Economic Burden of Rheumatoid Arthritis in Italy: Possible Consequences on Anti-Citrullinated Protein Antibody-Positive Patients

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Abstract
Background Rheumatoid arthritis (RA) is an autoimmune disease with a substantial medical and economic burden. In Italy, it affects approximately 280,000 people, therefore representing the musculoskeletal disease with the highest economic impact in terms of costs for the National Health Service and the social security system.

Objective The aim of this study was to estimate the annual economic burden of RA in Italy and determine the potential cost reduction considering the most effective biologic treatment for early rapidly progressing RA (ERPRA) patients.

Methods The model developed considers both direct costs that are mainly due to the pharmacological treatments, and indirect costs, which also include the productivity lost because of the disease. A systematic literature review provided the epidemiological and economic data used to inform the model. A one-way probabilistic sensitivity analysis based on 5000 Monte Carlo simulations was performed. Furthermore, specific scenario analyses were developed for those patients presenting an ERPRA, with the aim of evaluating the effectiveness of different biologic treatments for this subgroup of patients and estimating potential cost reduction.

Results The total economic burden associated with RA was estimated to be €2.0 billion per year (95% confidence interval [CI] €1.8–2.3 billion). Forty-five percent of the expenditure was due to indirect costs (95% CI €0.8–1.0 billion); 45% depended on direct medical costs (95% CI €0.7–1.1 billion), and the residual 10% was determined by direct non-medical costs (95% CI €0.16–0.25 billion). In particular, the costs estimated for ERPRA patients totalled €76,171,181, of which approximately €18 million was associated with patients with a high level of anti-citrullinated protein antibodies (ACPA). The results of the analysis outline how it is possible to obtain a cost reduction for ERPRA patients of between €1 and €3 million by varying the number of patients with a high level of anti-citrullinated protein antibodies (ACPA). The effects of the analysis outline how it is possible to obtain a cost reduction for ERPRA patients of between €1 and €3 million by varying the number of patients with a high level of anti-citrullinated protein antibodies (ACPA). The results of the analysis outline how it is possible to obtain a cost reduction for ERPRA patients of between €1 and €3 million by varying the number of patients with a high level of anti-citrullinated protein antibodies (ACPA). The results of the analysis outline how it is possible to obtain a cost reduction for ERPRA patients of between €1 and €3 million by varying the number of patients with a high level of anti-citrullinated protein antibodies (ACPA). The results of the analysis outline how it is possible to obtain a cost reduction for ERPRA patients of between €1 and €3 million by varying the number of patients with a high level of anti-citrullinated protein antibodies (ACPA).

Conclusions This study presents a pioneering approach to estimate the direct and indirect costs of RA. The model developed is a useful tool for policy makers as it allows to understand the economic implications of RA treatment in Italy, identify the most effective allocation of resources,
and select the most appropriate treatment for ERPRA patients.

### Key Points

This analysis is one of the first attempts to estimate health and social expenditure of rheumatoid arthritis (RA) treatment in Italy. The study highlighted that in 2015 the economic burden associated with the disease was approximately €2.0 billion, with a confidence interval of 95%, ranging from €1.78 to €2.3 billion.

The analysis does not only take into consideration the costs incurred by the National Health Service (NHS) to treat the disease but also the social relevance that may be quantified through indirect costs.

Following a correct prevention policy and selecting a suitable pharmacological treatment may allow a better allocation of resources and a potential saving for the NHS. For this purpose, the model simulated different scenarios related to a specific group of patients with early rapidly progressing RA (ERPRA), entailing a total expense of approximately €76 million.

### 1 Introduction

Rheumatoid arthritis (RA) is a chronic inflammatory-erosive arthritis, with autoimmune pathogenesis and unknown etiology, mainly affecting synovial joints. It may cause joint deformity that can lead to the loss of joint function and disability, and may also affect internal organs, such as the lung (causing the development of lung fibrosis) and the central nervous system, with compressive syndrome of the cervical spinal cord [1].

The first studies conducted in Italy to estimate RA prevalence date back to the 1950s and 1960s. They indicate values ranging between 0.38 and 0.43%, with a higher percentage of female affected subjects [2, 3]. In more recent works, similar prevalence rates are shown. A study conducted in 1998 detected a 0.33% prevalence using a questionnaire on the presence of pain and joint swelling in a sample of 3294 subjects [4]. More recently, two studies conducted in two Italian regions (Marche and Sardinia) reported an RA prevalence of 0.46% [4, 5].

In a limited number of cases (<10%), RA shows a chronic intermittent course, alternating relapse and remission, while the most frequent phenotype is characterized by a chronic progressive course, with relapses occurring in a persistently active disease.

The consequence is irreversible damage to joint tissues a few months after disease onset, resulting in joint deformity within a few years. Therefore, it is absolutely necessary to start a therapy with disease-modifying antirheumatic drugs (DMARDs) as soon as possible, such as methotrexate or leflunomide, which can interfere with RA pathogenetic mechanisms at more levels. However, DMARDs are inadequate in controlling the disease in 40–60% of cases, depending on the biologic-immunologic severity of RA. In line with international guidelines and those of the Italian Society of Rheumatology, in these cases it is necessary to use ‘biologic’ drugs, which proved more effective as they reduce the inflammatory processes and stop the evolution of the anatomic damage, selectively interfering with the single mediators (tumor necrosis factor [TNF], interleukin [IL]-6) or the co-stimulation process of T lymphocytes [6].

A significant aspect of RA is certainly the presence of comorbidities that cause a worse health state for the patient, influencing the response to therapy and entailing higher expense for their treatment. According to the data of the latest Social Report issued by the National Association of Rheumatic Patients (ANMAR) [7], 69.8% of interviewed patients also use drugs to treat other diseases, and this percentage increases with age.

A considerable share of workers are forced to be absent from work due to the disease, ranging from 35% for subjects aged less than 44 year, and 43.6% for subjects aged more than 44 years. Overall, 22.7% of interviewed subjects carrying out a working activity declared that they were forced to change the activity due to the disease. This percentage is directly proportional to the duration of the disease and its evolution stage, reaching 30.1% among those who were diagnosed with the disease more than 10 years beforehand. In particular, more than 10.4% of these patients were forced to change their job [7].

The impact of RA on social security expenditure may be identified by examining the data of the National Social Security Institute (INPS) and the National Institute for the Insurance of Work-Related Injuries (INAIL). A study conducted on INPS data estimated an INPS expense of over €2.8 billion for musculoskeletal diseases, and an estimated €1.2 billion for RA only [8].

To date, the available information in the literature regarding the epidemiological and economic burden is relatively scarce [9–11] and, despite the social and economic impact of RA, there are practically no national estimates.
Obtaining precise information on the social security flows, as well as the related expenditure, is fundamental to developing programs aimed at improving healthcare, guaranteeing compatibility with the National Health Service (NHS) resources. Therefore, one of the objectives of this analysis was to gather the information available nationally on the epidemiology of the disease and estimate the average annual cost for RA treatment from the NHS and social perspective.

This work specifically focused on early rapidly progressing RA (ERPRA). It uses an innovative approach based on the simulation of different scenarios of pharmacological treatment costs and the possibility of selecting the most appropriate treatment for each patient with high values of antibodies against cyclic citrullinated peptides (ACPA). Citrulline is a non-constitutive amino acid formed by enzymatic deimination of arginine present in many tissue proteins during a tissue damaging process. In the presence of a predisposing genetic substrate and environmental factors, such as cigarette smoke, T lymphocytes activate an autoimmune reaction against citrullinated peptides producing ACPA. These predict a more aggressive evolution of RA, with irreversible and early bone-erosive damage and high impairment of joint function. These effects are strictly linked to the ability of ACPA to interact and activate osteoclasts, stimulating resorption processes of subchondral bone. Evaluating ACPA is fundamental as they are highly RA-specific and allow for early identification of ERPRA patients. These are patients with a more ‘aggressive’ disease and higher impairment of working and functional abilities, and therefore they have a higher pharmacological and economic impact [9, 12].

This model of analysis highlights the advantages linked to the improvement of the patient’s conditions due to more effective pharmacological treatment, in turn causing higher productivity and lower absenteeism from work and global cost reduction. Therefore, the choice of a more suitable pharmacological therapy has important consequences, not only on the patient but also on the total expenditure linked to the disease.

2 Materials and Methods

2.1 Model Structure

To estimate the costs associated with RA in Italy, a probabilistic cost-of-illness (COI) model was developed aimed at reconstructing the distribution and number of treated patients and their disease state. A societal perspective was adopted, both direct medical costs (sustained by the NHSs) and indirect costs (caused by the loss of productivity of patients with the disease) of prevalent RA patients were estimated.

For the cost estimate, a bottom-up approach, widely used in the literature [8, 13–23], was applied, calculating the treatment costs of the disease by multiplying the average cost of each type of patient by the disease prevalence itself. The analysis was carried out in two different steps, as illustrated in Fig. 1, with the first step referring to RA in general. Figure 1a shows prevalent patients treated with biologics or more traditional DMARDs, while Fig. 1b distinguishes between patients under pharmacological treatment (ACPA-positive patients) and those who were ACPA-negative. Finally, patients were further distinguished between early (diagnosed within less than 1 year) and late diagnosis. Early diagnosis patients (ERPRA) show the following characteristics: ACPA and/or rheumatoid factor (RF) seropositivity; diagnosis formulated within less than 1 year; at least six to eight swollen joints; and high disease activity, indicated by a Disease Activity Score 28 (DAS28) higher than 3.2.

The model predicted a 1-year time horizon and considered the year 2015 for the cost analysis, adopting a social perspective.

In order to populate COI models with economic and epidemiological data, a systematic research of the literature was carried out through the main electronic databases, such as, for example, MEDLINE (PubMed) and the Cochrane Library. Further details on the information found and the methodology used are available in the electronic supplementary material.

2.2 Epidemiological Parameters

Table 1 reports the epidemiological parameters used to estimate the RA population nationally, both for the general COI model and the model estimated for the subpopulation with ERPRA. In Italy, the disease prevalence ranges between 0.33 and 0.51% [4, 5, 24, 25], in a resident population of approximately 61 million people (60,795,612) as of 1 January 2015 [26], and the population affected by RA was approximately 279,000 in 2015 (see Table 1).

Of the total number of subjects with RA, the model assumes that only 60% were actually diagnosed and/or treated [7]. As illustrated in Fig. 1a, the patients under treatment were submitted to therapy with DMARDs (approximately 75% of treated patients) and biologic drugs (approximately 25%) [27]. The model also assumes that between 70 and 80% of patients under treatment were ACPA-positive (75% average) [28]. The patients are then distinguished between those with a history of disease less than 1 year (18.2% of the total prevalent patients) [29] and those with a history of disease over 1 year.
According to the data of the Italian Group for the Study of Early Arthritis (GISEA) [30], approximately 173 of 1200 patients (14.4%) with a history of disease less than 1 year are estimated to have early aggressive RA. Applying this percentage to the number of incident patients in Italy, the number of ERPRA patients may be quantified in 4403.

Table 1 Epidemiological parameters (mean and range from the literature) for the COI model—Italy 2015

| RA COI general model | Precise estimate (%) | Range | References |
|----------------------|----------------------|-------|------------|
|                       | Min (%)               | Max (%)|            |
| Resident population in Italy as of 1 January 2015 | 60,795,612 | – | – | [26] |
| 2015 RA prevalence   | 0.46 | 0.33 | 0.51 | [4, 5, 24, 25] |
| Diagnosed patients (%) | 60.00 | 51.00 | 69.00 | [7] |
| Patients with DMARD treatment (%) | 75.00 | 79.00 | 71.00 | [27] |
| Patients with biologic treatment (%) | 25.00 | 21.25 | 28.75 | [27] |

| RA COI subpopulation model | Precise estimate (%) | Range | References |
|---------------------------|----------------------|-------|------------|
| ACPA-positive patients (%) | 75.00 | 70.00 | 80.00 | [28] |
| ACPA early (%)            | 18.20 | 15.00 | 25.00 | [30] |
| ERPRA patients (%)        | 19.22 | 15.00 | 25.00 | [30] |
| ERPRA patients with biologic treatment (%) | 32.40 | 20.00 | 40.00 | [30] |
| Anti-CCP2 IgG Q1–Q4 (%)   | 25.00 | 22.50 | 27.50 | [31] |

ERPRA early rapidly progressing rheumatoid arthritis, DMARD disease-modifying antirheumatic drug, ACPA anti-citrullinated protein antibodies, CCP2 anti-cyclic citrullinated peptide-2, COI cost-of-illness, RA rheumatoid arthritis, min minimum, max maximum, IgG immunoglobulin G, Qx quartile x
Cost of Rheumatoid Arthritis in Italy

subjects, equal to 19.2% of early RA and ACPA-positive patients (4403 ERPRA subjects/22,904 early and ACPA-positive patients). With reference to these patients, the GISEA registry indicates that 67.6% are currently treated exclusively with DMARDs or corticosteroids, and 32.4% are treated with at least a biologic drug. Finally, it is assumed that ACPA-positive patients are distributed in quartiles (Q), according to the ACPA concentration value, as indicated in a recently published study showing differences from ACPA Q1 to ACPA Q4, depending on ACPA levels [31]. In particular, ACPA Q4 indicates the group of patients with a higher concentration and possibly also a more unfavorable prognosis.

2.3 Cost Parameters

The systematic review of the literature allowed us to extract the main cost items associated with the RA population, particularly the identified data relating to the drug costs for patients being treated with DMARDs [11] and the cost of treatment with biologic drugs [32].

In the first of the mentioned studies, patients are broken down into the four functional areas of Steinbrocker RA adopted by the American College of Rheumatology (ACR). The average expense percentages per patient are broken down according to direct medical costs (routine tests, instrumental examinations, laboratory tests, physiotherapy, hospital admissions, hospital admissions for rehabilitation, and day hospital) and direct non-medical costs (transportation costs, any home support services, and auxiliary medical equipment). This breakdown was applied to both groups of patients treated with conventional DMARDs and biologics [11]. In addition, in the second study mentioned, patients eligible for the study were distinguished according to the biologic drug taken (abatacept, adalimumab, etanercept, infliximab, and tocilizumab). For each group, an annual average cost (drug, visit/test, and hospital admissions) was estimated and the final cost used in the model was obtained by a weighted average of the analyzed biologic treatment cost [33].

Indirect costs were estimated from a recent study conducted in Italy considering National Security System pension databases [8] and literature data [9, 34]. Specifically, indirect costs in terms of loss of productivity due to absence from work corresponded to approximately 78% of total indirect costs (on average €5348 a year per patient), while social security costs represented 22% of the total expense.

Yearly costs in the RA population analysis are summarized in Table 2.

No specific cost analyses are available in the ERPRA population. For this reason, the model assumes that the costs are associated with the ACR classes of patients, as estimated in the literature [11]. The relation between the Health Assessment Questionnaire (HAQ) score and costs has been widely demonstrated and used in the literature [35–39]. In this analysis, an average value of the HAQ was assumed for each ACR class equal to the value estimated in the literature [33]. An analysis of linear regression to estimate direct and indirect costs for each HAQ value (Fig. 2) was estimated.

The sample analyzed in the GISEA report [30] indicates that the average HAQ value of the ERPRA population at baseline (prior to starting the pharmacological treatment) was 1.37. Through a regression analysis [8, 34] an average annual cost of €4472 per patient for direct medical costs can be estimated, €1201 for direct non-medical costs, and €10,642 for indirect costs. Applying the HAQ value observed in the literature [31] to patients with higher ACPA values, equal to 1.70 for patients with higher concentrations of ACPA at baseline, these costs increased to €5232 for direct medical costs, €1556 for direct non-medical costs and €11,856 for indirect costs (Figs. 3, 4).

2.4 Scenario Analysis

In order to analyse the impact that more efficient management of ERPRA patient treatment may have on costs, a scenario analysis based on recent evidence presented in the literature [39] was developed. Patients with ERPRA represent a limited population, therefore the results of this COI analysis cannot be extended to the whole RA population. However, focusing on ERPRA only presents some strengths; patients have a poorer prognosis, therefore, within a health system that considers the centrality of patients, a prompt and effective treatment is mandatory. Moreover, the two scenarios envisaged for the analysis are not hypothetical but stem from real head-to-head clinical trials.

- **Scenario 1** Patients with more unfavorable prognosis (included in the Q4 ACPA) move from a less efficient biologic drug to one that is more efficient.
- **Scenario 2** All patients currently treated with a biologic drug are treated with an anti-TNF (base case), or more effective, biologic drug.

The considered effectiveness data for each therapeutic strategy are those reported in the literature. The estimated effects on the HAQ levels of patients are summarized in Table 3. Specifically, the first scenario is only based on ACPA Q4 patients treated with biologics. This scenario simulates the effects on HAQ levels and the economic consequences should these patients be treated with adalimumab (base case) or abatacept (Scenario 1). The model assumes that the HAQ level for this type of patient was
1.70 prior to starting therapy [31]. In this scenario, the
reduction in HAQ levels was assumed to be proportional to
the effects estimated in the comparison study between
adalimumab and abatacept in 2 years [31].

In Scenario 2, it is assumed that, among ACPA Q4
patients, those under treatment with traditional DMARDs
move to the biologic drug in the short term, and that
patients may be treated with an anti-TNF (base case) or
abatacept (Scenario 2). In this case, the effectiveness is
demonstrated by the improvement in the HAQ score
(Table 3) [31].

3 Results

3.1 Epidemiological Estimates of Rheumatoid
Arthritis (RA) in Italy

The COI model estimates that in total there are 279,660
prevalent patients in Italy. Of these, approximately
167,000 (143,000–192,000) are actually treated and
managed by the NHS. The analysis assumes that just less
than 126,000 patients (119,000–132,000) are treated with
traditional DMARDs, while approximately 42,000
(36,000–48,000) are being treated with a biologic drug
(Table 4).

### Table 2 Cost parameters
(mean and range from the
literature) used in the COI
analysis—Italy 2015

| Cost data                              | Mean (€) | Range (€) | References |
|----------------------------------------|----------|-----------|------------|
|                                        | Min      | Max       |            |
| Direct medical costs                   |          |           |            |
| Routine tests                         | 112      | 95–129    | [11]       |
| Instrumental examinations             | 93       | 79–106    | [11]       |
| Laboratory tests                      | 210      | 179–242   | [11]       |
| Physiotherapy                         | 108      | 92–125    | [11]       |
| DMARDs                                | 1,183    | 1,005–1,360| [11]     |
| Hospital admissions                   | 1,405    | 1,195–1,616| [11]    |
| Hospital admissions for rehabilitation| 125      | 106–143   | [11]       |
| Day hospital                          | 76       | 65–87     | [11]       |
| Total DMARD direct medical costs      | 3,312    | 2,815–3,809| [11]     |
| Total biologic direct medical costs   | 11,971   | 10,176–13,767| [32]   |
| Direct non-medical costs              |          |           |            |
| Transportation                        | 192      | 163–220   | [11]       |
| Home support                          | 836      | 710–961   | [11]       |
| Auxiliary medical equipment           | 178      | 152–205   | [11]       |
| Total direct non-medical costs        | 1,206    | 1,025–1,387| [11]    |
| Indirect costs                        |          |           |            |
| Indirect costs (lost working days)    | 1,150    | 978–1,323 | [8]        |
| Indirect costs of pensions            | 4,198    | 3,568–4,827| [8]      |
| Total indirect costs                  | 5,348    | 4,546–6,150| [8]      |

DMARD disease-modifying antirheumatic drug, COI cost-of-illness, min minimum, max maximum

3.2 Cost-of-Illness Estimates of RA in Italy

The model estimated a total yearly RA cost of over €2.0
billion (95% CI 1.6–2.1 billion), of which approximately
€931 million was attributed to direct medical costs incurred
by the NHS (45% of total economic burden), approxi-
mately €205 million was incurred by patients in terms of
direct non-medical costs, and over €899 million was
attributed to indirect costs due to the loss of productivity
for lost work days or social security services (Table 4).
This cost represents an estimate of total indirect costs due
to the actual loss of productivity associated with RA. An
important cost item that the model takes into consideration
is represented by the loss of productivity due to presenteeism,
consisting of the possibility that patients are able to
work but are much less productive than they would be
without the illness. This item is particularly important if we
consider that, in a chronic disease such as RA, the physical
and psychic limitations of normal daily activity are fre-
quent and highly impacting. Some studies assume that the
indirect costs represent over two-thirds of the total RA
economic burden [40]. In this scenario, indirect costs
would more than double compared with the estimates of
the model analysis (Table 5).

Observing the cost breakdown, over 58% of the expense
in terms of direct medical costs was due to drugs, 28% to
hospital admissions, and the remaining due to tests and specialist visits. Social security expenditure represented the highest cost item of indirect costs, i.e. over €700 million a year (78% of the total indirect costs), against €193 million

Fig. 2 Relation between average HAQ score by ACR class [33] and a direct medical costs, b direct non-medical costs, and c indirect costs [11]. HAQ Health Assessment Questionnaire, ACR American College of Rheumatology

Fig. 3 Distribution of a direct medical costs, b direct non-medical costs, and c indirect medical costs, Italy 2015
4 Results of the Scenario Analysis

4.1 Epidemiological Parameters

The model identified approximately 126,000 ACPA-positive patients, of which 23,000 had an early disease history. Of these, approximately 4402 were ACPA subjects, of which 1424 were treated with biologics and 2978 with traditional DMARDs.

4.2 Results of Cost Analysis for ACPA-Positive Patients

The model estimates total expenditure of over €76.1 million (4% of total RA expenditure in Italy) for the subgroup of ACPA-positive patients only. Of this total, 55% is attributed to patients treated with traditional DMARDs (approximately €36 million) and the remaining share is associated with patients being treated with biologic drugs (Table 6). Patients with high immunoglobulin G levels (ACPA; Q4) treated with biologic drugs represent an expense of €9.72 million, corresponding to 27% of total expense for patients under biologic treatment.

1. Scenario 1 only examined the subgroup of patients with more unfavorable prognosis (ACPA Q4) currently treated with biologics, and analyzed the cost differences should these patients be treated with anti-TNF or abatacept. In this scenario, the model does not estimate a change in pharmaceutical expense due to the fact that it conservatively assumes that the cost of therapy with an anti-TNF is comparable to the cost of therapy with abatacept (significant price changes between the different biologics are not assumed). The model estimates that, in addition to an improvement in HAQ levels, treatment with abatacept represents a reduction in expense of over €1.1 million (Fig. 5).
Scenario 2 assumes that all patients with higher ACPA levels (ACPA Q4; 1101/4403) are treated with a traditional anti-TNF or abatacept. The scenario analysis with the best economic advantages is the abatacept treatment, which, thanks to the advantages reported in the comparison study, allows a reduction in expense in terms of direct and indirect costs higher than €3.1 million (Fig. 6).

5 Discussion

RA is a widespread disease worldwide whose incidence and prevalence is doomed to increase due to different factors, including population growth, ageing and urbanization [8]. Although the disease causes disability and many complications in patients, political health authorities
are mainly unaware of the potential future cost increase related to RA.

In the last years, the prognosis and outcomes of RA have improved with the ‘treat-to-target’ strategy and the advent of therapy with biologic drugs. The treat-to-target principle is based on the assumption that each patient is different according to demographic characteristics, disease activities, prognostic factors (autoimmunity and erosive lesions), any comorbidities, and particularly disease duration. Based on the patient profile, after setting the objective, rheumatologists implement a tailored therapeutic strategy and then closely monitor, at short intervals (‘tight control’), the achievement of the objective, adjusting therapy if necessary, and hopefully the clinical remission or low disease activity [41].

In this first stage, DMARDs are used and, if the objective is not reached, therapy with biologic drugs is administered. In case of failure, treatment with a second or third biologic drug is started. A wide range of biologic drugs are currently available, directed against T lymphocytes (abatacept), B lymphocytes (rituximab), IL-6 (tocilizumab), and TNF (abatacept, adalimumab, certolizumab, etanercept, golimumab, infliximab). In the absence of experimental clinical evidence, current international guidelines do not recommend the sequence of biologic drugs. The choice is substantially empirical, in the absence of pharmacoeconomic considerations. Therefore, clinical studies evaluating not only the clinical profile of the patient but also the costs and any advantages according to the biologic drug used are required [42].

This analysis is one of the first attempts to estimate health and social expenditure of RA treatment in Italy. The study highlighted that the economic burden associated with the disease in 2015 was approximately €2.0 billion, with a confidence interval of 95%, ranging from €1.78 to €2.3 billion. The analysis does not only take into consideration the

![Table 6](image)

| Table 6  Estimate of patients by ACPA breakdown |
|------------------------------------------------|
| Epidemiological data                          | 2015 | 95% CI |
|                                               | Min  | Max   |
| Diagnosed RA population                       | 167,796 | 151,016 | 184,575 |
| ACPA-positive                                 | 125,847 | 117,457 | 134,237 |
| ACPA-negative                                 | 41,949  | 33,559  | 50,339  |
| ACPA-positive early                           | 22,904  | 18,877  | 31,462  |
| ACPA-positive late                            | 102,943 | 100,678 | 113,262 |
| ERPRA patients                                | 4403  | 3436  | 5726  |
| ACPA-positive early DMARDs                    | 2978  | 2680  | 3276  |
| ACPA-positive early biologic treatment         | 1424  | 1112  | 1853  |
| Anti-CCP2 IgG Q4 (ACPA) DMARD treatment       | 745   | 670   | 819   |
| Anti-CCP2 IgG Q4 (ACPA) biologic treatment    | 356   | 320   | 392   |

**ERPRa** early rapidly progressing rheumatoid arthritis, **DMARDs** disease-modifying antirheumatic drugs, **ACPA** anti-citrullinated protein antibodies, **CCP2** anti-cyclic citrullinated peptide-2, **CI** confidence interval, **Min** minimum, **Max** maximum, **RA** rheumatoid arthritis, **IgG** immunoglobulin G, **Q4** quartile 4

![Fig. 6](image)

**Fig. 6** Cost results of scenario 2: all ACPA Q4 patients treated with anti-TNF or abatacept. **ACPA** anti-citrullinated protein antibodies, **ERPRA** early rapidly progressing rheumatoid arthritis, **Q** ACPA quartile levels, **DMARDs** disease-modifying antirheumatic drugs, **TNF** tumor necrosis factor
costs produced by the NHS to treat the disease but also the social relevance that may be quantified through indirect costs. This aspect shall not be underestimated. More than half of the total estimated costs may be allocated to this cost item.

The RA expense incurred by the NHS in our country in 2015 was approximately €1 billion, with the cost of the drugs being the main medical expense item, representing a cost of over €0.5 billion, followed by the hospital admission cost, which exceeded €257 million.

Following correct prevention policy and selecting suitable pharmacological treatment may allow better allocation of resources and potential savings for the NHS. For this purpose, the model simulated different scenarios related to a specific group of patients with ACPA, entailing a total expense of approximately €76 million. These patients showed an RA phenotype characterized by a high production of RF/ACPA, high disease activity, severe disability with a high HAQ score, and fast-developing erosive joint damage. This represents the most severe outcome of RA. There is recent evidence that RF/ACPA and bone damage association is regulated by pathogenetic mechanisms. In fact, osteoclast precursors express citrullinated vimentin on the surface and ACPA may activate differentiation and maturation of osteoclasts [43]. The role of RF is marginal and, in cases of ACPA/RF double positivity, the erosive damage is higher [12].

The analysis of this study considered the possibility of treating all these patients (or those with worse prognosis) with more effective drugs, as demonstrated by clinical studies [44], which would allow an expenditure reduction ranging from €1 to €3 million a year compared with current expenditure. In fact, even if moving to DMARD treatment with a biologic drug causes an increase in pharmaceutical expense, the reduction of direct and indirect costs should also be considered. This cost reduction is due to the fact that the higher effectiveness of the drug improves the health state of patients, who can restart working, even if partially, and increase the level of productivity, with a consequent reduction of indirect costs.

As in all scenario approaches, this study had some limitations. First, epidemiological and cost data cannot be easily found, and the different sources examined may not agree. It is often necessary to use sample data or data based on the epidemiological situation of a single region. The application of the sensitivity probabilistic analysis is due to these circumstances. In fact, this analysis considers the heterogeneity of the available sources. Second, there is not a single national body presenting all cost and epidemiological data related to the disease of interest, especially if the type of patients by the type of treatment is considered. In this case, the current study bypasses this problem by making a systematic revision of the literature, according to precise guidelines accepted by international literature. This procedure systematizes the data in a clear and scientific way so as to extrapolate as much evidence as possible.

6 Conclusions

While not being a perfect tool for estimating the economic burden of such a complex disease, this work may be considered a valid/useful support tool for public decision makers/policy makers to adequately understand the economic implications of RA treatment in Italy, and to promote the appropriate treatment based on the available clinical evidence.

Compliance with Ethical Standards

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Conflict of interest Francesco Saverio Mennini, Andrea Marcellusi, Lara Gitto, and Florenzo Iannone have no conflict of interests to declare.

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