Impact of rheumatoid arthritis on quality of life, work productivity and resource utilisation: an observational, cross-sectional study in Brazil

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Abstract

Objective

Increasing severity in rheumatoid arthritis (RA) may result in poorer health-related quality of life (HRQoL), reduced work productivity and increased resource utilisation. This study investigated the impact of RA severity on HRQoL and healthcare resource utilisation among RA patients in Brazil.

Methods

Data were drawn from an observational cross-sectional study of consulting RA patients undertaken in November–December 2007. Rheumatologists (n=55) provided information for 526 RA patients, 521 of whom also completed patient self-completion (PSC) questionnaires. Physicians subjectively rated each patient's RA as mild, moderate or severe. The PSC included the Work Productivity and Activity Impairment questionnaire (WPAI), Health Assessment Questionnaire Disability Index (HAQ-DI) and HAQ-Pain score, EuroQoL-5D (EQ-5D) and Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue. Data on the number of hospitalisations and consultations to healthcare professionals in the past 12 months and RA drug therapy class received were also collected.

Results

Patients with severe RA had significantly impaired health and work status compared to those with mild/moderate disease. Overall work and activity impairment rose with increasing disease severity. Health status deteriorated as disease severity increased with worsening disability, pain, fatigue, quality of life and perceived general health status. Hospitalisation rate and frequency of physician consultations were also significantly greater among those with severe RA.

Conclusion

In Brazil, moderate to severe RA is associated with significant functional disability and morbidity. Disease severity should be considered when treating patients with RA. More aggressive treatment strategies may be needed to effectively manage patients with moderate to severe RA.

Key words

rheumatoid arthritis, work, productivity, disability, pain, quality of life, health resources, Brazil

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A. Rose and J. Piercy, employees of Adelphi Real World, were paid consultants to Pfizer in the analysis of these data and for the development of this manuscript;
R.K. Khandker was an employee of Pfizer;
R. Sato is currently employed by Pfizer;
G. da Rocha Castelar Pinheiro has declared no competing interests;
all authors had full access to all the data in the study and take responsibility for the decision to submit for publication.

Introduction

Rheumatoid arthritis (RA) is a chronic systemic autoimmune inflammatory disease affecting the joints, connective tissues, muscles, tendons, and fibrous tissue. Its onset commonly occurs between the ages of 20 and 40 with clinical symptoms, including pain and deformity (1). The World Health Organization estimates prevalence of RA at between 0.3% and 1% and it is more common in women than men. Senna *et al*. placed the prevalence of RA in Brazil at 0.46% (2).

RA places a significant burden on both society and patient in terms of economic impact, morbidity, long-term disability and adverse effects on quality of life (3, 4). The major costs associated with RA in Brazil are driven largely by losses due to reduced performance while at work, absenteeism and early retirement (4) and a similar situation is observed in other countries including the USA (5), Germany (6), Italy (7) and other European countries (8). In 2009, Sokka *et al*. stated countries with low GDP have worse clinical status (greater disease activity) than high GDP countries, resulting in the burden of arthritis appearing to be greater in low GDP countries than high GDP countries (9).

Few studies have investigated resource utilisation, costs and loss of productivity associated with RA in Brazil. In 2008, Chermont *et al*. estimated the average annual direct medical costs per RA patient in Brazil as $370.36 (10). The same year, de Azevedo *et al*. estimated the indirect costs per RA patient in Brazil as $2.423.51 per year (4). Compared with other countries (5-8), the direct costs per patient in Brazil are generally lower. Assessing the impact of RA and its severity on HRQoL and resource utilisation is an important area as total societal costs, direct plus indirect, increase as the severity of RA increases (8).

This study was initiated to investigate the impact of RA severity on HRQoL and healthcare resource utilisation among RA patients in Brazil.

Methods

Study design

The Rheumatoid Arthritis Disease Specific Programme (DSP), a cross-sectional observational study, was conducted by Adelphi Real World (Macclesfield, UK) in Brazil between November and December 2007. The study included 55 rheumatologists who provided detailed records for 526 RA patients. All patients with RA, as diagnosed by their physician, were eligible for inclusion in the study. The real world design of the study ensured collection only of information available to the physician/patient at the time of consultation; therefore no tests or investigations were required or conducted for a patient to be included in the study. A key inclusion criterion for physicians was that they had to have the ability to initiate or renew biologic therapy in order to ensure that the patient sample had access to all treatment options available. Physicians who were not eligible or did not prescribe biologics were therefore excluded.

Physicians completed a patient record form (PRF) for their next 8 consecutive presenting RA patients. Patients were invited to fill out a patient self-completion form (PSC). All responses were anonymous to preserve patient confidentiality and to avoid bias at the data collection and analysis phases.

The study protocol followed ethical procedures including informed consent of all patients for anonymous and aggregated reporting of research findings based on the questionnaires employed. Patients were instructed by the physician to complete the PSC independently and return it in a sealed envelope. Matching the physician and patient responses via patient/physician study numbers allowed the PSC data to be linked with comparable data recorded on the physician-completed PRF to highlight any areas of disparity and/or agreement. The analyses conducted for the purposes of this paper investigated data from the matched PRF and PSC records. The full DSP methodology was outlined previously (11).

Data elements assessed

The physician-completed PRFs included the following elements:

- patient demographics,
- physician's subjective rating of each patient's overall RA severity; phy-

sician rating of severity based on a question asked of the physician about his or her patient – "what is the current level of severity for this patient?", physicians were invited to respond: mild, moderate or severe;
- disease activity score 28 (DAS28) (12) (score provided on a subset of patients) with higher score indicating greater disease activity; frequency of hospitalisations and health care visits.

The matched patient-completed PSCs included the following HRQoL measures:
- needing help with daily activities;
- HAQ-DI and pain (13) – both the HAQ-DI and pain scales range from 0–3, categorised in 3 groups: 0 to 1, 1 to 2 and 2 to 3, where the higher the score the greater the disability/pain;
- hospital anxiety and depression scale (HADS) – the HADS-anxiety scale and HADS-depression scale both range from 0 to 21, with levels ≥11 considered to be moderate-to-severe (14);
- EQ-5D global health visual analogue scale (GH VAS) (15) – EQ5D GH VAS ranges from 0 to 100 with a higher score indicating better health;
- the Work Productivity and Activity Impairment (WPAI) questionnaire (16). Impairments are asked with reference to a specified health problem (arthritis) during the past 7 days. Impairments are first measured on a scale from 0 to 10, with 0 representing *no effect* (on work or activity) and 10 representing *completely prevented* the patient from doing either work or activity. Impairments at work and activity are calculated as a percentage (of a maximum potential score of 10). The higher the percentage, the greater the impairment.
- FACIT-fatigue (17) – FACIT ranges from 0 to 52, with the highest score indicating less fatigue.

Statistical methods

Statistical analysis focused on contrasting the HRQoL and resource burden between mild, moderate and severe RA patients as classified by their physician.

At the unifactorial level, standard summary statistical measures such as means and proportions together with appropriate statistical tests (ANOVA, *t*-tests, chi-square) were applied. Bonferroni corrections were applied to *p*-values in order to account for multiple testing.

In order to examine whether perceived differences between severity groups occurred owing to disparities on confounding factors such as age, multifactorial methods were employed. Generalised Estimating Equations (18) (GEE) models were applied to each HRQoL and resource burden outcome measure. Severity of RA was entered as an explanatory factor variable serving as the primary variable of interest. Confounding factors included age, gender, five separate comorbidity measures (presence/absence of any other autoimmune disease, hypertension, other cardiovascular conditions, any gastric conditions, and diabetes type II) and years diagnosed with RA.

GEE models were applied because of their flexibility in modelling outcomes of different types (continuous, count, percent, binary data) and because they could account for inter-patient correlations that may arise from patients consulting the same physician. Various 'family' distributions were used in the GEE – Gaussian, negative binomial and binomial for continuous, count and percent data respectively. For continuous outcome data, tests (19) were conducted for the transformation that results in the best approximation to normally distributed data. This transformation was then applied to the 'link' function of the GEE. GEE models are very pertinent to modelling health outcomes/economic data as they explicitly model the expected (average) value of the outcome measure which is of most interest in model predictions. They are similar in spirit to Generalised Linear Models with the added advantage that they can account for inter-correlations among observation units.

Potential co-linearity problems amongst the predictor variables, particularly between years diagnosed and severity, were assessed by Variance Inflation Factors and the Condition Number. Statistical significance between the severity groups was determined by Wald tests using robust standard errors. Point estimates of average scores within severity groups were obtained by computing predictive margins.

All the analyses were conducted using Stata version 11.1. 9.

Results

Demographic and socioeconomic characteristics

Demographic and socioeconomic characteristics of RA patients consulting in Brazil are summarised in Table I. The mean age of the overall sample was 51 years and the majority of patients were female (80%). In all, 2% of patients were unemployed due to arthritis and average disease duration was 6.5 years. When compared across severity, severe RA patients had more unemployment due to arthritis (mild 0%, moderate 2%, severe 11%; moderate-to-severe $p<0.05$) and greater disease duration (mild 5.7 years, moderate 6.3 years, severe 9.3 years; mild-to-severe $p<0.001$, moderate-to-severe $p<0.01$).

Concerning the multifactorial GEE analysis, co-linearity amongst the predictors was not a problem, (all VIFs below 3 and condition numbers under 15). Given these facts, all multifactorial results are presented where years diagnosed has been included as a confounding factor. No qualitative differences were found between models including and excluding years diagnosed.

Disease activity and functional disability

DAS28 and HAQ-DI and HAQ-Pain were analysed to assess disease activity and functional disability amongst RA patients.

DAS28 consists of four components, two subjective (GH VAS and tender joints) and two objective (swollen joints and ESR) (18). DAS28 scores were provided on a subset of the population (n=67). Overall DAS28 scores correlation with subjective severity ratings show significance at $p<0.001$ (Spearman's), while Table II shows increasing severity ratings result in higher DAS28 score (mild 2.95, moderate 4.14, severe 5.73 (mild-to-moderate, mild-to-severe $p<0.001$).

Overall, HAQ-DI scores correlate with subjective severity ratings ($p<0.001$)

(Spearman's), while Table II shows increase in HAQ-DI scores with increasing severity (mild 0.65, moderate 1.13, severe 1.57; $p<0.001$). Within the severe disability cohort (HAQ-DI score ≥2), the proportion of patients within each severity rating increased as severity increased as shown in Table II (mild 6%, moderate 11% [$p<0.05$]; severe 26% [mild-to-severe $p<0.001$; moderate-to-severe $p<0.01$]). Results among the HAQ-DI ≤0.5 cohort; normal functioning have been excluded owing to a small number of severe patients.

The mean HAQ-pain scores (Table II) indicated greater impact with higher severity (mild 0.82, moderate 1.46, severe 1.93; $p<0.001$ for each comparison). Overall HAQ-pain scores correlation with subjective severity ratings show significance at $p<0.001$ (Spearman's).

HRQoL

The mean FACIT-fatigue score was lower at higher severity levels (mild 42, moderate 35; $p<0.001$), severe 31 (moderate-to-severe $p<0.05$, mild-to-severe $p<0.001$) (Table III). Additionally, the level of general health, as measured by EQ-5D GH VAS, was poorer at higher perceived severity levels (mild 74, moderate 63, severe 50; each $p<0.001$). HADS-depression score (amongst the moderate-to-severe depression cluster) was significantly higher among patients considered to have severe RA compared with those considered to have mild or moderate RA (each $p<0.001$) (Table III). HADS-anxiety score (amongst the moderate-to-severe anxiety cluster) is significantly higher among patients considered to have moderate or severe RA compared with those considered to have mild RA (moderate-to-mild $p<0.001$, severe to mild $p<0.01$).

Burden of disease

From the WPAI (Fig. 1A-C), impairment at work affected 15% of mild patients compared with 34% of moderate patients and 64% of severe patients (each $p<0.001$).

The overall work impairment score was 19% in mild patients compared with 36% in moderate patients ($p<0.05$) and 65% in severe patients (mild-to-severe $p<0.01$, mild-to-moderate $p<0.05$). Activity impairment also increased with increasing RA severity (mild 27%, moderate 46%, severe 65%; each $p<0.001$). Significant differences across severity groups occurred with reference to help needed with daily activities (mild 12%, moderate 26%, severe 56%; each $p<0.001$), plus percent per severity cohort hospitalised in the last 12 months (for any condition) (mild 3%, moderate 6%, severe 18%; mild-to-severe $p<0.01$, moderate-to-severe $p<0.01$) (Table IV). No statistical differences were observed in terms of percentage of patients undergoing outpatient surgery for their arthritis, although distribution is limited overall (4% of total population considered).

Overall consultation rates (across health care professions) over a 12-month

Table I. Demographics and socioeconomic characteristics of the patients with rheumatoid arthritis by severity.

	Total (n=526)	Mild (n=219)	Moderate (n=227)	Severe (n=55)
Age (years) mean	51	51	51	50
Gender (% female)	81	80	78	93[b]
Employment status (% employed)	29	31	29	25
Unemployed, %	4	4	4	4
Retired, %	24	24	25	25
Student, %	2	1	1	-
Unemployed due to arthritis, %	2	-	2	11[a,b]
Self employed, %	8	8	10	7
Home maker, %	29	32	29	27
Disease duration, yrs	6.5	5.7	6.3	9.3[a,b,c]

[a]$p<0.001$ *vs*. mild, [b]$p<0.05$ *vs*. moderate, [c]$p<0.01$ *vs*. moderate. For 25 respondents a subjective severity rating was not provided.

Table II. Disease activity and functional disability (DAS [n=67] and HAQ calculations); GEE results controlling for differences in confounding factors.

	Mild (n=219)	Moderate (n=227)	Severe (n=55)
DAS28* (mean, n)	2.95 (31)	4.14[a] (28)	5.73[a,b] (8)
HAQ-DI** (mean, n)	0.65 (215)	1.13[a] (226)	1.57[a,b] (55)
HAQ-DI** ≥2 (% patients)	6 (215)	11[c] (226)	26[a,b] (55)
HAQ-pain** (mean, n)	0.82 (190)	1.46[a] (209)	1.93[a,b] (53)

[a]$p<0.001$ *vs*. mild, [b]$p<0.001$ *vs*. moderate, [c]$p<0.05$ *vs*. mild, [d]$p<0.01$ *vs*. moderate.
*Data on DAS28 were only available for a subset of patients. DAS28 score ranges from 0 to 9.4 with higher score indicating greater disease severity.
**Both the HAQ-DI and pain scales range from 0–3, categorised in 3 groups: 0 to 1, 1 to 2 and 2 to 3, where the higher the score the greater the disability/pain.

Table III. HRQoL (FACIT-fatigue, EQ-5D, HADS-depression, HADS-anxiety); GEE results controlling for differences in confounding factors.

	Mild (n=219)	Moderate (n=227)	Severe (n=55)
FACIT fatigue score* (mean, n)	42 (213)	35[a] (223)	23[a] (209)
EQ-5D GH VAS score** (mean, n)	74 (204)	63[a] (217)	50[a,c] (52)
HADS-depression score*** amongst moderate-to-severe depression cluster (HADS-depression score >11) (% of patients, base)	14 (204)	20 (218)	46[a,c] (54)
HADS-anxiety score*** amongst moderate-to-severe anxiety cluster (HADS-anxiety score >11) (% of patients, base)	9 (197)	23[a] (209)	25[d] (52)

[a]$p<0.001$ *vs*. mild, [b]$p<0.05$ *vs*. moderate, [c]$p<0.001$ *vs*. moderate, [d]$p<0.01$ *vs*. mild*FACIT score ranges from 0 to 52, with higher score indicating less fatigue**. EQ5D GH VAS ranges from 0 to 100, with a higher score indicating better health***. The HADS-anxiety scale and HADS-depression scale each ranges from 0 to 21, with levels ≥11 considered to be moderate to severe.

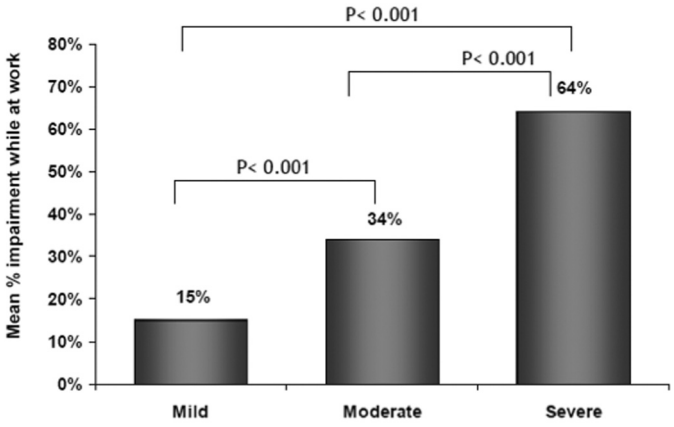

Fig. 1A. RA severity and impairment while at work. GEE results controlling for differences in confounding factors.

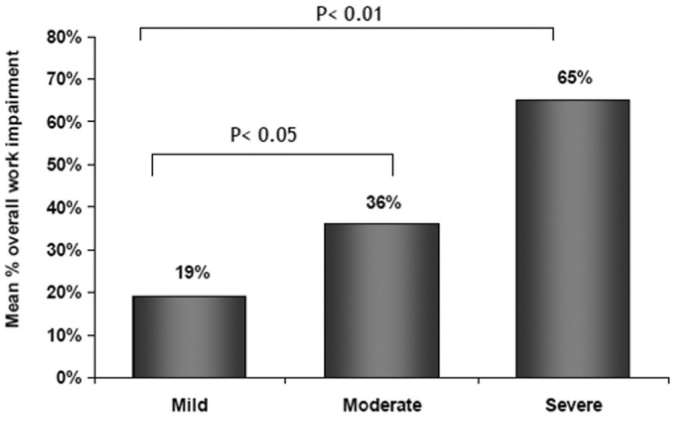

Fig. 1B. RA severity and overall work impairment*. GEE results controlling for differences in confounding factors.
*Overall work impairment takes into account work time missed as well as impairment while at work.

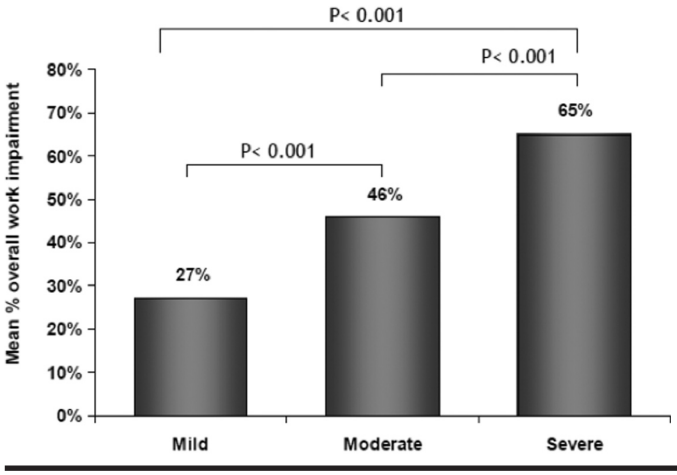

Fig. 1C. RA severity and activity impairment*. GEE results controlling for differences in confounding factors.
*Activity impairment measures the degree of inability to do regular daily activities other than at a job.

period were 5.3 in mild patients, 6.0 in moderate patients (mild-to-moderate $p<0.05$) and 7.1 in severe patients (mild-to-severe $p<0.001$, moderate-to-severe $p<0.05$).

Current prescribed treatment by severity is summarised in Table V. Traditional DMARDs are the most widely used drugs across all severity categories (83% to 88%), followed by corticosteroids (43%, 58% and 70%, respectively, among mild, moderate and severe patients). NSAIDs and biologics were also widely used in these cohorts, with higher use rates for more severe patients. These drug utilisation rates are based on current usage, and do not necessarily reflect the disease state when the drugs were first prescribed.

Discussion

To date, no studies have examined the impact of severity on HRQoL among patients with RA in Brazil, and few studies have investigated the impact of RA on their health care resource utilisation. In this study, several morbidity measures were used to assess the impact across three severity cohorts (mild, moderate and severe) in a patient population identified through their consulting physicians. Results highlight the detrimental impact of RA, particularly amongst those with moderate-to-severe disease, on functional disability and other HRQoL measures, as well as on work and non-work productivity. In addition, the results presented here indicate that severity of RA poses an increasing burden on patients and health care resources. It should be noted that other measures are available such as Salaffi *et al*. ROAD alternative to HAQ-DI (20).

An important finding of the study was that 58% of the severe RA patients are treated with a biologic agent (compared with 49% of moderate patients and 27% of mild patients). These figures may be a reflection, at least in part, of the physicians recruited for the study, who had to be able to provide at least two patients receiving a biologic agent. This has the implication that the distribution of physician assessed disease severity (mild, moderate, severe) may be different among all RA patients or RA patients seen by general practitioners (who may not routinely prescribe biologics). The impact of the use and cycling of biologics on patient outcomes was beyond the scope of this study, but may be an important area for further research. Cimmino *et al*. suggest the use of abatacept second-line as better for achieving remission (21). The different impact on HRQoL dimensions between patients on biologics and those on traditional DMARDs only was not undertaken in this analysis, but also warrants further investigation.

Dimensions of HRQoL analysed in this study also reflect the need for physicians to understand and consider a wide range of morbidity measures when making medical management and treatment decisions. Active consideration of HRQoL measures as part of treatment strategy may help to mitigate the burden of disease among RA patients in Brazil. In 2010, Linde *et al*. found RA patients in clinical remission had EQ-5D scores approaching those

Table IV. Resource utilisation by severity; GEE results controlling for differences in confounding factors.

	Mild (n=219)	Moderate (n=227)	Severe (n=55)
Any hospitalization in 12 months (% of patients, n)	3 (212)	6 (216)	18[a,b] (54)
Needed help with daily activities (% of patients, n)	12 (213)	26[c] (224)	56[c,d] (54)
Outpatient visits per year to all health care professional (mean, n)	5.3 (210)	6.0[e] (215)	7.1[c,f] (53)

[a]$p<0.01$ *vs*. mild; [b]$p<0.01$ *vs*. moderate, [c]$p<0.001$ vs. mild, [d]$p<0.001$ *vs*. moderate, [e]$p<0.05$ *vs*. mild, [f]$p<0.05$ *vs*. moderate.

Table V. Drugs currently prescribed for the treatment of rheumatoid arthritis.

Drug groups (% patients)	Mild (n=219)	Moderate (n=227)	Severe (n=55)
Traditional NSAID	39	48	54
COX 2 inhibitor	8	18	11
Traditional DMARD	88	83	88
Biologics	27	49	58
Analgesic	17	31	25
Corticosteroid	43	58	70

of the general population, suggesting that treating patients to remission can align HRQoL measures in patients with RA with the general (non RA) population (22). However, in 2011, Salaffi *et al*. found EQ-5D results can be significantly influenced and expressed caution on its employment especially in RA patients with severe disease (23).

The current study has a number of limitations; all responses were restricted to RA patients presenting for treatment. Patients consulting more frequently are more likely to be included in the sample. Such patients are more likely to be treated more intensely, which could result in an over-estimation of the burden of RA. Equally, should a different physician sample be selected (*e.g*. primary care physicians), it would be expected to yield a different distribution of mild, moderate, severe patients overall (and therefore different proportions of patients receiving biologic medications). By the same token, severity ratings assigned by the physicians were subjective and may not necessarily reflect more objective severity markers based on Disease Activity Scores or patient reported outcomes.

One of the criteria in selecting physicians in this study was their ability to initiate or renew biologic therapy to ensure that patients had all treatment options open to them. This may have caused an oversampling of patients who were candidates for biologic therapy. This may explain why a high percentage of moderate patients were receiving biologic treatment. Alternative explanations are also possible (*e.g*. subjective rating of severity by physicians, different times of onset of therapy).

Another limitation is that the study was cross-sectional, which makes it difficult to determine cause and effect. For example, current severity does not necessarily reflect the impact of current drug therapy, since severity at the time of onset of therapies is not known. Likewise, the HRQoL measures are collected at a distinct time point and may not reflect patient reported outcomes over the entire disease continuum. Other limitations include possible physician recall bias to questions asked and, as mentioned previously, both the selection of physicians and potential variation in their subjective rating of RA severity. In addition, physician subjective severity rating and patient-reported severity and HRQoL measures also have potential variation. Barton *et al*. found a third of RA patients indicated their RA severity was greater than the corresponding physician assessment (24).

Conclusion

This study presents a snapshot of the impact of RA severity on patient HR-QoL in Brazil. The results indicate that patients with moderate-to-severe RA experience a significant disease burden across a number of morbidity measures, including functional impairment, mobility, pain, general health status, fatigue, and work and non-work productivity compared to those with mild-to-moderate disease. Severity of RA is also strongly correlated with levels of healthcare resource utilisation, posing a significant burden to patient wellbeing and financial resources. It is important not only to further understand the full extent of the disease burden, but also to understand how more effective disease management and treatment strategies may mitigate such a burden.

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