Prognostic Factors for Permanent Work Disability in Patients With Rheumatoid Arthritis Who Received Combination Therapy of Conventional Synthetic Disease-Modifying Antirheumatic Drugs

A Retrospective Cohort Study

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Background: There is limited information about the factors related with the development of long-term permanent work disability (PWD) in rheumatoid arthritis (RA) treated with a combination of conventional synthetic disease-modifying antirheumatic drugs (cs-DMARDs).

Objective: The aim of this study was to evaluate incidence and factors associated with the development of PWD in RA treated with combination therapy using conventional synthetic cs-DMARDs.

Methods: We assessed in multivariate models the effect of clinical and demographic factors in the development of PWD in a long-term retrospective cohort of 180 workers with RA who were treated with a combination of cs-DMARDs.

Results: Incidence rates of PWD were 2.2% at 1 year, 7.7% at 5 years, 24.9% at 10 years, 34.9% at 15 years, and 45% at 20 years. In the adjusted Cox regression analysis, factors associated with PWD development were the first failure with combination of cs-DMARDs (hazard ratio [HR], 2.4; 95% confidence interval [CI], 1.05–5.46; $P = 0.03$), poor functioning at time of cohort onset (HR, 2.2; 95% CI, 1.05–4.70; $P = 0.03$), and requirement for joint replacement (HR, 3.3; 95% CI, 1.28–8.79; $P = 0.01$).

Conclusions: Around 25% of workers with combination therapy with cs-DMARDs developed PWD in 10 years following the diagnosis of RA. Some factors increase the risk of disability. Permanent work disability generates a relevant society burden and increases health care costs. Therefore, indicators predicting failure of combination therapies with cs-DMARDs might provide clinicians of useful tools for modifying treatments avoiding the disease progression.

Key Words:
conventional synthetic disease-modifying antirheumatic drugs, permanent work disability, prognostic factors, rheumatoid arthritis

(*J Clin Rheumatol* 2017;23: 376–382)

Rheumatoid arthritis (RA) is an autoimmune rheumatic disease with a high risk of functional disability and substantial negative consequences for the workforce.[1,2] In the workplace, the impact of RA includes a decrease in the ability to perform the job,[2,3] higher rates of sick leave, work days lost, and permanent work disability (PWD).[4,5] Permanent work disability in RA is associated with several demographic and clinical factors, including manual work, worse functioning evaluated with the Health Assessment Questionnaire–Disability index score, positive rheumatoid factor, and joint replacement.[5,6] Delay of treatment with conventional synthetic disease-modifying antirheumatic drugs (cs-DMARDs) has also been considered a factor associated with higher rates of PWD.[6] European League Against Rheumatism recommendations for RA management consider the combination of cs-DMARDs for patients with a poor response to monotherapy with methotrexate (MTX).[7] A similar recommendation has appeared in the Mexican guidelines, in which the strategy of a combination of cs-DMARDs is suggested in patients who remain with active disease despite monotherapy.[8]

Emery et al.[9] described a number of factors that are predictive for RA progression, including joint damage and signs of disease activity. Therefore, the use of more intensive therapy based on a combination of cs-DMARDs provides a tight control of disease activity when compared with the care based on monotherapy. In addition, Krause et al.[10] observed in a long-term prospective cohort that patients with severe RA refractory to MTX treatment had a more than 4-fold increased mortality ratio compared with the general population. Instead, the standardized mortality ratio in MTX users has been observed as an approximately 40% decrement in the mortality risk.[11] This effect might be attributable to a decrement of disease activity and other biomarkers of severe disease.[11]

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The study protocol was approved by the Research Ethics Committee of IMSS (approval 2009-1303-13) and was performed in accordance with the principles of the Declaration of Helsinki.

The authors declare no conflict of interest.

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Supplemental digital content is available for this article. Direct URL citation appears in the printed text and is provided in the HTML and PDF versions of this article on the journal's Web site (www.nuclearmed.com).

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ISSN: 1076-1608
DOI: 10.1097/RHU.0000000000000582

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Combination therapy with cs-DMARDs has shown an earlier decrement of disease activity compared with the strategy of single therapy with DMARDs.[12]

However, information on PWD rates after utilization of combination therapy with cs-DMARDs continues to be inconsistent. Puolakka et al.,[13] who compared 2 treatment strategies concerned with the development of work disability, observed that 20% of patients with a combination of cs-DMARDs retired prematurely because of RA compared with 29% of those who received monotherapy (hazard ratio [HR], 1.27; 95% confidence interval [CI], 0.65–2.44), although this trend did not achieve statistical significance. To date, there is limited information concerning which factors predict PWD in patients utilizing a combination of cs-DMARDs. Therefore, the aim of this study was to evaluate the incidence and prognostic factors for the development of PWD in patients with RA treated with combination therapy based on cs-DMARDs.

MATERIALS AND METHODS

Retrospective Cohort

This study included 180 workers with a diagnosis of RA who were seen at a clinical visit between years 1992 and 2012 in an outpatient rheumatology clinic at a secondary care center (Hospital General Regional 110, IMSS) in Guadalajara, Mexico. Inclusion criteria were as follows: (*a*) diagnosis of RA according to the 1987 American College of Rheumatology[14]; (*b*) age 18 years or older; (*c*) paid job before the cohort onset; (*d*) these patients were included in the cohort at the time when they received a combination of cs-DMARDs (according to the clinical guidelines for the pharmacological treatment of RA followed by the Department of Rheumatology in our center, a patient is considered candidate to receive combined therapy with cs-DMARDs when he/she develops a failure to achieve low disease activity or remission after at least 3 months with monotherapy with a cs-DMARD, or they might also have star with a combination of cs-DMARDs); and (*e*) patients must have had clinical chart available at the hospital.

We excluded: a) patients with overlapping syndrome and b) workers with RA who already had PWD at the time of cohort onset. We excluded from the analysis those patients who were seen by the rheumatologists only once and did not have a follow-up. The reasons for these exclusions were that we had no information on patients with only 1 single visit about whether they had taken the combination of cs-DMARDs as they were prescribed or whether these patients developed PWD during their disease evolution.

Study Development

All clinical charts were reviewed by 3 researchers (M.L.V.-V., D.S.-M., L.F.C.T.), who were trained in clinical charts evaluation and supervised by another researcher (L.G.-L.). Factors assessed in a structured format were the following:

(*a*) Demographic and lifestyle characteristics, including age, sex, years of formal education, marital status, smoking, and alcohol consumption. Criteria used for smoking or alcohol consumption consisted of the description by the rheumatologists of these 2 exposure factors.
(*b*) Comorbidities: diabetes mellitus, high blood pressure, fibromyalgia, and depression.
(*c*) Disease characteristics at time of cohort onset: These variables were taken at the time of the patient's first visit with the rheumatologist reported on the chart: duration of symptoms of RA prior to first visit, global functional status, radiological stage according to Steinbrocker criteria,[15] and positivity for rheumatoid factor.
(*d*) Disease characteristics investigated at any time of cohort development. The following variables were identified at any time during the cohort: (1) treatment with DMARD (synthetic and biologic); (2) extra-articular manifestations were recorded if they met the criteria described by Turesson et al.[16]; otherwise, the patient was considered without extra-articular manifestations; (3) joint replacement surgery during cohort; and (4) type of cs-DMARDs prescribed (drug prescription: patients with RA in our clinical setting usually received, as first-line treatment, MTX as monotherapy or in combination therapy, unless there were contraindications to the prescription of this drug). Therefore, the majority of combination therapy schemes evaluated in this study included MTX. Study onset: These patients were included in the cohort when they received the combination of cs-DMARDs.
(*e*) Occupational variables: type of job *c*lassified as (1) manual work (including jobs related to the agricultural, industrial, and transport sectors) and (2) nonmanual work (including jobs related with administrative, services, specialized, or managerial sectors).[17]

Structured Assessment of Permanent Work Disability

The clinical charts were assessed from the first rheumatologist evaluation up to the development of the PWD or until the last reported visit of each patient described in the clinical chart. Permanent work disability was defined as the permanent withdrawal from the labor force as a result of RA indicated by the Labor Medicine Normative of the Social Health Insurance. Briefly, in our institution, all patients who were proposed for a disability pension were sent to the Labor Medicine Department and had a clinical report from the specialist in labor medicine, who determined that the patient was permanently disabled from work because of RA.

In addition, sick-leave episodes were identified as temporal work disability. In this case, the rheumatologist determined and registered the number of days during which the patient was temporarily disabled.

Failure of Combination Therapy With cs-DMARDs

This was defined as the explicit description in the clinical chart by the rheumatologist of persistence of moderate or severe disease activity after at least 3 months of the therapy leading to changing these drugs to biologic DMARDs.

Statistical Analyses

Qualitative variables are expressed as numbers and percentages, whereas quantitative variables are expressed as means ± SD. Incidence density for disability pension was obtained in RA patients included in the cohort at different years.

Kaplan-Meier analysis was used to estimate medians and ranges for PWD development in the presence or absence of each risk factor. Kaplan-Meier survival curves were used to estimate probability, adjusted for follow-up time to develop PWD by the presence of risk factors, and the log-rank test was applied.

Cox regression analysis was used to identify factors associated with PWD development. Several models were tested, using PWD as the dependent variable and using as covariates the variables that had $P < 0.20$ in the univariate analysis or that were considered meaningful for the development of this outcome. Hazard ratios and their 95% CIs were obtained for each risk factor, and all of the models included sex, age, and time of follow-up in the adjustment. P value was set at the 0.05 level. All statistical analyses

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were performed using the software SPSS Statistics for Windows (version 20.0; IBM Corp, Armonk, NY).[18]

RESULTS

Of the 614 patients with RA included in the cohort, 372 had a paid job (susceptible to develop the outcome); 192 of these patients were excluded because of the following reasons: (*a*) at the time of the cohort onset, 96 RA workers were already unemployed; (*b*) 7 workers had PWD at the time of the cohort onset; (*c*) 12 RA patients had an overlapping syndrome with other autoimmune rheumatic diseases; (*d*) 56 RA workers had only 1 single visit with the rheumatologist; and (*e*) 21 RA patients after a strict review of their clinical charts had had only monotherapy with cs-DMARDs during all the visits.

We also took into account other causes of censored data during the follow-up; from the total patients who started in the cohort, 20 patients were censored during the follow-up because they developed PWD because of non–RA-related causes. From them, 18 workers during the follow-up in this cohort became retired by age, and 2 other workers who were RA patients received disability pension as a consequence of injuries secondary to traffic accidents.

One hundred eighty patients were included in the cohort, with 83% females, who accumulated a whole follow-up time of 1184 years, equivalent to 6.57 person-years (range, 1–20 years).

Table 1 describes the baseline characteristics of patients included in the cohort, as well as the frequency of patients who had joint replacement during the follow-up. Mean age of these patients was 42 years, and 75% of patients performed manual work. This table also describes that 23% of patients had a Steinbrocker functional status III or IV at baseline. During follow-up, 6% of patients had joint replacement surgery due to RA. Finally, 52% of these workers developed at least 1 sick-leave episode.

Other variables that were evaluated were not included in the table: number of years of education (9 ± 3 years), symptoms of depression (21%), fibromyalgia (11%), mean of sick-leave episodes in the entire cohort (4 ± 4), and sick-leave days (58 ± 68 days). All patients who were considered to have failure with the combination of cs-DMARDs received biologic DMARDs as a rescue strategy.

Supplementary Table A, http://links.lww.com/RHU/A78, describes the types of drugs used in the combination of cs-DMARDs. A total of 69% of patients received combination treatment with at least 3 cs-DMARDs. In data that are not shown in tables: from 35 patients who were considered by the rheumatologists as having a failure of treatment with a combination of cs-DMARDs, 18 patients received biologic DMARDs, and 11 of 18 recovered their working ability. Seven patients with biologic DMARDs developed PWD.

The Figure shows the incidence of PWD at different follow-up times using Kaplan-Meier analysis. Incidence for PWD using was 2.2% at 1 year, 7.7% at 5 years, 24.9% at 10 years, 34.9% at 15 years, and 45% at 20 years.

Table 2 describes the results of the univariate analysis comparing selected characteristics at time of study entry between patients who developed PWD and those who did not. Factors associated with PWD included married or being part of a couple, smoking, alcohol consumption, a higher proportion of impairment on global functional (class III or IV), and joint replacement surgery follow-up.

Table 3 shows the PWD-associated variables in the Kaplan-Meier analysis. Factors related to lower survival time for PWD development were as follows: being married or being part of a couple ($P = 0.007$), smoking ($P = 0.003$), alcohol consumption ($P = 0.005$), joint replacement surgery ($P = 0.02$), and poor global functional status of III or greater ($P = 0.02$).

Table 4 shows the final model in the Cox regression analysis, adjusting by factors associated with PWD development. Associated predictors with PWD were joint replacement surgery (HR, 3.3; $P = 0.01$), functional class III to IV (HR, 2.2; $P = 0.03$), and no response to treatment with combination of cs-DMARDs (HR, 2.4; $P = 0.03$).

DISCUSSION

In the present study, we observed that approximately 24.9% of patients receiving combination therapy with cs-DMARDs will develop PWD at 10 years after diagnosis. This number increased to 34.9% at 15 years of diagnosis and to 45% at 20 years. Relevant risk factors for PWD in our cohort included patients who, during disease evolution, required a joint replacement, those who had worse functional class at time of cohort onset, and patients who failed to respond to the combination of cs-DMARD.

In terms of PWD incidence, we observed a substantial increase during follow-up, starting with 2.2% at the first year and rising to 45% in patients who were pensioned because of RA at 20 years. Although these disability rates are high, these incidence figures can continue to be considered relatively low as compared with the incidence of PWD observed in workers from developed

TABLE 1. General Characteristics of RA Patients Included in the Cohort

Variables	Total (n = 180)
Sociodemographic and lifestyle characteristics	
Age, mean ± SD, y	42 ± 9
Female, n (%)	150 (83)
Educational level: elementary school or lower, n (%)	108 (60)
Married or being part of a couple, n (%)	125 (69)
Active smoking, n (%)	34 (19)
Active alcohol consumption, n (%)	23 (13)
Job characteristics	
Type of work: manual, n (%)	135 (75)
Comorbidity	
Diabetes mellitus, n (%)	20 (11)
High blood pressure, n (%)	30 (17)
Disease characteristics	
Disease duration of RA, mean ± SD, y	7 ± 5
Presence of extra-articular manifestations, n (%)	103 (57)
Global functional status (III–IV), n (%)	41 (23)
Radiological stage by Steinbrocker (III–IV), n (%)	26 (14)
Rheumatoid factor (+), n (%)	102 (57)
Failure with combination of cs-DMARDs, n (%)	35 (19)
Joint replacement surgery during cohort, n (%)	11 (6)
Characteristics of sick leave	
Patients with at least one episode of sick leave, n (%)	93 (52)
Total working days lost in the entire cohort	5411
Characteristics of PWD	
Potential years of working life lost, mean ± SD	15 ± 9
Total potential years of working life lost	442

All the data of the variables shown in this table were at the baseline of the cohort except joint replacement surgery and characteristics of sick leave that were observed during the entire follow-up of this cohort. Qualitative variables are expressed in frequency (%); quantitative variables are expressed in mean ± SD.

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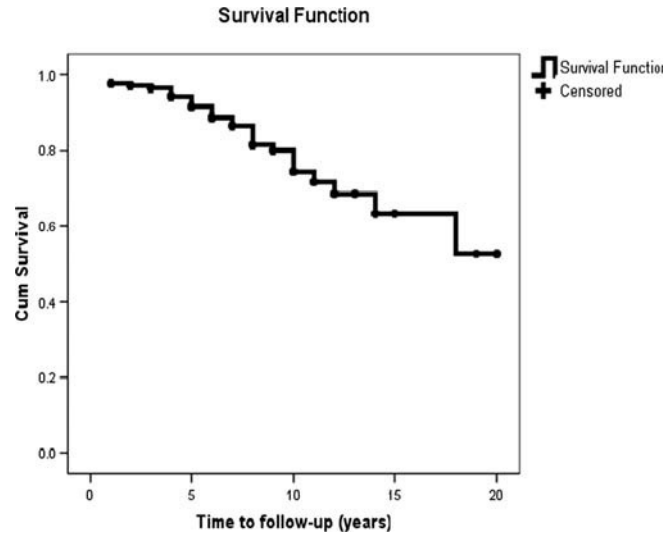

	0	1 yr	5 yr	10 yr	15 yr	20 yr
Patients remaining in cohort, n	180	176	94	29	6	5
Patients developing PWD, n	0	4	12	25	28	29
Patients censored, n	0	0	74	126	146	146
Incidence rate (%)	0%	2.2%	7.7%	24.9%	34.9%	45%

FIGURE. Incidence rate of PWD during the follow-up in the cohort.

countries. Eberhardt et al.,[19] in a Swedish cohort, observed that 35% of patients were work disabled at 5 years of follow-up, a rate considerably higher than our observed PWD incidence of 7.7% at 5 years. The differences between these PWD figures can be attributed to several factors. Herein, we report the incidence observed in patients treated with a combination therapy of cs-DMARDs, whereas

TABLE 2. Comparison in Characteristics Between Patients With PWD Versus Without PWD

Variables	Developed PWD (n = 29)	Did Not Develop PWD (n = 151)	HR	95% CI	*P*
Sociodemographic and lifestyle characteristics					
Males, n (%)	5 (17)	25 (17)	1.2	0.4–3.1	0.69
Age ≥40 y	17 (59)	95 (63)	0.9	0.4–1.9	0.89
Education level (≤elementary school), n (%)	17 (59)	91 (60)	1.1	0.4–2.4	0.89
Married or being part of a couple, n (%)	25 (86)	100 (66)	3.8	1.3–11	0.01
Active smoking, n (%)	10 (35)	24 (16)	3.0	1.4–6.6	0.005
Active alcohol consumption, n (%)	9 (31)	14 (9)	2.9	1.3–6.3	0.008
Job characteristics					
Type of work: manual, n (%)	22 (76)	113 (75)	1.1	0.4–2.6	0.77
Disease characteristics					
Disease duration before the visit to the rheumatologist, mean ± SD, y	2.9 ± 4.8	2.7 ± 4.7	1.01	0.94–1.09	0.70
Duration before starting combination of cs-DMARDs, mean ± SD, y	11 ± 5	7 ± 5	0.97	0.89–1.05	0.46
Extra-articular manifestations, n (%)	16 (55)	87 (58)	0.7	0.3–1.4	0.37
Global functional status (III or IV) at baseline, n (%)	13 (45)	28 (19)	2.2	1.1–4.7	0.03
Severe radiographic damage in hands at cohort onset (Steinbrocker III or IV), n (%)	7 (24)	19 (13)	1.0	0.4–2.4	0.99
Rheumatoid factor (+), n (%)	17 (59)	85 (56)	1.04	0.4–2.1	0.90
Failure with combination of cs-DMARDs, n (%)	11 (38)	24 (16)	2.0	0.9–4.2	0.06
Joint replacement during follow-up, n (%)	6 (21)	5 (3)	2.6	1.1–6.5	0.03

Qualitative variables are expressed in frequency (%); quantitative variables are expressed in mean ± SD; HR was computed using univariate Cox regression analysis.

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TABLE 3. Variables Associated With PWD

Variables	Total, n	PWD, n (%)	Time to Develop PWD, y		*P* (Log Rank)
			Median	Range	
Marital status					
Part of a couple	125	25 (20)	14	13–16	**0.007**
Not a couple	55	4 (7)	17	15–20	
Smoking					
Yes	34	10 (29)	11	8–14	**0.003**
No	146	19 (13)	17	15–18	
Alcohol consumption					
Yes	23	9 (39)	11	8–14	**0.005**
No	157	20 (13)	16	15–18	
Joint replacement					
Yes	11	6 (54)	12	8–16	**0.02**
No	169	23 (14)	16	15–18	
Global functional status					
III–IV	41	13 (32)	14	11–16	**0.02**
I–II	139	16 (11)	16	14–18	
Failure with combination of cs-DMARDs					
Yes	35	11 (31)	13	11–16	0.06
No	145	18 (12)	16	15–18	

Kaplan-Meier analysis. Other factors not associated with PWD tested in the Kaplan-Meier analysis were age older than 40 years, sex, educational level, diabetes mellitus, hypertension, fibromyalgia, depression, job type, radiographic stage at onset of cohort, extra-articular manifestations, and positive rheumatoid factor.

Significant *P*-values are described using bold font.

other studies included in their cohorts patients in monotherapy with cs-DMARDs. Another issue to be considered is the possibility of selection bias of "healthy workers." Because we included patients with RA who were paid workers at the cohort onset, these patients may have a lower probability of developing PWD. Even if bias was present, we observed that a significant proportion of patients with a combination therapy of cs-DMARDs developed PWD during the follow-up.

To the best of our knowledge, this is one of the few long-term studies based on a real-life cohort evaluating the rate of PWD in patients with combination therapy with cs-DMARDs.

The guidelines proposed by the European League Against Rheumatism for management of RA recommend, in the first phase after clinical diagnosis of RA is established, starting with MTX alone or in combination with cs-DMARDs,[7,20] although these guidelines also recommend considering combination therapy with cs-DMARDs as an option in the second phase after failure with or toxicity to drugs used in phase 1.[7,20] In unpublished observations, we observed that a proportion of 50% to 70% of patients with RA may require a therapy combination with cs-DMARDs, that is, according to the proportion of patients with reported failure of MTX in clinical trials.[21]

TABLE 4. Risk Factors for Development of PWD in RA Treated With Combination of cs-DMARDs

Factors Related to PWD	HR	95% CI	*P*
Age,[a] y	1.0	0.98–1.07	0.25
Male	0.8	0.31–2.56	0.84
Disease duration,[a] y	0.9	0.89–1.02	0.22
Joint replacement	3.3	1.28–8.79	**0.01**
Functioning status at baseline (III or IV)	2.2	1.05–4.70	**0.03**
Failure with combination of cs-DMARDs	2.4	1.05–5.46	**0.03**

Multivariate Cox regression analysis identifying risk factors for the development of PWD in RA treated with a combination therapy of cs-DMARDs. Variables in the univariate survival analysis with $P < 0.20$ were included.

Significant *P*-values are described using bold font.

[a]Age and RA disease duration were included as quantitative variables. Functioning status at baseline was assessed with Steinbrocker classification.

Our results concerning the low rate of long-term failure using combination therapy with cs-DMARDs in patients with RA as identified by the rheumatologist in real life are also supported by the proportion of patients who achieved remission or exhibited low disease activity in clinical trials. Emery et al.[22] reported that the remission rate at 52 weeks was approximately 2 times higher among patients who received combination therapy compared with MTX alone (50% vs. 28%).

Puolakka et al.[13] compared 2 strategies, single therapy versus combination therapy, and observed the risk of development of retirement due to RA. The authors reported a nonsignificant trend for a higher risk of retirement in patients using single therapy. In addition, these authors[9] observed a significant difference in the cumulative duration of sick leaves between these 2 groups. There was a median of 30 sick-leave days per patient-year in the single therapy group compared with 11.7 sick-leave days per patient-year in the combination therapy group.

Barrett et al.[23] described the time between prescription of cs-DMARDs and development of work disability in 2 cohorts of workers with RA (the first cohort included 160 RA patients between the years of 1989 and 1992 with a mean follow-up time of 8.6 years, and the second cohort included 134 RA patients between the years of 1994 and 1997 with a mean follow-up time of 4.1 years). The authors reported that at less than 12 months, patients could stop work after the onset of therapy with cs-DMARDs and observed that PWD incidence at 1 year in cohort 1 was 14%, whereas that in

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cohort 2 was 23%. These rates are elevated compared with patients in our study, perhaps because these authors did not differentiate patients with combination therapy who may have a low probability of developing PWD compared with patients receiving monotherapy.

However, relevant discussion ensues on whether using combination of cs-DMARDs can obtain similar results to using biologic agents in long-term outcomes, such as a disability pension. Allaire et al.,[24] in a case-control study, has an interesting observation regarding the effect of anti–tumor necrosis factor (TNF) agents on the rate of work disability. In that study, Allaire et al.[24] were unable to find a protective effect versus nonusers in the risk of permanent work loss (odds ratio, 1.1; 95% CI, 0.7–1.6). In contrast, Olofsson et al.,[25] in a population-based cohort, identified that users of anti-TNF agents demonstrated a decrease in disability pension during the first 12 months after initiating treatment with TNF antagonists. We observed in our multivariate analysis that factors associated with PWD included failure to respond to combination therapy with cs-DMARDs, although because of the characteristics of the present study and current guidelines for treatment of RA, we did not evaluate patients who received anti-TNF early at the onset of RA.

Many studies have evaluated the rates of PWD in RA, although patient selection criteria were included to explain some of the differences in the results. Eberhardt et al.[19] identified that approximately 28% of their patients who accounted for their PWD rates were work disabled at time of study onset, although Eberhardt et al.[19] did not exclude patients who had already developed the event at cohort onset. This strategy may clearly increase the observed rate of PWD reported by these authors. Instead, we selected only patients who were all active workers at the time of initiating their follow-up and excluded those already disabled at time of cohort onset. On the other side, Tiippana-Kinnunen et al.[26] described, in a Finnish cohort, work disability rates that were higher compared with our observations. These authors identified that 7% of their patients were considered for RA-related work retirement at the first year, increasing to 19% at 5 years, to 33% at 10 years, and to 39% at 15 years, in comparison with our observed PWD rate of 24.9% at 10 years. Similar results were reported by Sokka et al.,[27] with a rate of 44%, and by Wolfe and Hawley,[28] with a rate of 31.5% at 10 years, whereas Jäntti et al.[2] reported the highest rate of disability: 80% at 20 years.

Only a few studies have assessed the rates of PWD in RA treated with combination therapy with cs-DMARDs. In the Finnish Rheumatoid Arthritis Combination Therapy Trial, Puolakka et al.[13] identified that 20% of their patients randomized to combination therapy retired prematurely from work at 5 years of study onset. Although in the study of Puolakka et al.[13] patients receiving a combination of cs-DMARDs had a trend toward lower rates of RA-related PWD compared with patients with monotherapy with cs-DMARDs, this trend did not achieve statistical significance, probably because of a small sample size.

This study has several limitations, including those inherent in its retrospective design, depending on the accuracy of registries elaborated with clinical intent, and we cannot exclude that some relevant data may be lacking. However, the present cohort also possesses interesting strengths, as follows: the first observed in this study in comparison with others is that we selected patients who were event-free (PWD) at time of cohort onset; all of the patients were formal workers included under a strict registry that systematized their work status; all of these patients were assessed following the structured guidelines of the Rheumatology Service, and those considered as candidates for pension were confirmed by the Labor Medicine Department, which was independent of the rheumatologist's opinion in terms of PWD labeling. In addition, this cohort used an adjusted survival analysis to identify factors associated with PWD, including a time-adjusting strategy. All of these aspects increase the validity of our results.

In comparison with our data on the PWD incidence in patients with RA treated, the rate of PWD in Mexican workers during 2013 was only 11.6 per 1000 persons.[29] Therefore, patients with RA entertained a higher risk compared with the total worker population. These data support that RA constitutes a relevant cause of PWD in Mexico, even if combination therapy with cs-DMARDs is utilized. We concluded that early detection of failure of combination therapy with cs-DMARDs should be added as established criterion to escalate the therapeutic intensity with other therapeutic options, such as biologic DMARDs or small-molecule DMARDs as suggested by the Mexican College of Rheumatology Guidelines for the Pharmacologic Treatment of Rheumatoid Arthritis.[8]

Another limitation in our study is that our results can be extrapolated only to patients starting with a combination of cs-DMARDs. These patients might differ in several characteristics from patients initiating with monotherapy of cs-DMARD. It seems to be a reasonable thinking that patients with RA selected by the rheumatologists initiating a combination of cs-DMARDs may differ in risk factors for a more severe disease from patients initiating with monotherapy with MTX. In Mexico, it has been reported that approximately 44% of patients use a combination of 2 or more cs-DMARDs.[30] Therefore, studies reporting outcomes as PWD in this group of patients are relevant. One of the main contributions of this study is that at 10 years of follow-up almost 1 in 4 patients using a combination of cs-DMARDs has developed PWD, and at 20 years, approximately half of the patients have developed this outcome.

Another contribution of this study was to identify by a robust multivariate model some indicators that at baseline or during the follow-up may predict PWD; these factors include having a worse functioning at baseline, developing structural damage requiring joint prosthesis, or diagnosis by the rheumatologist of a failure with combination of cs-DMARDs. All of these factors have biological plausibility.

We have another limitation in our study. As described for any study with retrospective design, the rheumatologists selected the variables that they considered useful for the clinical care, but other variables that are relevant for research might be underrecorded. That is the case for the scales of impairment in functioning and in radiographic damage. We were able to obtain only information about Steinbrocker scales for functioning and radiographic damage, and at present, it has been proved that these scales have lower sensitivity to change, as compared with other newer scales that in prospective cohorts and clinical trials have proportionated more valuable information for progression of the radiological damage or impairment of functioning. Nevertheless, the Steinbrocker scale still is very useful in the clinic and up to present is widely used in the clinical context because of its feasibility and good intraobserver reliability. Therefore, an additional utility is easy for the clinicians to extrapolate the data derived from this study using these scales to their own context. Finally, because this information was based on information registered in charts, we have no data of patients who died during the follow-up. These limitations should be addressed by future prospective studies linking their follow-up with other registries and systems to improve the capture of other relevant outcomes. In addition, there was no information about changes in outcome measures such as the American College of Rheumatology response criteria or the Disease Activity Score in 28 Joints. Although this was not the main objective of this study, this information is quite valuable in terms of our analysis of potential risk factors. Future prospective cohorts should incorporate these important scales used for therapeutic response. Although our study had these limitations, we were able to find valid results regarding our main objective of the present study related to the rate of development of PWD, because according to the regulations of the Mexican Institute of Social

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Security (IMSS), the status of PWD is obtained exclusively by a validated certification of the Labor Medicine Board.

In conclusion, this long-term retrospective cohort shows that approximately a quarter of patients receiving combination therapy with cs-DMARDs will develop PWD at 10 years of disease diagnosis, increasing to one third of patients after 15 years and to nearly 1 of every 2 patients after 20 years. We detected receiving combination therapy with cs-DMARDs, requiring a joint replacement, having worse functional class at onset, and having failure of response to combination with cs-DMARDs according to the rheumatologist as risk factors for PWD. However, the use of combination therapies with cs-DMARDs comprises a good strategy for the treatment of patients with RA with aggressive disease or failure with monotherapy, and combination therapy can be the main option for patients without access to biologics. These data confirm that a significant proportion of workers with RA continue to develop PWD even if they received combination therapy with cs-DMARDs. Therefore, patients with risk factors should be treated more aggressively, and other treatment strategies that limit damage should be evaluated in these patients.

Key Points

In workers with RA receiving a combination of cs-DMARDs, poor functioning at onset or joint replacement requirements at follow-up increase risk of PWD. Failure with combination of cs-DMARDs predicts PWD, although they may be substituted with biologic DMARDs. A reassessment of therapeutic strategies should be made in patients with these factors to decrease the impact of RA in PWD and the cost to society.

ACKNOWLEDGMENTS

The authors thank to Maggie Brunner for English editing.

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