

Determinants of Disability in Rheumatoid Arthritis: A Community-Based Cohort Study

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Abstract: Longitudinal care of a community-based cohort of patients with rheumatoid arthritis (RA) was evaluated retrospectively. Candidate determinants of disability included visual analog scales (VAS) for patient global assessment and pain, comorbidities, and medications. The outcome was the 'patient-acceptable symptom state' for disability as defined by the Health Assessment Questionnaire (HAQ) disability index, using a cutoff of <1.04. Two-sample t tests and multivariable logistic regression were used to determine odds ratios (OR) for associations between predictor variables and disability. Out of a total of 99 patients, 28 (28%) patients had HAQ ≥ 1.04 at their last visit. The greatest odds of not attaining the patient-acceptable symptom state in a multivariable model was associated with corticosteroids (OR: 5.1; $p=0.02$), antidepressants (OR: 5.3; $p=0.02$), and female sex (OR: 6.5; $p=0.05$). In the era of biologic therapy, female sex, corticosteroids, and antidepressants remain profound determinants of disability highlighting the need to understand the underlying mechanisms.

Keywords: Depression, disability, rheumatoid arthritis.

INTRODUCTION

In the era of increasing use of biologic therapy and data regarding comparative effectiveness of treatment regimens, patients continue to experience significant disability secondary to rheumatoid arthritis (RA). While there is evidence of declining overall disability in large cohorts, disability continues to be prominent and serves as a frequent cause of permanent loss of employment [1-3]. Even in the ideal setting of clinical trials with aggressive therapy regimens, the impact of RA on disability is not eliminated [4-6].

Cohort studies of patients with RA demonstrate the importance of baseline health assessment questionnaire (HAQ), erosions, autoantibody status, swollen joint counts, and age as predictors of future disability [7-9]. Further, the importance of comorbidity on disability progression has been emphasized in a large RA cohort, particularly cardiovascular disease and higher overall burden of comorbidities [10]. In these cohort studies, data were obtained at baseline and then at different subsequent time points; however it is often unclear if data such as HAQ or patient assessments of disease were available in real time to clinicians to allow for adjustment in management. Further, these cohorts are variable in terms of the utilization of biologic therapies due in part to the time of publication before high rates of biologic use. In addition to the medical features, socioeconomic status

and psychosocial factors such as learned helplessness serve as potential mediators of future disability; however it is unclear how these factors acted upon by clinicians if at all [11-13].

The goal of this study was to evaluate a community-based cohort of persons with RA with ready access to biologic therapy for patient-centered determinants of disability. This study utilized the Rochester Epidemiology Project (REP), a unique cohort that allows for retrospective evaluation of clinical data that was obtained during routine clinical care [14]. As this data was generated as part of routine clinical care, it was available to clinicians in real time to make adjustments to the management strategy for individual patients. Understanding the factors that drive disability is relevant not only in contemplating intensification of therapy, but also in considering non-immune approaches of improving function. Even if inflammation is controlled, other disease-associated factors may need to be modified to optimize physical function. This comprehensive approach will allow for a high quality, patient-centered management plan.

MATERIALS AND METHODS

Patient Cohort

A retrospective chart review of a random sample of 100 patients with RA as part of a population-based cohort, utilizing the REP RA cohort including a total of 501 patients, was performed [14]. The information obtained from the chart review was used in the care of patients and was available to

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clinicians at the point-of-care. This study included patients fulfilling the 1987 American College of Rheumatology (ACR) classification criteria for RA [15]. In order to evaluate for change in disability and disease activity, eligible patients must have been evaluated by a rheumatologist on 3 occasions such that the index visit occurred after 1/1/2009 with requirement for a second visit within 12 months followed by a third visit within six to eighteen months of the previous visit. Patients were followed until 3/1/2012.

Baseline characteristics, including age, sex, race, ethnicity, education level, alcoholism, smoking status, current employment status, and current relationship status, were identified based on patient provided information. Other information regarding comorbidities was obtained, including clinical diagnoses of anxiety, depression, fibromyalgia, or obstructive sleep apnea by chart review including clinical notes and diagnosis lists. Diabetes mellitus was defined by physician diagnosis and/or documented use of insulin and/or oral hypoglycemic agents [16].

Information regarding the date of RA diagnosis, extra-articular manifestations of RA, radiographic evidence of erosions, and history of joint surgery were identified [17]. Serologic status including rheumatoid factor (RF) and anti-citrullinated protein antibodies (ACPA) were identified including any history of positive results and the most recent value to index date.

As part of all visits to the Inflammatory Arthritis Clinic, patients complete a global assessment of disease activity on a visual analog scale (VAS; 0-100 mm), patient pain assessment VAS (0-100 mm), and HAQ (0-3) prior to the appointment, hence this data was available to their rheumatologists in real time to assist in management decision-making [18]. Providers' assessments, including swollen and tender joint counts (0-28 joints), global VAS (0-100 mm), and qualitative assessment of disease activity (active *versus* inactive), were abstracted if the rheumatologist had documented these during their visit. Inflammatory markers (ESR, CRP) were abstracted at each visit when available.

Baseline medications specific to RA were determined at the index appointment. Both previous and current use of methotrexate, other disease modifying antirheumatic drugs (DMARDs) (including hydroxychloroquine, sulfasalazine, and leflunomide), tumor necrosis factor (TNF α) inhibitors, and other biologics (including abatacept, rituximab, and tocilizumab) were identified. Corticosteroid use was recorded as current use (≤ 4 weeks), recent use (>4 to ≤ 12 weeks), or no recent use (>12 weeks). At each appointment, changes to medications were recorded in the form of start, increase, discontinue, decrease, or no change for the categories methotrexate, other DMARDs, TNF α inhibitors, other biologics, or corticosteroids. Identified side effects related to medications were also recorded. Information regarding the timing and number of joint injections was also abstracted. Use of adjuvant medications, including opioids, tramadol, anxiolytics, antidepressants, muscle relaxants, pregabalin/gabapentin, and sleep aids, were evaluated at each appointment.

Data Analysis

Study data were recorded and managed using the Research Electronic Data Capture system [19]. Research Electronic Data Capture is a secure, web-based application designed to support data capture for research studies.

For the descriptive statistics, continuous variables were described using mean \pm standard deviation (SD), and categorical variables were described with percentages. The "patient-acceptable symptom state" for physical disability was defined by the HAQ disability index using a cutoff of <1.04 [20]. The range of HAQ is 0-3 with <1 felt to represent mild disability and <2 moderate disability [21]. This patient-acceptable symptom state was identified in a cohort of RA patients using a question regarding satisfactory condition both with 75th percentile estimation as well as receiver operating characteristic analysis. Two-sample t tests and multivariable logistic regression were used to determine odds ratios (OR) for associations between predictor variables and disability.

RESULTS

Patient Characteristics

One hundred patients of the population cohort were evaluated, and HAQ data were available for 99. The mean age at first visit was 59.9 ± 14.0 , with 76.8% females. The mean duration of RA at the first index visit was 9.5 ± 6.4 years. RF status was available in 95 of 99 patients, with 82.1% positive for RF. The ACPA status was available in 74/99 and positive in 54.1%. Joint erosions visualized on x-ray and/or MRI were present in 63.6%, and 34.3% had undergone at least one joint surgery. The patients were followed for a median of 2.5 years with range of 0.6-3.2 years. The mean value of the patient global VAS at the index visit was 28 ± 24 . At the final visit, the patient VAS global was 31 ± 26 .

Factors Predictive of Patient-Acceptable State at Final Visit

In this cohort, 28 of 99 patients (28%) did not attain the patient-acceptable symptom state for physical disability as defined by HAQ <1.04 at their last visit. In terms of baseline characteristics, older patients, women, and patients who were not actively employed were more likely to have elevated final HAQ values. Higher initial HAQ and patient global VAS both at the index and final visit were associated with an elevated HAQ at the concluding visit. Joint surgery was associated with higher disability at patients' last visit. Increased number of tender joints, but not of swollen joints, was significantly associated with not reaching the patient-acceptable symptom state. Previous use of methotrexate and recent or increasing corticosteroid use were associated with elevated HAQ values. No prior use of other DMARDs was also associated with failing to attain the patient-acceptable state. Use of antidepressants, anxiolytics, or tramadol/opioids was associated with an elevated HAQ value (Table 1).

Table 1. Characteristics associated with final patient-acceptable symptom state.

Variable	HAQ <1.04 (N=71)	HAQ ≥ 1.04 (N=28)	p-Value
Age at first visit, years	57 ± 13.1	67.5 ± 13.6	0.003
Sex (female)	50 (70.4%)	26 (92.9%)	0.017
Duration of RA, years	9.2 (6.3)	10.2 (6.6)	0.372
RF positive status	57 (83.8%)	21 (77.8%)	0.488
ACPA positive status	31 (58.5%)	9 (42.9%)	0.224
ESR	13.8 (11.0)	17.0 (13.9)	0.313
CRP	12.3 (26.8)	15.8 (23.1)	0.152
Patient global VAS (mm), first visit	22.4 ± 21.9	41.7 ± 21.9	<0.001
Pain VAS (mm), first visit	29.8 ± 24.6	44.4 ± 22.6	0.008
Tender joint count, max	3.9 ± 5.6	7.3 ± 7.9	0.018
Swollen joint count, max	4.4 ± 5.2	6.8 ± 7.1	0.122
Methotrexate use, ever	60 (84.5%)	28 (100%)	0.027
Other DMARD use, ever	63 (88.7%)	20 (71.4%)	0.035
Biologic use	25 (35.2%)	15 (53.6%)	0.094
Corticosteroid use	20 (28.2%)	17 (60.7%)	0.003
Any medication start/increase	52 (73.2%)	23 (82.1%)	0.352
Tramadol/opioid use	25 (35.2%)	17 (60.7%)	0.021
Antidepressant use	14 (19.7%)	13 (46.4%)	0.007
Anxiolytic use	3 (4.2%)	8 (28.6%)	0.001
Depression	21 (29.6%)	12 (42.9%)	0.207
Fibromyalgia	5 (7.0%)	3 (10.7%)	0.546

Values are reported as mean ± SD or N (percentage value). CRP = C-reactive protein, DMARD = disease modifying antirheumatic drug, ESR = erythrocyte sedimentation rate, HAQ = Health Assessment Questionnaire, RA = rheumatoid arthritis, RF = rheumatoid factor, VAS = visual analog scale

Pertinent factors not predictive of disability included autoantibody status, inflammatory markers at index visit, duration of RA, and smoking status. Comorbidities including diabetes mellitus, fibromyalgia, and obstructive sleep apnea were also not associated with disability. Current use or initiation of TNF inhibitors or other biologic therapies were not associated with the final patient-acceptable symptom state. Further, combining all medication initiations and dosage increases as a surrogate of escalation of therapy was also not associated with the final patient-acceptable symptom state.

Multivariable logistic regression was performed utilizing a model both with and without baseline HAQ (Table 2). When baseline HAQ was in the model, age and the absence of other DMARD use were significantly associated with decreased likelihood that the patient reached an acceptable symptom state, HAQ ≥ 1.04. If baseline HAQ was removed from the model, corticosteroid use (OR 5.1), antidepressant use (OR 5.3), and female sex (OR 6.5) were the most strongly associated with failure to reach the patient-acceptable symptom state.

Factors Associated with Antidepressant Use

Twenty-seven patients were utilizing antidepressants during this study. Patients who used antidepressants were less likely to be ACPA positive. These patients were more likely to have a higher tender joint count. They were more

likely to have undergone joint surgery. Further, patients who used antidepressants were more likely to use an anxiolytic or sleep aid. There was no difference in terms of duration of RA, employment status, joint erosions, or use of RA-specific medications (Table 3).

Physician Assessment of Disease Activity

At the first visit providers felt that disease was active in 30.3%, which decreased slightly to 27.3% at the last visit. Of the 30 who were considered to have active disease at the first visit, 11 were considered to have persistently active disease at the last visit. In contrast, among 69 considered initially to have inactive disease, 16 patients were considered to have active disease at the final visit. Among individuals who had a HAQ ≥ 1.04 at the final visit, only 3 of 28 (10.7%) were considered to have active disease at both the first and last visit. These 3 patients were all women with nonerosive seronegative arthritis. One of the three was currently smoking. Further 2 had a diagnosis of depression and one of these also had a diagnosis of fibromyalgia.

DISCUSSION

By evaluating a modern community cohort outside of clinical trials in the setting of increasingly available biologic therapy, this study sought to update our understanding of

Table 2. Determinants of the final patient-acceptable symptom state.

Effect With Baseline HAQ	Odds Ratio	95% CI		p-Value
Age	1.073	1.015	1.133	0.0130
Female	2.591	0.350	19.231	0.3517
Corticosteroid use	3.094	0.677	14.144	0.1452
Other DMARD use	0.124	0.020	0.776	0.0258
Tramadol/Opioid use	3.997	0.916	17.437	0.0652
Antidepressant use	3.446	0.779	15.250	0.1031
Patient Global VAS at first visit	1.024	0.993	1.057	0.1321
HAQ at first visit	5.645	1.534	20.775	0.0092
Effect Without Baseline HAQ	Odds Ratio	95% CI		p-Value
Age	1.075	1.023	1.130	0.0042
Female	6.494	1.04	40.0	0.0456
Corticosteroid use	5.099	1.290	20.159	0.0202
Other DMARD use	0.137	0.028	0.674	0.0145
Tramadol/Opioid use	3.272	0.901	11.888	0.0717
Antidepressant use	5.255	1.324	20.852	0.0183
Patient Global VAS at first visit	1.041	1.012	1.071	0.0055

The results of multivariable logistic regression are shown. The dependent variable was patient-unacceptable disability defined by the final HAQ value ≥ 1.04 .

Table 3. Characteristics associated with antidepressant use.

Variable	No Antidepressant (N=73)	Antidepressant (N=27)	p-Value
Age at first visit, years	59.8 \pm 14.6	60.0 \pm 12.4	0.966
Sex (female)	53 (72.6%)	24 (88.9%)	0.086
ACPA positive status	33 (62.3%)	8 (36.4%)	0.040
Joint erosions	49 (67.1%)	14 (51.9%)	0.160
Joint surgery	19 (26%)	15 (55.6%)	0.006
Tender joint count, max	3.7 \pm 5.9	7.6 \pm 7.1	0.002
Anxiolytic use	3 (4.1%)	8 (29.6%)	<0.001
Sleep aid use	6 (8.2%)	12 (44.4%)	<0.001

Values are reported as mean \pm SD or N (percentage value).

what factors are associated with disability. Ultimately, preventing disability is a shared goal of patients and providers. Fortunately, disability rates are declining in the biologic era and goals of tight control of inflammation but continue to have significant impact on patients [1-3]. Multiple clinical factors are associated with disability based on previous cohort data, including age, RF positivity, tender joint count, inflammatory markers including ESR and CRP, and joint damage [7-9, 22]. Further, psychosocial factors further modify these clinical factors and contribute to the ultimate experience of disability by the patient [11, 13]. In our study, age and tender joint count were associated in the univariate analysis with disability while RF status, inflammatory markers, and joint erosions were not.

Our study demonstrated that the use of other DMARDs such as hydroxychloroquine, leflunomide, and sulfasalazine

was associated with a lower disability, likely representing patients with low disease severity whose disease did not require further escalation. All patients with an end HAQ ≥ 1.04 and a vast majority of those with a lower rating had previously tried methotrexate. The minority with low disability who had not taken methotrexate likely represent the same group of other DMARD users with mild disease severity. Despite the era of biologic therapy, with 39 patients having exposure to TNF α inhibitors and 12 patients having exposure to other biologics, corticosteroid use remained one of the strongest predictors of future disability. Biologic therapy was not associated with the final symptom state which is likely a reflection that this study is longitudinal and not a clinical trial and thus confounding variables may interfere with association.

Depression has a major impact on patients with RA and is associated with higher patient-reported global disease activity and pain as well as disability and mortality [23-25]. In this study, antidepressant use was associated with final disability status. Interestingly, patients treated with antidepressants were less likely to be ACPA-positive, which has been variably associated with disability in other studies [26, 27]. While antidepressant use was significantly associated with ultimate HAQ status, the clinical diagnosis of depression was not. This finding could potentially be explained if medication lists are more routinely updated at each follow-up visit than the clinical problem list or past medical history. Alternatively, antidepressant use could be reflective of more severe depression.

Interestingly, a clinical diagnosis of fibromyalgia was not associated with disability as previously demonstrated [28]. However, this is likely due to the relatively low number with a clinical diagnosis of fibromyalgia, 8 patients in the cohort. This number may under-represent the patients with components of peripheral or central pain sensitization because the abstraction required a formal diagnosis of fibromyalgia to be listed in the clinical notes.

Pain sensitization impacts the experience of patients with RA [29]. It may in part explain why escalation of therapy, as represented by initiation or increase in dose, was not associated with disability. In some clinical scenarios, symptoms were not felt to be driven by acute inflammation. This discordance between patients and clinicians has been demonstrated in previous RA cohorts and raises the possibility of pain sensitization as an underlying mechanism [30, 31]. Further, pain thresholds in patients with RA are known to be associated with depression, which corroborates the finding of an association between antidepressant use and disability [32]. The use of antidepressants in this cohort could speculatively reflect an attempt by clinicians to target patients' pain experience and may explain why antidepressant use and not depression was associated with higher disability rates. Relatively low use of pain modulators such as duloxetine, pregabalin or gabapentin was observed in this study, suggesting that these agents represent an underutilized therapeutic option to manage pain in community dwellers with RA.

This study was limited by its retrospective nature, and there were missing data including joint counts and provider global VAS. Further, the qualitative assessment was dependent on the interpretation of the clinician's documentation, so there was potential for misclassification. The requirement for 3 visits over the course of 3 years potentially may have excluded patients with more severe disability or fewer resources by their inability to follow-up with appointments, which could have reduced the power to identify factors associated with disability.

The strengths of this study included evaluation of a community cohort in the era of biologic therapy. We were able to evaluate diverse factors that could impact disability including demographic data, laboratory data, radiographic data, medication use, patient assessments, and provider assessments. Further, it was a longitudinal study allowing for evaluation of future outcomes with baseline characteristics. This study utilizes a HAQ defined patient acceptable state which has been used by other studies to assess outcomes

with importance identified by patients with RA [33]. Further, this technique to generate the patient acceptable state has been expanded upon in other disease such as systemic lupus erythematosus and osteoarthritis [34, 35].

Even in the era of biologic therapies, patients' experiences of pain and disease activity, treatment for mood and anxiety disorders, and RA treatment characteristics are still important determinants of disability. The findings underscore the utmost importance of incorporating patient perspectives and disease assessments in discussing options for treatment/prevention of disability. Future research should investigate the underpinnings of persistent corticosteroid use and antidepressant use, which could enlighten new interventions for improvement of outcomes.

CONFLICT OF INTEREST

Its contents are solely the responsibility of the authors and do not necessarily represent the official views of the NIH.

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