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ORIGINAL ARTICLE

Diagnosis and referral of rheumatoid arthritis by primary care physician: results of a pilot study on the city of Pisa, Italy

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Abstract The aims of the present study were to evaluate, in the city of Pisa: (1) the prevalence of rheumatoid arthritis; (2) the reliability of the prevalence estimated by primary care physicians, using the rheumatologist's diagnosis as the "gold standard" and (3) the economic impact of the disease. The Tuscany registry of primary care physicians constituted the framework from which a sample of subjects was selected. The rheumatoid arthritis (RA) subjects >18 years followed by each primary care physician constituted the population studied. Each general practitioner (GP) was asked to fill out a questionnaire regarding their patients affected by RA and to send it to the tertiary rheumatologic centre, where the diagnosis was confirmed/discarded, the clinical and epidemiological data were collected in a standardized form and a number of data for the estimation of costs were gathered. The estimated prevalence of RA was 5.1 per thousand (CI, 4.4–5.7). The reliability of general practitioners in the diagnosis of rheumatoid arthritis was on the whole 69%. However, when an analysis of every physician was carried out, a high degree of heterogeneity in the prevalence of RA per physician was found. Overall, the mean annual cost per patient with RA was estimated at about 5,878 euros (€; median, 6,434 €; inter quartile range, 669–7,052 €), with a high variability mainly dependent on the degree of patient disability. More than 90% of the overall annual cost per patient was due to the medical and non-medical direct components of costs. The prevalence of RA in Tuscany seems highly comparable with similar prevalence studies in Italy. The annual cost per patient with RA was highly variable and strictly dependent on the level of disability. More than 90% of the overall cost was due to the direct burden of costs.

Keywords Clinimetrics · Economic implications · Epidemiology · Prevalence · Primary care · Quality of life · Reliability · Rheumatoid arthritis

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Introduction

Defining the prevalence of a rheumatic disease is of paramount importance not only for clinical practice and research purposes, but also for health care provision. The knowledge of a rheumatic disorder in its epidemiology and

pattern of clinical features (clinical manifestations but also severity of the disease, degree of disability, co-morbidities, etc) in a particular area also have impact on the allocation of public resources [1, 2]. RA is a chronic inflammatory disease affecting diarthroidal joints [3]. Numerous studies have shown that the prevalence of the disease is more common in northern Europe as compared with the Mediterranean area. These studies also claim that there has been a decline in the prevalence of RA over the past century [4, 5]. These discrepancies have been attributed to heterogeneity in methodologies, but true differences in ethnicity, geographic background and environmental factors have been advocated as well [4]. In Italy, prevalence rates vary from 3.3 to 4.6 per thousand [6–9]. To our knowledge, no study on the pattern of diagnosis and referral of RA by primary care physicians has been performed in the city of Pisa to date. This depends on the particular pattern of referral of patients: patients can choose where they wish to be treated, regardless of the area of residency. This makes the creation of registries particularly difficult.

The aim of the present study was to evaluate the following aspects of RA in Tuscany: (1) the prevalence of the disease, its clinical presentation and therapeutic modalities; (2) the pattern of diagnosis and referral among primary care physicians and the reliability of the prevalence estimated by primary care physicians, using the rheumatologist's diagnosis as the "gold standard" and (3) the economic impact of the disease, with its reflection on public resources.

Patients and methods

This was a multi-centre study involving the provinces of Pisa, Siena and Florence in Tuscany (Italy) and was performed in the years 2006–2007. Since the task was carried out in the province of Pisa, the present report will describe the final results of this city. The protocol was submitted and approved by each ethics committee. The Tuscany registry of primary care physicians (general practitioners (GPs)) constituted the framework from which a sample of subjects was selected. A stratified random sample of GPs was drawn. Size of municipality where GP has outpatient activity (distinguishing from municipalities with less than 4,000 inhabitants, 4,000 to 9,000 inhabitants, more than 9,000 inhabitants and Auto Representative municipality i.e. the main town of the province), use of personal computer during clinical practice (yes or no) and GP's age, as a proxy variable of length of service, (distinguishing from aged 50 or less and aged over 50) were used as stratification variables. In each stratum, GPs were selected randomly with a probability proportional to the population assigned. Considering GP's patients as a cluster, a stratified cluster sample of them was drawn. It was hypothesized that it would involve 100 general practitioners (GPs) in the three provinces, with the aim of recruiting a final number of patients between 300 and 150 (if the mean number of patients for each physician was between 500 and 1,000, and the estimated prevalence rate was 0.3%). Figure 1 shows the province of Pisa and the number of physicians assigned to each area according to the previous selection criteria.

Each primary care physician was asked to complete a standardized questionnaire for patients affected by RA. This simple questionnaire was created by two rheumatologists in accordance with a GP, with the aim of making it easy and quick to use during clinical activity. The GP was required to enumerate the RA patients followed in his clinic and, after asking for their informed consent, he registered patients for demographic and clinical data, such as the presence and number of co-morbidities and related current therapies.

Each RA-diagnosed patient was, in turn, given an appointment at the Rheumatology Unit of the University of Pisa, where the specialist confirmed/discarded the diagnosis according to the American College of Rheumatology (ACR) criteria for epidemiological studies [10] and a clinometric evaluation was performed [11–15]. Clinical and economic section of a Case Report Form (CRF) specifically drawn for patients with confirmed diagnosis were filled in respectively by the rheumatologist and the patient. Information about patient's past and current therapies, a physical examination with 44 and 28 [14, 15] joint count, swollen and tender and the Ritchie articular index [16] were collected in the clinical section of the CRF by the rheumatologist. The Health Assessment Questionnaire (HAQ), the Visual Analogue Scale (VAS) for pain and disease activity valued respectively by the doctor and the patient, and global health were assessed and registered [11, 12]. The Disease Activity Score (DAS) was calculated both with 44 joint and 28 joint counts [14, 15]. Patient's information about the number of specialist visits performed in the last year, the need to ask for help in performing housework, as well as data on the working condition and the productivity losses were filled in the economic section of the CRF by the patient himself.

Statistical analysis

The prevalence of people with rheumatoid arthritis, with a 95% confidence interval, was calculated as a weighted prevalence, with weights corresponding to the patients followed by GPs in each strata and the correspondent distribution for age and sex, starting from three samples: (1) patients claimed by GPs as RA; (2) patients claimed as RA and visited in the tertiary care centre and (3) patients visited

Town	N	%
Calci	1	5%
Capannoli	1	5%
Cascina	2	11%
Palaia	1	5%
Pisa	6	32%
Ponsacco	1	5%
Pontedera	1	5%
San Giuliano Terme	1	5%
Santa Maria a Monte	1	5%
Terricciola	1	5%
Vecchiano	1	5%
Vicopisano	2	11%
Total	19	100%

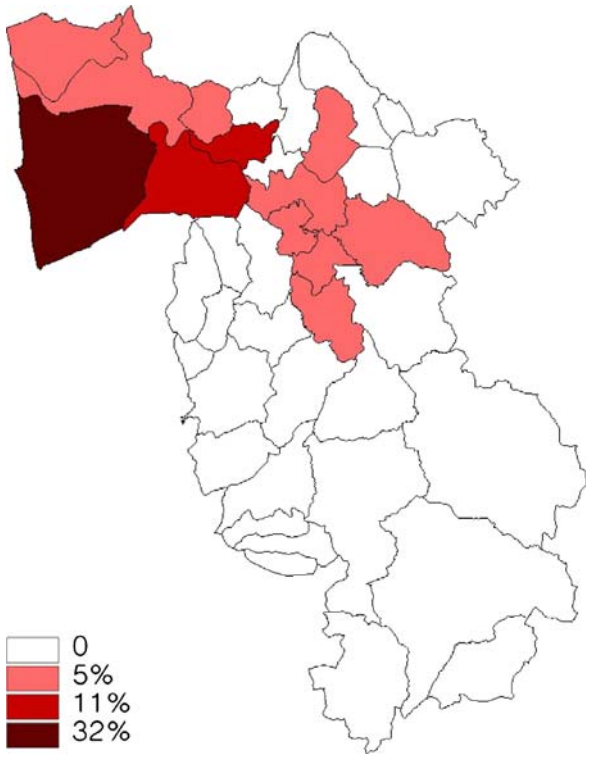

Fig. 1 Distribution of the general practitioners according to the area of the province of Pisa (data are resumed in table)

in the tertiary care centre and confirmed as true RA according to ACR criteria. The rate of concordance between the last and the second estimate of the prevalence (pertinence coefficient of prevalence) was used to calculate the final prevalence, obtained from the whole series of patients claimed as RA.

Statistical analyses of the results were carried out using Mann–Whitney test and Spearman's correlation. Qualitative variables were compared using contingency table analysis and Fisher's exact test where appropriate. Descriptive analyses were performed using the STATA software (StataCorp. 2007. Stata Statistical Software: Release 10. College Station, TX: StataCorp LP).

Estimation of costs attributable to rheumatoid arthritis

A social perspective was taken to identify the economic burden of RA and the cost of illness approach was used to estimate direct, indirect and intangible costs attributable to RA for patients with confirmed diagnosis through the bottom-up method [17]. Data collected in the clinical and economic section of the CRF, such as the patient's specialist visits, drug therapies and the need to ask for help in performing housework, as well as data on the working condition, productivity loss by the patient and the main caregiver were used to estimate respectively medical and non-medical direct costs and indirect costs. Economic information was related to the 12 months before filling in the questionnaire. The lowest fee for an *intramoenia* specialist visit was adopted. In the *intramoenia* regimen, the doctor runs his own private practice within the public hospital using the hospital's facilities. The patient pays a fee which will remunerate both the doctor and the hospital. With the *intramoenia* regimen, the patient has the possibility to choose the doctor, the date and time of the appointment and can benefit from a shorter waiting list. So the lowest fee for an *intramoenia* specialist visit represented the minimum out of pocket cost, supported by the patient, for a rheumatologist's visit. Information about disease-modifying antirheumatic drug (DMARDs) therapies, such as the name of the drug, its prescribed daily dosage, the start and finish date of the treatment, it is possible toxicity and interruption, were investigated by the clinical section of the CRF and linked to the corresponding market prices. The cost of DMARD treatment per patient per year was calculated by multiplying the daily dosage (in milligrams of active principle) of the drug for the patient by the cost per milligram of the drug and by the number of treatment days in the year of reference. The total cost of DMARD treatment for each patient per year was determined by summing the costs of the different DMARDs taken by the patient. Drugs were stratified into two groups, Group 1, corticosteroids and DMARDs and Group 2, biological DMARDs, according to the reimbursement

classes. These classes were respectively, class A, including essential drugs and for chronic disease charged to the National Health System (NHS), and class H, comprising drugs used only in hospital settings and borne by the NHS. The non-medical burden of direct costs was considered as the direct care due to RA provided by a housekeeper for the patient. The working hours requested for home cleaning, meal preparation, shopping and house work over the past year were multiplied by the hourly wage of a housekeeper based on the National Agreement for Home Labour Service [18]. Indirect costs were determined through the human capital method. Values of the productivity loss for working patients and carers were measured by multiplying the working hours lost due to RA visits over the past year by the average hourly earned income in different economic activity sectors, according to data from the National Statistics Institute survey on "Labour and Salary" [19, 20]. The replacement-cost approach was applied to non-working patients and carers, such as housewives and retirees, by evaluating their productivity losses with the current market value of a housekeeper. The yearly hours lost for RA visits were multiplied by the hourly wage of a housekeeper based on the National Agreement for Home Labour Service [18]. Intangible costs were not monetized due to lack of information about the quality of life of RA patients. Cost data are presented as arithmetic mean and median values in Euros (€) respectively for providing the total cost of RA and for taking into account the skewed distribution of cost [21]. Measure of the variation of observation about the median was calculated as the inter quartile range (IQR).

Results

Nineteen physicians from the city of Pisa and province were selected, each with a mean number of patients of 1,300 (range, 951–1,468; Fig. 1). With this procedure, a total of 26,709 inhabitants aged over 18 years were screened. Ninety patients were considered to have RA by GPs. Fifty-six patients agreed to attend the Rheumatology Unit. The diagnosis was confirmed in 34/56 (60%).

Figure 2 shows the diseases of the patients in whom the diagnosis of rheumatoid arthritis was not confirmed. The most frequent diagnosis was primary osteoarthritis (47%), followed by psoriatic arthritis (20%). Other diagnoses were connective tissue disease, spondyloarthritis, polymyalgia rheumatica and fibromyalgia.

Prevalence estimates

The prevalence estimated according to the 90 patients claimed to have RA was 7.4 per thousand; the prevalence estimated according to the 56 patients suspected to have RA was 5.8 per thousand and, finally, the prevalence estimated according to the patients confirmed by the tertiary care rheumatology centre was 4.0 per thousand (Table 1). The pertinence coefficient for the diagnosis of RA was 0.69. The estimated prevalence of rheumatoid arthritis was $0.69 \times 7.4 = 5.1$ per thousand (CI, 4.4–5.7). When an analysis of every physician was carried out, however (Table 2), a high degree of heterogeneity resulted, with a concordance between primary care physician and rheumatologist ranging from 0% to 100% and four out of 19 of the GPs (21%) showing no or little concordance with the rheumatologist's diagnosis. However, half of the GPs were reliable at 100%, and 70% showed a concordance in more than 60% of the cases.

When a sub-analysis was made and the GPs were stratified according to a number of variables, such as age, year of graduation, ownership of personal computer and geographic area (i.e. proximity to the tertiary care centre), no significant difference emerged.

Demographic and clinical data of RA patients

Table 3 shows the main demographic and clinical features of the 34 patients affected by rheumatoid arthritis. Extra-articular manifestations were present in 53% of the cases. The most common manifestation was Sicca syndrome (41%), followed by Raynaud's phenomenon (8.8%) and carpal tunnel syndrome (8.8%). Sicca syndrome was most frequent among females (52.2% females vs 18.2% males), whereas carpal tunnel syndrome prevailed in males (18.2% males vs 4.3% females). Raynaud's phenomenon was

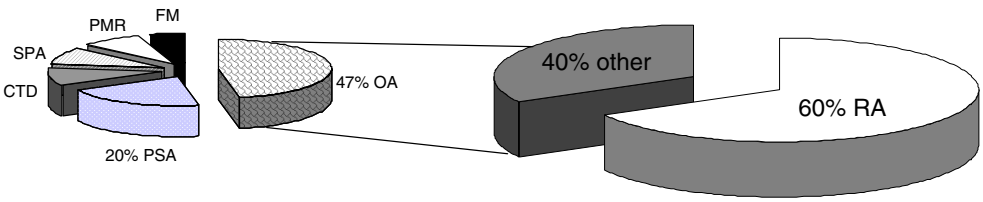

Fig. 2 Diagnosis in the patients not affected by rheumatoid arthritis

Legend to the figure: RA = Rheumatoid Arthritis, OA = Osteoarthritis, FM = Fibromyalgia, PMR = Polymyalgia Rheumatica, SPA = Spondyloarthritis, CTD = Connective Tissue Disease, PSA = Psoriatic Arthritis

Table 1 Prevalence of rheumatoid arthritis in the province of Pisa

Age	GPs diagnosis—prevalence per 1,000 adult population								Confirmed diagnosis by the tertiary care rheumatologist—prevalence per 1,000 adult population							
	Male			Female			Total		Male			Female			Total	
	Raw prevalence	Weighted prevalence	CI 95%	Raw prevalence	Weighted prevalence	CI 95%	Raw prevalence	Weighted prevalence	CI 95%	Raw prevalence	Weighted prevalence	CI 95%	Raw prevalence	Weighted prevalence	CI 95%	Raw prevalence	Weighted prevalence	CI 95%
<50 years	0.5	0.9	0.2 1.6	0.9	1.4	0.6 2.2	0.7	1.1	0.6 1.7	0.2	0.1	0.0 0.2	0.4	0.8	0.2 1.4	0.3	0.4	0.1 0.7
50–59 years	4.0	4.8	1.8 7.7	4.7	13.3	7.8 18.9	4.4	9.2	6.0 12.4	1.2	1.5	0.0 3.5	3.2	10.7	5.8 15.6	2.2	6.3	3.6 9.0
60–69 years	3.9	8.5	4.4 12.6	11.8	27.2	20.0 34.4	8.2	18.8	14.4 23.3	2.6	5.7	2.4 9.1	6.2	14.8	9.4 20.1	4.5	10.6	7.3 13.9
70–79 years	4.5	6.8	2.5 11.2	10.9	23.4	15.6 31.3	8.2	16.6	11.7 21.5	0.9	1.0	0.0 2.1	5.1	11.9	6.4 17.4	3.4	7.4	4.2 10.6
≥80 years	6.0	6.1	1.7 10.5	6.6	14.9	7.2 22.5	6.4	11.8	6.5 17.1	4.0	3.7	0.3 7.1	2.8	7.3	1.4 13.2	3.2	6.0	1.9 10.1
Total	2.1	3.5	2.5 4.5	4.6	10.8	9.2 12.4	3.4	7.4	6.4 8.3	0.9	1.4	0.8 1.9	2.4	6.3	5.0 7.6	1.7	4.0	3.2 4.7

equally distributed between both sexes. Mean body mass index revealed that the majority of patients were overweight. Figure 3 shows the main co-morbidities of the same series of patients. The most common disorders were hypertension in half of the patients and osteoporosis in 35% of the cases. Thirty-two percent of the patients were affected by osteoarthritis. It needs to be underlined that co-morbidities were most often combined and the majority of patients had two or more co-morbidities co-existing. About 30% of the patients underwent joint surgery, 18% at the hips and 21% at the knees. None of the patients underwent hand and/or feet surgery.

Assessment of the disease

The first diagnosis of rheumatoid arthritis was confirmed in the majority of the cases (85%) by a rheumatologist, in 12% of the cases by the GPs and in the remainder by an internist. In 58% of the cases, the diagnosis was made in the same year as the onset of symptoms; 93% were diagnosed within 3 years of the onset of the disease. The mean lapse time between disease onset and diagnosis was 1 year. The mean lapse time between the diagnosis of the disease and the onset of treatment was 10 months. Seventy-nine percent of the subjects started treatment in the same year as the diagnosis.

The mean value of classical DAS was 2.9, indicating moderate disease activity. The mean DAS for 28 joints was 4.0.

As regards Steinbrocker's classes [13], 26.5% of the subjects were able to perform daily living activities without limitation (class I), 32.4% were able to perform usual self-care and vocational activities but were limited in avocational activities (class II), 26.5% were able to perform usual self-care activities but were limited in vocational and avocational activities (class III) and finally, 8.8% were limited in their ability to perform usual self care, vocational and avocational activities (class IV). Reflecting these results, the Health Assessment Questionnaire [22, 23] showed a score between 0 and 1 in 52% of the subjects, 28% of the subjects scored between 1 and 2 and 20% rated between 2 and 3. The degree of functional disability, measured by the Steinbrocker's criteria, increased with the progression of the RA clinical severity, measured by the HAQ, from 0.28 in class I to 2.54 in class IV. The degree of difficulty encountered by the RA patients in tasks such as personal hygiene, take and performance of various activities worsened respectively from 0.50 in class I to 3.00 in class IV and from 0.38 in class I to 3.00 in class IV, where the score 3.00 represented "to be unable to do." No correlation between delay in diagnosis and activity and severity of the disease and functional status was found.

Table 2 Analysis of the estimated prevalence in each general practitioner who participated in the study

GP's id	Strata			Confirmed/Visited (%)[d]	GP's prevalence[e]
	Population[a]	Personal computer[b]	GP's age[c]		
1	<4,000	Yes	>50	100	6.2 (3.38–9.02)
2	<4,000	Yes	>50	61	7.0 (4.06–9.90)
3	>9,000	No	≤50	100	5.2 (1.17–9.25)
4	>9,000	No	>50	100	1.4 (0.10–2.65)
5	>9,000	No	>50	33	4.2 (1.64–6.82)
6	>9,000	Yes	≤50	73	4.0 (0.37–7.57)
7	>9,000	Yes	>50	100	2.5 (0.81–4.24)
8	>9,000	Yes	>50	100	1.4 (0.06–2.69)
9	>9,000	Yes	>50	100	2.9 (1.18–4.56)
10	4,000–9,000	No	≤50	100	3.2 (0.45–5.87)
11	4,000–9,000	No	>50	0	3.5 (0.00–7.09)
12	4,000–9,000	Yes	≤50	77	2.7 (0.21–5.14)
13	4,000–9,000	Yes	>50	26	8.8 (3.63–14.06)
14	AR	No	≤50	100	2.5 (0.17–4.82)
15	AR	No	>50	100	3.4 (0.59–6.12)
16	AR	Yes	≤50	46	1.4 (0.15–2.61)
17	AR	Yes	>50	79	3.9 (1.85–6.02)
18	AR	Yes	>50	68	3.1 (1.29–4.84)
19	AR	Yes	>50	63	2.7 (1.04–4.30)

[a] Size of the municipality where GPs have outpatient activity: less than 4,000 inhabitants, from 4,000 to 9,000 inhabitants, more than 9,000 inhabitants, Auto Representative municipality

[b] Use of personal computer for clinical practice

[c] GP's age: aged 50 or less, aged over 50

[d] Percentage of patients visited and confirmed as true RA

[e] Estimated prevalence per 100 adult patients claimed as RA

Therapeutic modalities

Figure 4 shows the therapeutic modalities performed in the past before the assessment of the patients and Fig. 5 shows the current therapies taken by the patients. The first line therapies were most often corticosteroids ± antimalarials followed by methotrexate, sulfasalazine, leflunomide and other medications (such as gold salts and cyclosporine-A). Biologic drugs and in particular anti-TNF were the least prescribed.

In 10% of the cases, disease-modifying anti-rheumatic drugs (DMARDs) were stopped for drug toxicities, in 8% for non-efficacy and in 4% for loss of efficacy. Drug toxicity was most evident for gold salts; the type of adverse effect was mainly related to leucopoenia and abnormal liver function tests. When the patients were divided according to referral (i.e. tertiary centre versus local rheumatologist), no differences emerged in therapeutic modalities, except for a more frequent use of combination therapy in the tertiary care centre.

Table 3 Main epidemiological and clinical features of RA patients

	n=34	(100%)
Sex		
Female	23	(67.6)
Male	11	(32.4)
Age (years)[a]		66.5 (40–86)
Disease duration (years)[a]	14 (0.5–63)	
BMI	28 (18–38)	
Extra-articular manifestations:	18	53%:
Sicca syndrome	14	41
Raynaud's phenomenon	3	8.8
Carpal tunnel syndrome	3	8.8
Cutaneous vasculitis	1	2.9

Mean±standard deviation

BMI body mass index

[a] Mean and range

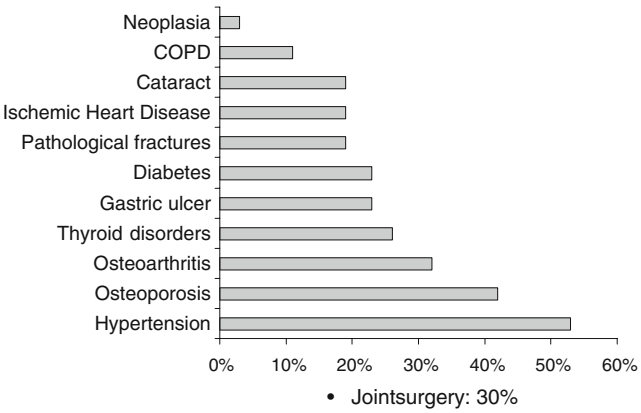

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Fig. 3 Comorbidities in the patients affected by rheumatoid arthritis

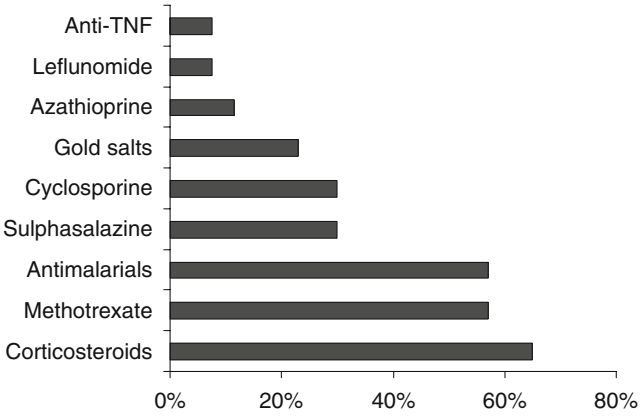

Fig. 4 Past therapies (therapies performed before the assessment) of the patients affected by rheumatoid arthritis

Economic implications

Twenty-seven (79.4%) of the 34 patients with confirmed RA diagnosis underwent at least one specialist visit over 12 months (Table 4). Considering that the lowest *intramoenia* fee for a rheumatologist's visit was 90 €, the patient's out of pocket mean expenditure was 177 € (median, 90 €; IQR, 90–270 €), for being visited at an average of almost twice a year. At least one drug for the treatment of RA among corticosteroids and DMARDs, as methotrexate, antimalarials, sulfasalazine, cyclosporine and leflunomide, was assumed by 29 (85.3%) patients over the period of study. The mean cost of treatment with corticosteroids and DMARDs was 743 € (median, 533 €; IQR, 108–734 €) per patient per year with a minimum cost of 30 € and a maximum cost of 4,997 € represented, respectively, by a patient assuming only corticosteroids and a patient treated with corticosteroids, antimalarials, cyclosporine and leflunomide. Two patients assumed biological DMARDs, such as adalimumab, with the same dosage and duration of treatment, in the hospital setting at a cost of 21 €, 917 per patient per year. Direct non-medical costs were valued through the domestic help for home cleaning, meal preparation, shopping and house work required by 18 (53%) patients in the year before being interviewed. It has been estimated that a patient affected by RA needs 2 h and 30 min direct domestic care each day [24]. The hourly wage of a housekeeper amounts to 6.8 € which over 1 year made a total of about 6,205 € spent by patients on direct non-medical care. Overall mean direct costs amounted to 5,682 € (median, 6,310 €; IQR, 627–6,899 €) per patient per year.

The yearly mean number of visits due to RA was 1.7 for non-working patients, such as housewives and retired people (68% of the 34 patients with a median age of 76 years), and 1.9 for patients in work (29% of the 34 patients with a median age of 53 years). The loss of productivity has been estimated for those patients who have been visited at least once a year, and it has been supposed that for each visit they lost one working day, i.e. 8 h. Mean indirect costs resulted as 206 € (median, 170 €; IQR, 85–340 €) for each of the seven working patients and 100 € (median, 54 €; IQR, 54–109 €) for each of the 19 non-working patients (Table 4). A total of 19 patients required the involvement of a carer in order to reach the hospital. Ten of the 19 carers were workers who lost a working day to drive their RA relative to a hospital visit, resulting in a mean cost of 195 € (median, 127 €; IQR, 85–340 €) per carer over 1 year. A mean cost of 109 € (median, 109 €; IQR, 54–163 €) was estimated for the nine non-working carers. The mean indirect cost per patient and carer was estimated at 242 € (median, 155 €; IQR, 109–279 €). As per studies [24, 25], in our data, the total direct and indirect costs per patient increased as the functional capacity in RA worsened with higher Steinbrocker's class results. More than a twofold increase was found in the mean direct cost from 3.036 € (median, 910 €; IQR, 627–6,739 €) in class I to 6.561 € (median, 6,528 €; IQR, 6,422–6,733 €) in class IV and in the mean indirect cost: from 161 € (median, 139 €; IQR, 109–218 €) in class I to 351 € (median, 218 €; IQR, 139–696 €) in class IV.

Discussion

A number of studies have focused on the prevalence of RA in Italy [7–9]. However, to our knowledge, none of them have analyzed the pattern of diagnosis and referral among GPs.

The prevalence of RA as diagnosed by the patients' own GP was found to be higher than in previous studies (Table 1). However, when the 56 patients who agreed to be visited were screened by the tertiary care rheumatology centre, the diagnosis was confirmed only in 60% of the cases, giving a prevalence of 4.0 per thousand, which is between the three per thousand of Cimmino [7] and 4.6 per thousand of Marotto [8] and Salaffi [9]. This figure

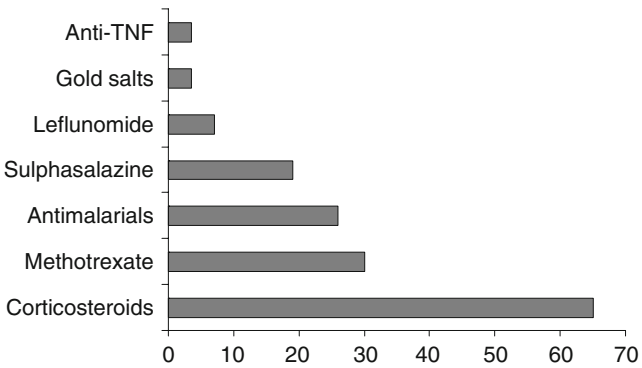

Fig. 5 Current therapies (therapies taken at the time of the assessment) of the patients affected by rheumatoid arthritis

Table 4 Direct and indirect mean costs per patient over 12 months (in Euros)

n=34		(100%)	Costs per patient/year		
			Mean	Min	Max
Direct costs					
Direct medical costs					
Diagnostics					
Specialist visits			176.7	90.0	450.0
	27	(79.4)			
Drugs					
Corticosteroids and DMARDs			742.5	30.0	4,997.1
	29	(85.3)			
Biological DMARDs			21,917.4	21,917.4	21,917.4
	2	(5.9)			
Direct non-medical costs					
Domestic help			6,205	6,205	6,205
	18	(52.9)			
Steinbrocker classes					
I			3,035.9	156.8	7,580.1
	8	(23.5)			
II			5,577.7	90.0	29,216.5
	11	(32.4)			
III			8,488.7	108.4	28,512.3
	9	(26.5)			
IV			6,561.2	6,422.5	6,733.4
	3	(8.8)			
Total direct costs			5,682.1	90	29,216.46
	32	(94.1)			
Indirect costs					
Patients					
Working status					
Working			206.1	84.9	424.4
	7	(20.6)			
Housewives/retired			100.2	54.4	272.0
	19	(55.9)			
Caregivers					
Working status					
Working			195.2	84.9	424.4
	10	(29.4)			
Housewives/retired			108.8	54.4	217.6
	9	(26.5)			
Steinbrocker's classes					
I			161.0	84.9	254.6
	5	(14.7)			
II			271.4	54.4	848.8
	10	(29.4)			
III			213.3	108.8	435.2
	8	(23.5)			
IV			351.1	139.3	696.4
	3	(8.8)			
Total indirect costs			241.5	54.4	848.8
	26	(76.5)			

increased to 5.1 per thousand when the prevalence on the whole series of supposedly RA patients was corrected according to the reliability of the GPs (see above). Table 5 shows the prevalence found in the present series as compared with other prevalence studies found in the literature [7–9, 26–43].

We have chosen to formulate an idea of the epidemiology of RA in our area with this novel approach for a number of reasons: (1) a formal study on the general population would have screened a huge number of subjects, with the need for enormous resources. We therefore decided to apply formal epidemiology to the population of GPs

Table 5 Comparison of the present study with other prevalence studies in the literature

Author (ref.)	Country	Type of study	Prevalence ($n/10^3$)			
			Total	Males	Females	Population Age (years)
Pountain 1991 [26]	Oman	Cross-sectional	3.6[a]	16		
Hakala 1993 [27]	Finland	Retrospective	8.0[a]	6.1	10	≥16
Lau 1993 [28]	China	Cross-sectional	3.5[a]			≥16
Drosos 997 [29]	Greece	Retrospective	3.5	1.9	4.5	≥16
Kvien 1997 [30]	Norway	Cross-sectional	4.4[a]	1.9	6.7	20–79
Cimmino 1998 [7]	Italy	Cross-sectional	3.3[a]	1.3	5.1	≥16
Stojacovic 1998 [31]	Yugoslavia	Cross-sectional	1.8[a]	0.9	2.9	≥20
Gabriel 1999 [32]	USA	Retrospective	10.7	7.4	13.7	≥35
Simmonson 1999 [33]	Sweden	Cross-sectional	5.1[a]			20–74
Saraux 1999 [34]	France	Cross-sectional	5.0	2.4	7.6	≥18
Power 1999 [35]	Ireland	Cross-sectional	5[a]			
Riise 2000 [36]	Norway	Retrospective	4.3[a]	2.7	5.8	≥20
Symmons 2002 [37]	UK	Cross-sectional	8.5 [a]	4.4	11.2	≥16
Carmona 2002 [38]	Spain	Cross-sectional	5[a]	2	8	≥20
Spindler 2002 [39]	Argentina	Retrospective	2.0[a]	0.6	3.2	≥16
Andrianakos 2003 [40]	Greece	Cross-sectional	7.0[a]		19	
Dai 2003 [41]	China	Cross-sectional	2.8	1.4	4.1	≥16
Akar 2004 [42]	Turkey	Cross-sectional	3.6[a]	1.5	7.7	≥20
Guillemin 2005 [43]	France	Cross-sectional	3.1	0.9	5.1	≥18
Marotto 2005 [8]	Italy	Cross-sectional	4.6	0.73	0.19	≥18
Salaffi 2005 [9]	Italy	Cross-sectional	4.6			≥18
Present study	Italy	Cross-sectional	5.1	1.4	6.3	≥18

[a] Raw prevalence

instead of to the general population. This novel approach allowed us to reduce costs as compared with classical epidemiological approach. (2) The involvement of the GPs enabled the study to facilitate an improvement of the GP's relationship with the RA specialist, guaranteeing a continuing exchange and possibly a better service to the patient. (3) The knowledge of the reliability of the GPs would allow an educational effort tailored to the single individual, reducing waste of time and public funds. We are aware that this method is largely empirical and does not provide a formal, statistically proven and comprehensive screening of the population, but we believe that with this pragmatic approach we were able to screen the clinically significant population and, finally, to mirror the patients who really need the allocation of public resources.

According to the present evaluation, the prevalence of RA in the city of Pisa appears to be comparable to the results of other prevalence studies throughout the literature, although it seems to be slightly higher than in previous studies in Italy [7–9]. The pattern of diagnosis among primary care physicians shows globally a reliability of 69%, although with a closer analysis, a high degree of heterogeneity has been observed among GPs.

Total costs were available for 32 of the 34 patients with confirmed diagnosis: the other two patients had missing cost data information for resource consumption items used to compute the total cost. The economic evaluation results agree with the scientific literature on RA showing that as the illness progressed, direct and indirect costs increased [24, 25]. In our pilot study, overall, the mean annual cost per patient with confirmed RA was estimated at about 5,878 € (±7,045 €, standard deviation) and the median annual cost per patient was 6,434 € (669–7,052 €, inter quartile range). The high variability observed suggested the different consumption of healthcare resources, such as visits and drugs as well as the different values of productivity losses observable among patients, with a small proportion of persons characterized by complications or severe level of disease absorbing additional costly treatments or requiring to leave work activities for rheumatologist visits. More than 90% of the overall annual cost per patient was due to the direct medical and non-medical burden of costs. Despite the fact that our pilot study did not take into account the important components of direct medical and non-medical costs such as hospitalizations, day hospital admissions, diagnostic tests, physiotherapy sessions and travel

expenses, it confirmed how the introduction of the biological DMARDs has led to an increase in drug costs and in medical costs as a whole and the economic burden of the informal care required by RA patients [24, 44]. Differences were observed between our indirect cost estimates and those of the existing literature; this is probably due to the lack of information in our study on patient and carer productivity losses as a consequence of RA, death or other treatment of the illness rather than visits and to the misleading imputation of the burden of direct costs, such as informal care, to indirect cost [24, 45]. In conclusion, this pilot study represents a novel approach through which we were able to screen a huge number of subjects, obtaining important information about the epidemiology of RA in the area of Pisa and preliminary data on the economic implications of the disease.

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