ORIGINAL RESEARCH

The Burden of Rheumatic Diseases: An Analysis of an Italian Administrative Database

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ABSTRACT

Introduction: Chronic inflammatory rheumatic diseases (RDs) trigger high costs for healthcare systems and society due to the disability and comorbidity associated with these disease entities. The aim of this study was to analyze patients with RD, assess the use of conventional synthetic and biologic therapies, and estimate the overall cost of treatment in Italy.

Methods: Administrative healthcare claims from the Piedmont region in Northwest Italy were reviewed to identify patients who received disease-modifying antirheumatic drugs

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(DMARDs) between 2007 and 2010. Confirmation of RD was based on: (1) diagnosis-specific exemption code; (2) hospitalization or emergency care events characterized by disease-specific ICD9 codes; (3) inclusion in the regional registry of biologic drugs. The follow-up period was 3 years.

Results: A total of 9560 subjects, of whom the majority were women (58.1%), were entered into the study; the average age of the study population was 55.3 years. On the index date 12.9% of patients were receiving a biologic DMARD, with adalimumab the most frequently prescribed biologic DMARD (4.7%), followed by etanercept (4.4%). The average total healthcare expenditure was €377.98 per patient per month (patient-month). In the subgroup analysis of healthcare costs according to use of biologics, the total expenditure was €1037.97/€230.86 patient-month for those receiving/not receiving at least one biologic DMARD. In the subgroup analysis of healthcare costs according to type of biologic used, the total expenditure ranged from €657.61 (golimumab) to €1384.15 (rituximab) patient-month.

Conclusions: A substantial difference in the total costs according to treatment/no

treatment with a biologic and the specific biologic DMARD prescribed was identified. However, this result should be interpreted with caution as a bias in terms of patient selection was most likely present. The results of this study shed some light on RD in an relevant sample of Italian patients. The preliminary conclusions need to be confirmed by further analysis.

Keywords: Antirheumatic drugs; Biologics; Burden of disease; Italy; Rheumatic diseases

INTRODUCTION

Inflammatory rheumatic diseases (RDs) in general and rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis specifically are chronic systemic disorders which significantly affect patients' quality of life. These pathologies are debilitating and progressive and are associated with severe functional impairment and pain [1, 2]. The worldwide prevalence of RDs is high (about 1%) [3–6], with rheumatoid arthritis alone accounting for 0.3–1% of all RDs identified [7].

First-line treatments for inflammatory RDs include non-steroidal anti-inflammatory drugs, conventional disease-modifying anti-rheumatic drugs (DMARDs; e.g., methotrexate), and corticosteroids; immunosuppressants and systemic corticosteroids are also used [8–13]. In the last 15 years the development of biologic drugs, such as infliximab, etanercept, adalimumab, certolizumab, golimumab, tocilizumab, rituximab, anakinra, abatacept, and ustekinumab, has resulted in a significant improvement in the prognosis of rheumatic patients. Patients who are intolerant to the chosen treatment or show an inadequate response (IR) to traditional synthetic DMARDs

are often treated with a biologic drug [14–17]. The treatment of rheumatic patients with an IR to DMARDs alone usually consists of combination therapy with a biologic and traditional DMARD, primarily methotrexate; however, a number of biologics have been shown to be efficacious and approved for monotherapy [18–20].

The aim of this study was to analyze the characteristics of patients with rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis in Italy, assess the use of conventional synthetic and biologic DMARDs, and estimate the overall cost of managing these patients within the framework of the Italian National Health Service (NHS).

METHODS

The data for this analysis was based on the administrative healthcare claims of the Piedmont region, which is located in Northwest Italy and is the second largest administrative region by area in Italy and the sixth largest by number of inhabitants (about 4.4 million) [21]. Due to the administrative nature of the data used, all data was de-identified, and no clinical or personal information was available.

An information network is maintained in each Italian administrative region that routinely records the healthcare expenditures for services covered by the NHS. The pharmaceutical registry for each region routinely records the costs of dispensing drugs to those registered in the system. Data available for each prescription claim include the patient's national health number, the Anatomical Therapeutic Chemical Classification System code (ATC) [22] of the drug dispensed, the number of packages dispensed, the number of

units per package, the dose, the unit cost per package, and the prescription date. The outpatient services registry tracks all laboratory investigations, instrumental tests, and specialist visits. These databases were analyzed along with the database of hospital admissions (SDO), emergency care and the regional registry of biologic drugs in rheumatology. The RDs considered were rheumatoid arthritis, psoriatic arthritis and ankylosing spondylitis. The study population was identified as patients who received at least one prescription of a synthetic or biologic DMARD during the period between 1 January 2007 and 31 December 2010. The first prescription represented the index date for each patient.

The biologic drugs considered in the study were: etanercept (ATC: L04AB01), infliximab (ATC: L04AB02), adalimumab (ATC: L04AB04), certolizumab (ATC: L04AB05), golimumab (ATC: L04AB06), tocilizumab (ATC: L04AC07), rituximab (ATC: L01XC02), anakinra (ATC: L04AC03), abatacept (ATC: L04AA24), and ustekinumab (ATC: L04AC05).

The synthetic DMARDs considered were: methotrexate (ATC: L01BA01; L04AX03), azathioprine (ATC: L04AX01), leflunomide (ATC: L04AA13), sulfasalazine (ATC: A07EC01), and hydroxychloroquine (ATC: P01BA02).

The data were analyzed with the aim to link subjects to a diagnosis of the RD of interest (rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis). For a diagnosis of the target RD, at least one of the following criteria had to be met: (1) diagnosis-specific exemption code; (2) hospitalization or emergency care events marked with disease-specific ICD9 codes (696.0 and 696.1 for psoriatic arthritis; 714.0, 714.1, 714.2, 714.30, 714.32, and 714.33 for rheumatoid arthritis; 720.0 for ankylosing spondylitis) (3) inclusion in the special

rheumatology registry of biologic drugs. In addition, patients who received at least one prescription of methotrexate or leflunomide in the 3 years of analysis were considered to be rheumatic patients and included in the analysis.

Patient data were anonymously linked and imported into STATA version 13.1 (StataCorp, College Station, TX), and clinical (comorbidity), pharmacological (treatment pattern), and economic (total healthcare costs) indicators were analyzed. Each patient was followed from the index date up to 3 years. The total healthcare cost was estimated taking drug prescription (synthetic and biologic DMARDs and co-medications), hospital, and outpatient costs into account. The cost analysis was developed for the entire population and also for subgroups of patients identified on the basis of biologic DMARD use.

RESULTS

In total, 12,455 subjects with at least one prescription for a synthetic or biologic DMARD was identified in the period 2007–2010. Of these, 2895 subjects were excluded because they did not meet any of the conditions required for a confirmed RD. The category of indistinct RD was defined to include those cases in which, despite the certainty of the presence of RD, it was not possible to assign the condition to one of the three rheumatic diseases of interest. This category included patients with a discordant definition of more than one disease of interest ($n = 584$; 4.7%), those who were identified as RD patients only on the basis of a prescription for methotrexate ($n = 710$; 5.7%), and those with juvenile idiopathic arthritis ($n = 6$; $\approx 0.0\%$). Following exclusion of those who did not meet the inclusion criteria, the overall study population

consisted of 9560 patients, among whom 1855 had psoriatic arthritis (19%), 5989 had rheumatoid arthritis (63%), and 416 had ankylosing spondylitis (4%). The majority of patients were women (58.1%), and the mean [$\pm$ standard deviation (SD)] age of the study population was 55.3 ($\pm$ 17.4) years. The analysis of presence of comorbidity in the study population ($N = 9560$) is shown in Table 1.

Of the 9560 patients entered into the study, 4153 (43%) reported at least one hospitalization between the index date and the end of the 3-year observation period, among whom were 2655 of the 5989 patients with rheumatoid

arthritis (44%), 149 of the 416 patients with ankylosing spondylitis (36%), and 651 of the 1885 patients with psoriatic arthritis (35%). Of the 1300 patients diagnosed with indistinct RD, 698 (54%) reported at least one hospitalization during the index date and the end of the 3-year observation period.

On the index date 12.9% of the study population were receiving a biologic DMARD. The distribution of all prescriptions on the index date is shown in Table 2. The total study population of 9560 patients received 9963 prescriptions in the first year (some patients received more >1 biologic DMARD). The

Table 1 Comorbidities in the study population ($n = 9560$)

Comorbidity	Patients (n)	Percentage of patients in the overall study population ($n = 9560$) with a specific comorbidity	Percentage of patients with a comorbidity with ≥ 1 hospitalization ($n = 4153$)
Cardiopathy	43	0.45	1.04
Conduction disorders	37	0.39	0.89
Arrhythmias	253	2.65	6.09
Heart failure	153	1.60	3.68
Other undefined heart diseases	48	0.50	1.16
Myocardial infarction	87	0.91	2.09
Other acute and subacute forms of ischemic heart disease	62	0.65	1.49
Previous myocardial infarction	73	0.76	1.76
Angina pectoris	52	0.54	1.25
Other forms of ischemic heart disease	151	1.58	3.64
Cerebrovascular disease	278	2.91	6.69
Hypercholesterolemia	100	1.05	2.41
Hyperuricemia	19	0.20	0.46
Infections	332	3.47	7.99
Diabetes mellitus	305	3.19	7.34
Neoplasms	688	7.20	16.57
Obesity	106	1.11	2.55

Table 2 Number of prescriptions on the index date in the study population ($n = 9560$) according to drug

Prescription drug	Prescriptions (n)	Prevalence (%)
Biologic DMARDs		
Rituximab	50	0.5
Abatacept	8	0.1
Etanercept	425	4.4
Infliximab	292	3.1
Adalimumab	451	4.7
Anakinra	5	0.1
Total	1231	12.9
Synthetic DMARDs		
Sulfasalazine	671	7.0
Methotrexate	4452	46.6
Azathioprine	126	1.3
Leflunomide	547	5.7
Hydroxychloroquine	2936	30.7
Total	8732	91.3
Total number prescriptions	9963	

DMARD Disease-modifying antirheumatic drugs

highest number of prescriptions were written for methotrexate (46.6%) and hydroxychloroquine (30.7%); the mostly highly prescribed biologic DMARDs were adalimumab (4.7%) and etanercept (4.4%). Tocilizumab, certolizumab, golimumab, and ustekinumab were not available in Italy on the index date and therefore not prescribed at that time.

The prescription of concomitant medications during the 3 years of follow-up was also analyzed, revealing that concomitant medications were used by 92.5% of the study population in follow-up year 1, 97.2% in follow-up year 2, and 97.5% in follow-up year 3 (Table 3). The highest number of prescriptions

was for non-steroidal anti-inflammatory drugs (60.4–59.6%) and corticosteroids (58.3–57.7%).

The total monthly healthcare expenditure for hospitalizations, emergency care, outpatient care, and pharmacological therapy (synthetic and biologic DMARDs, concomitant drugs) was assessed for the study population during the 3 years of follow-up. The total expenditure was €377.98 per patient per month (patient-month), attributable to the costs of synthetic DMARDs (€17.03), biologic DMARDs (€149.75), concomitant medications (€61.07), emergency care (€4.55), hospitalization (€92.61), and visits (€52.96) (Table 4).

The mean cost per patient per month was analyzed in the subgroups of patients who received or did not receive at least one prescription of biologic DMARD in a specific year. During years 1, 2, and 3 of the follow-up 17.7%, 17.5%, and 19.4% of patients, respectively, had at least one prescription for a biologic DMARD. The mean total cost per patient per month including the cost of biologics was €1037.97 (€1061.20, €1002.23 and €1050.48 in years 1, 2, and 3, respectively, of the follow-up) (Fig. 1). The cost of biologic DMARDs was the most important component of this total expenditure, totaling €821.54 (€829.17, €798.27, and €837.17 in years 1, 2, and 3, respectively, of the follow-up). The mean total cost per patient per month in the subgroup of patients who did not have prescriptions for biologic DMARDs was €230.86 (€241.25, €222.58 and €228.74 in years 1, 2, and 3, respectively, of the follow-up). In this subgroup the cost for hospitalization was the most important component of the healthcare expenditure, totaling €94.64 (€99.42, €90.40 and €94.10 in years 1, 2, and 3, respectively, of the follow-up).

The average monthly total cost per patient was also analyzed by stratifying the cohort on

Table 3 Prevalence of prescriptions for concomitant drugs in the study population ($n = 9560$) during the 3-year follow-up

Concomitant drugs	Patients (n)			Prevalence (%)		
	Year 1	Year 2	Year 3	Year 1	Year 2	Year 3
Antihypertensives	330	339	355	3.5	3.7	3.9
Hypouricemic agents	492	522	558	5.1	5.6	6.2
Statins	1128	1290	1366	11.8	13.9	15.1
Anti-diabetics	733	798	845	7.7	8.6	9.3
Anti-coagulants	923	977	1003	9.7	10.5	11.1
Anti-platelets	1318	1438	1502	13.8	15.5	16.6
Non-steroidal anti-inflammatories	5779	5543	5412	60.4	59.7	59.6
Analgesics	1642	1750	1907	17.2	18.9	21.0
Corticosteroids	5570	5278	5234	58.3	56.9	57.7

the basis of the specific biologic DMARD received. In this subgroup analysis, the total cost per patient per month ranged from a low of €657.61 (golimumab) to a high of €1384.15 (rituximab) (Table 5).

DISCUSSION

Rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis are immune-mediated inflammatory diseases that lead to severe functional impairment, pain and a significant decrease in quality of life. These pathologies determine a relevant economic burden for healthcare services because of significant epidemiological impact [3–6].

The aim of this study was to analyze the characteristics, treatment patterns, and emerging costs of rheumatic patients. In total, we identified 9560 patients who had been prescribed at least one synthetic or biologic DMARD in the period 2007–2010. The prevalence of comorbidities was generally low in the study population and similar to that reported in the general population. When the

prevalence of Comorbidities was analyzed in the subgroup of patients who had at least one hospitalization during the study period, we noted that it was consistently higher, possibly indicating a correlation between the comorbid condition and need for hospital care. The most commonly prescribed DMARDs were methotrexate and hydroxychloroquine (46.6 and 30.7% of prescriptions, respectively). The use of biologic DMARDs was in general low, with only about 13% of the cohort receiving them on the index data. The most commonly prescribed biologic DMARDs were adalimumab and etanercept.

Degli Esposti and colleagues analyzed the use of healthcare resources in 1219 patients with rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, Crohn's disease, psoriasis, and ulcerative colitis [23]. The mean age ($\pm$ SD) of their study population was 49.6 ($\pm$ 14.6) years, 47% were men, and all patients were treated with biologic drugs (34% with adalimumab, 51% with etanercept, and 15% with infliximab). The data on these patients were derived from the administrative databases

Table 4 Mean total monthly costs in the study population ($n = 9560$)

Targeted rheumatic diseases	Monthly healthcare expenditure per healthcare category (Euro/patient)					Total monthly healthcare expenditure (Euro/patient)
	Synthetic DMARDs	Biologic DMARDs	Concomitant medications	Emergency care	Hospitalization	Visits
Psoriatic arthritis	12.78 (10.55–15.01)	239.08 (181.25–296.91)	52.76 (41.85–63.68)	3.85 (2.90–4.79)	57.18 (37.04–77.33)	46.36 (34.63–58.09)
Rheumatoid arthritis	19.55 (16.77–22.33)	90.08 (56.96–123.21)	58.60 (46.02–71.18)	4.67 (3.46–5.89)	93.26 (66.98–119.53)	49.54 (43.27–55.81)
Ankylosing spondylitis	6.84 (5.34–8.33)	384.68 (319.80–449.55)	39.39 (27.01–51.76)	4.23 (3.16–5.30)	52.57 (32.94–72.20)	56.81 (39.88–73.74)
Indistinct rheumatic disease	14.76 (12.27–17.24)	221.97 (169.53–274.41)	91.23 (54.03–128.44)	5.10 (3.84–6.36)	153.00 (106.26–199.74)	76.92 (58.58–95.25)
Total	17.03 (14.45–19.61)	149.75 (104.27–195.23)	61.07 (42.83–79.30)	4.55 (3.40–5.70)	92.61 (62.88–122.34)	52.96 (42.03–63.89)
						377.98 (314.99–440.95)

Data are presented as the mean with the 95% confidence interval (CI) in parenthesis

of five local health units in Italy (Emilia-Romagna, Lazio, Tuscany, Campania, and Lombardy). The analysis of these authors revealed that the overall mean annual total healthcare expenditure for each patient was of €11,120, of which non-pharmacological costs were €1177 (10.58%) and pharmacological costs were €9943 (89.42%). This total expenditure is significantly higher than that determined in our study population (about €4500 patient-year). One possible explanation for this difference is that the rate of use of biologic DMARDs was higher in the study of Degli Esposti et al. [23]; it may be that the cost of these drugs drove up the overall estimate. When we compare the total costs which we estimated in the subgroup of patients who received at least one prescription of biologic DMARDs (around €1000 patient-month) to the estimate of Degli Esposti and colleagues, the costs seem to be more aligned.

Based on our data it appears that a substantial difference exists in the total costs of patients treated with different biologic DMARDs, with a range of about €650 to €1380 patient-month. Beyond the effect of different prices for the different biologic DMARDs, this difference could be explained by an implicit treatment algorithm applied by the clinicians during the study period. For example, it can be assumed that only severe and difficult to treat patients who had been not responding to other classes of biologic DMARDs were prescribed rituximab—the reasoning being that this drug is not recommended as a first-line biologic in clinical guidelines. As a consequence, patients treated with rituximab in our study probably, on average, were in a more advanced stage of disease progression, had received different lines of treatment prior to being placed on rituximab, and had clinically complex disease in comparison to those treated with other

Fig. 1 Average healthcare expenditure per patient per month according to whether a patient received or did not receive a prescription for biologic disease-modifying antirheumatic drugs (DMARDs) in a specific year of the follow-up

biologics. This line of reasoning could explain the high costs for concomitant medication, emergency care, hospitalizations that, compared with those related to other treatments, appear to be driving the higher total cost. From another point of view, it seems reasonable to believe that products launched in more recent years were used only in patients who received older treatments first due to the time usually necessary for new products to be considered part of the routine clinical practice. Finally, it should be considered that the route of administration (e.g. intravenous vs. subcutaneous) plays an important role in the selection of the treatment as the treating physician must take into account the characteristics of the patient (e.g., presence of disability) and the aggressiveness of the disease. We therefore suggest that the total healthcare costs of the patients treated with different biologic DMARDs in our analysis should be interpreted with caution as they were probably biased by the selection of the patients. The main

limitation of the study is the lack of an analysis which adjusts for such baseline characteristics; such an adjustment was not possible given the administrative (and not clinical) nature of the database used.

CONCLUSION

The results of this study shed some light on the healthcare cost of rheumatic patients treated in Italy with biologic DMARDs. The prevalence of comorbidities in our study population was generally low and similar to the distribution reported in the general population, but our results do suggest the existence of a possible correlation between the comorbid condition and need for hospital care. The use of biologic DMARDs was generally low, with only about 13% of the cohort receiving them on the index data, but they had a major impact on the total healthcare expenditure. A substantial difference, however, seems to exist in the total costs of patients treated with different

Table 5 Mean total monthly costs during the 3 years of follow-up stratified by the type of biologic disease-modifying antirheumatic drug

Biologic DMARD	Number of patients	Mean total monthly healthcare expenditure per type of biologic DMARD ^a (Euro/patient)					Total
		Synthetic DMARD	Biologic DMARD	Concomitant medications	Emergency care	Hospitalization	Visits
Etanercept	711	11.94 (9.48–14.54)	780.97 (723.50–839.95)	44.11 (31.47–57.21)	3.55 (2.28–4.81)	62.90 (28.21–97.03)	56.86 (48.25–65.57)
Adalimumab	694	11.76 (9.16–14.36)	791.88 (737.25–846.66)	43.49 (31.01–55.90)	4.19 (2.80–5.60)	70.92 (37.10–105.08)	58.78 (51.89–65.79)
Infliximab	317	9.16 (6.66–11.19)	696.33 (634.16–757.93)	42.67 (26.93–58.02)	4.39 (2.90–5.88)	71.26 (41.15–106.3151)	68.32 (60.75–74.66)
Rituximab	59	8.48 (4.58–10.99)	513.64 (457.79–578.46)	216.45 (147.81–306.94)	9.90 (5.79–13.61)	450.92 (251.50–700.93)	184.77 (149.92–242.69)
Abarcept	53	11.97 (10.47–17.13)	509.01 (484.07–588.95)	68.45 (60.41–82.94)	6.39 (2.89–10.43)	82.44 (48.23–130.50)	102.17 (97.29–115.53)
Golimumab	24	22.74 (21.05–25.45)	432.42 (420.14–463.45)	36.00 (31.14–55.66)	5.94 (2.74–9.88)	101.88 (63.55–143.01)	58.62 (47.58–63.76)
							657.61 (632.87–712.13)

Data are presented as the mean with the 95% CI in parenthesis

^a The 6 most commonly used biologic DMARDS are reported

biologic DMARDS. These preliminary results need to be confirmed by further analysis.

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Compliance with Ethics Guidelines. This study is based on administrative database from Regione Piemonte. As such, all data used for the study were de-identified, and no clinical or personal information was available to the authors of this study.

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