.: The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. *Arthritis Rheum* 1988; 31: 315-24.
14. KOBELT G, WORONOF AS, RICHARD B, PEETERS P, SANY J: Disease status, costs and quality of life of patients with rheumatoid arthritis in France: The ECO-PR study. *Joint Bone Spine* 2008; 75: 408-15.
15. PINCUS T, BERGMAN MJ, YAZICI Y, HINES P, RAGHUPATHI K, MACLEAN R: An index of only patient-reported outcome measures, routine assessment of patient index data 3 (RAPID3) in two abatacept clinical trials: similar results to disease activity score (DAS28) and other RAPID indices that include physician-reported measures. *Rheumatology* (Oxford) 2008; 47: 345-9.
16. LILLEGRAVEN S, KVIEN TK: Measuring disability and quality of life in established rheumatoid arthritis. *Best Pract Res Clin Rheumatol* 2007; 21: 827-40.
17. BOONEN A, SEVERENS JL: The burden of illness of rheumatoid arthritis. *Clin Rheumatol* 2011; 30 (Suppl. 1): S3-8.
18. GUILLEMIN F, DURIEUX S, DAURÈS JP *et al*.: Costs of rheumatoid arthritis in France: a multicenter study of 1109 patients managed by hospital-based rheumatologists. *J Rheumatol* 2004; 31: 1297-304.
19. VERSTAPPEN SM, VERKLEIJ H, BIJLSMA JW *et al*.: Determinants of direct costs in Dutch rheumatoid arthritis patients. *Ann Rheum Dis* 2004; 63: 817-24.
20. WESTHOVENS R, BOONEN A, VERBRUGGEN L *et al*.: Healthcare consumption and direct costs of rheumatoid arthritis in Belgium. *Clin Rheumatol* 2005; 24: 615-9.
21. HUSCHER D, MITTENDORF T, VON HINÜBER U *et al*.: Evolution of cost structures in rheumatoid arthritis over the past decade. *Ann Rheum Dis* 2015; 74: 738-45.
22. International Monetary Fund, World Economic Outlook Database, October 2015; http://www.imf.org/external/pubs/ft/weo/2015/02/weodata/index.aspx
23. MOOTS RJ, MAYS R, STEPHENS J, TARALLO M: Burden of dose escalation with tumour necrosis factor inhibitors in rheumatoid arthritis: a systematic review of frequency and costs. *Clin Exp Rheumatol* 2015; 33: 737-45.
24. LAPADULA G, FERRACCIOLI GF: Biosimilars in rheumatology: pharmacological and pharmacoeconomic issues. *Clin Exp Rheumatol* 2012; 30 (Suppl. 73): S102-6.