Sustained moderate-to-high disease activity and higher Charlson score are predictors of incidental serious infection events in rheumatoid arthritis patients treated with conventional disease-modifying anti-rheumatic drugs: a cohort study in the treat-to-target era

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Abstract

Objective

Rheumatoid arthritis (RA) guidelines have moved toward intensive treatment aimed at remission. Treatment and disease activity are predictors of infections; patients from developing countries have additional predictors that may further impact the infection spectrum. Our aim was to describe serious infection events (SIEs), predictors and impact on RA outcomes, in a cohort of Mexican Mestizo patients.

Methods

Up to February 2015, charts from 176 early RA patients were reviewed by a single data abstracter. SIEs were defined according to strict criteria. RA patients with ≥1 SIE up to last follow-up were considered cases. Descriptive statistics were used; cases and paired controls (no SIE up to last follow-up) were compared by uni-variate analysis and multiple logistic regression.

Results

The cohort contributed to 948 patient-years of follow-up. There were 34 SIEs in 15 patients, at a (mean±SD) follow-up of 5±4 years. Incidence rate of SIE was 8.7 infections per 100 patient-years. Twenty-four isolated SIE were present in 14 patients. The most frequent SIEs were complicated urinary tract infections and pneumonia (each, n=8) and soft-tissue infections (n=7). In the case-control analysis, higher Charlson score (OR: 2.04, 95%CI: 1.001-4.164, p=0.05) and higher cumulative DAS28 (OR: 3.08, 95%CI: 1.91-4.98, p=0.000) were predictors of SIE; in patients with at least moderate disease activity, risk of SIE increased with higher level of cumulative disease activity.
However, SIEs did not impact subsequent DAS28, HAQ and SF-36.

Conclusion

Comorbidity and cumulative disease activity increased serious infection risk in early RA patients treated with conventional drugs, but SIEs did not impact disease outcomes.

Key words

rheumatoid arthritis, infection, comorbidity, anti-rheumatic agents.

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Introduction

Patients with rheumatoid arthritis (RA) are at increased risk of serious infections (1-2) which contributes to an excess in morbidity and mortality when compared to the general population (3, 4). Immunologic disturbances associated to the disease itself (5), the iatrogenic effects of therapeutic agents (5-7), comorbidities (6, 8), disease activity (9, 10) and disability (2, 9, 10) are among the predictors associated to such increased risk. Additional predictive factors are older age, presence of extra-articular manifestations, disease severity and leukopenia (6, 11).

Early RA is characterised by the recognition of the disease soon after symptoms onset; immediate aggressive disease-modifying anti-rheumatic drugs (DMARDs) institution is recommended, and intended to achieve and maintain remission. Early (rheumatoid) arthritis clinics (EAC) are the perfect setting to care for such patients as frequent and validated assessments of disease activity are implemented during follow-up and the intensity of the treatment is adapted to minimise disease activity level which gives a particular clinical context regarding patient´s infectious risk as both, RA specific treatment and disease activity are recognised infection predictors in longstanding and early (12, 13) disease.

In 2004, we established an EAC at a referral centre for rheumatic diseases in México City. Traditional DMARDs were used in 99% of our population, with or without corticosteroids (14-16). Our population of Mexican Mestizo patients has distinctive epidemiological, serological and clinical characteristics also shared by RA patients from Latin-American countries (16, 17). In addition, patients from developing countries are frequently uninsured, had a low socio-economical status and are lesser educated than RA patients from developed countries, and such conditions may additionally impact infections risk and outcomes (17-19).

Actually, most of the knowledge related to infections and predictors in RA has arisen from studies performed in developed countries, in patients with longstanding disease and from clinical trials (in early disease), which limits the comprehensiveness of the topic.

The objectives of the study were:

1. To describe the incidence rate of serious infection events (SIEs) in a cohort of Mexican Mestizo early RA patients treated with conventional DMARDs.
2. To describe the spectrum of SIEs and tuberculosis in the target population.
3. To investigate predictors of SIEs.
4. To define the impact of SIEs on disease outcomes specifically disease activity, health-related quality of life and disability.

Materials and methods

Setting and study population

Patients with RA were identified from the EAC of the Instituto Nacional de Ciencias Médicas y Nutrición "Salvador Zubirán", a national referral centre for rheumatic diseases in Mexico City. Patients entering the clinic had disease duration of less than a year when first evaluated and no specific rheumatic diagnosis except RA. Patients were evaluated every two months during the first 2 years of follow-up and thereafter every 2, 4 or 6 months (fixed for all the patients from the baseline evaluation). Treatment was prescribed by the rheumatologist in charge of the EAC and was "treat-to-target" oriented.

At study entry a complete medical history and demographic data were recorded along with rheumatoid factor (RF) and antibodies to cyclic citrullinated peptides (ACCP). Follow-up evaluations were standardised and included swollen and tender joint counts, patient- and physician- reported outcomes (20), comorbidity, and treatment assessment (name/s, dose/s and schedule/s of all DMARDS and corticosteroids they were taking since last visit). In addition, complete laboratory parameters were determined at follow-up evaluations. Finally, hand and feet x-rays were performed at baseline and thereafter every year.

Study design

Up to February 2015, charts from 176 patients from the EAC initiated in 2004 were reviewed and incidence rate of SIE was calculated along with their description (objectives 1 and 2).

Nested within a cohort case-control studies were designed to accomplish objectives 3 and 4. For objective 3, cases were defined as RA patients with a first SIE (see definition below) and controls were defined as RA patients who never developed a SIE during their entire follow-up. Controls were paired to cases according to: age (± 5 years), gender, follow-up to 1st SIE (or equivalent in controls), baseline RF or ACCP, baseline erosions and diabetes mellitus (DM). For objective 4, controls were paired to cases according to gender, age (±5 years), presence of RF and/or ACCP, DAS28 European League Against Rheumatism (EULAR) category (21), Charlson score, follow-up, number of DMARDs/patients and corticosteroids use.

Data collection

A single and trained data abstracter retrospectively reviewed all the charts and corroborated the integrity of data collected that included: socio-demographics, anthropometric variables, RA-related characteristics, RA treatment and comorbid conditions.

In addition, all the patients currently attending the EAC (87% of the sample, 11.3% lost to follow-up and 1.7% dead) underwent a direct interview in order to have their status confirmed (case or control); also, patients were asked about other potential SIEs attended at a different hospital during the study period; there were 3 patients with such situation; due to the impossibility to have confident data, we excluded those events. All SIEs were confirmed by an independent observer.

One patient had one SIE 5 months before RA diagnosis and data corresponding to that event were not included in the analysis. Two additional patients had one SIE each, diagnosed within 2 months of the RA diagnosis and their data were included in analysis.

Infection definition and ascertainment

SIE was *defined* if the infection met any criteria consistent with the Food and Drug Administration (FDA) AND if the patient was hospitalised. We also included the use of parenteral antimicrobial therapy and the clinical context of neutropenic fever episode. Table I, summarises definitions.

Tuberculosis cases were analysed as a distinct subgroup.

Ascertainment of every SIE was done by a member from the department of Infectious diseases according to reliable clinical findings, radiologic evaluations and confirmed identification of pathogenic microorganism from at least one culture from blood, cerebrospinal fluid, skin, sputum, tracheal aspirates, urine and other fluid collections, antigen tests of *L. pneumophila* and *S. pneumoniae*, sputum and gastric juice acid-fast bacilli smears, stool analysis tests and enzyme immunoassay for toxins, nucleic amplification tests for detection of *S. pneumoniae, N. meningitidis*, *Mycobacterium tuberculosis*, Varicella Zoster Virus, Herpes Simplex Virus, Epstein-Barr virus, Cytomegalovirus, KOH test and finally Gram and Grocott stains. Previous information was recorded on an electronic database, where the status of inpatient was confirmed.

Table I. Operational definition of SIEs in the target population.

Serious infection event	Operational definition
Soft tissue infection (STI)	Included cellulitis, abscesses and wound infections based on clinical findings and: gram stain and culture of the pus or exudates from lesions (Infectious Diseases Society of America, 2014) or response to antibiotic treatment.
Urinary tract infection (UTI)	Included pyelonephritis and urosepsis, isolation of $>10^5$ CFU/ mL of urine or positive urine leukocyte esterase and/or nitrite and pyuria in the presence of suggestive clinical features (Infectious Diseases Society of America, 2010).
Pneumonia	Presence of suggestive clinical features and demonstrable new infiltrate by chest radiograph or other imaging technique, with or without supporting microbiological data (Infectious Diseases Society of America, 2007).
Disseminated herpes zoster	Presence of vesicular eruption with a well dermatomal distribution in >1 dermatome.
Central nervous system infection	Brain abscess in the settings of focal neurological symptoms and signs, besides imaging studies including computed tomographic scan with contrast and magnetic resonance imaging with direct surgical observation.
Intra-abdominal infection	Peritonitis secondary to anastomotic dehiscence, based on clinical and radiologic evaluation corroborated with morphological exploration. Pseudomembranous colitis with Clostridium difficile-associated diarrhea confirmed by enzyme immunoassay for toxins.
Neutropenic fever	Periodontal abscess and upper respiratory tract infection based on clinical diagnosis in the context of fever (single oral temperature of ≥ 38.3ºC or ≥ 38ºC sustained >1 hour) and an absolute neutrophil account < 500 cells/mm^3 (Infectious Diseases Society of America, 2011)
Bacteremia	Isolation of E. coli in 2 blood cultures with fever (>38ºC).
Invasive pneumococcal disease	Isolation of Streptococcus pneumoniae from blood culture, PCR positive in cerebrospinal fluid and pneumococcal antigen test positive in urine sample.

Ethics

The study was approved by the Ethics Committee of the Instituto Nacional de Ciencias Médicas y Nutrición. Written informed consent was obtained in order to have patients' charts reviewed and data presented in scientific forums or published.

Statistical analysis

Descriptive statistics was used. Student *t*-test and χ^2 were used for normally distributed variables and Mann-Whitney U for non-normally distributed variables. Time to each SIE was assessed using the Kaplan-Meier curves. Logistic regression model were used to identify predictors of the first SIE. The selection of variables to be included was based on their statistical significance in the bivariate analysis; *p* cut-off ≤0.05 was established based on the number of variables a priori included in order to avoid over-fitting of the models; variable a priori considered were demographic (at baseline), disease-related

Table II. Patient and disease's characteristics, comorbidity and treatment in the whole population and comparison between patients with/without SIE.

Characteristics	RA population n=176	Patients with SIE, n=15	Patients without SIE, n=161	*p*
Socio-demographic (on entering the clinic)				
Female gender, n (%)	157 (89.2)	12 (80)	145 (90.1)	0.21
Years of age, mean±SD	38.6 ± 12.8	41.2 ± 15.5	38.3 ± 12.6	0.41
Years of formal education, mean±SD	11 ± 3.9	8.5 ± 3.7	11.3 ± 3.8	0.01
Current smokers, n (%)	16 (9.1)	2 (13.3)	14 (8.7)	0.63
Disease characteristics				
Disease duration, months	5.3 (3.3-6.9)	4.2 (3-7)	5.3 (3.5-6.8)	0.26
Patients with RF, n (%)	146 (83)	12 (80)	134 (83.2)	0.72
Patients with ACCP, n (%)	150 (85.2)	13 (86.7)	137 (85.1)	1
DAS 28	6 (4.9-7)	6.8 (5.7-7.6)	5.9 (4.9-6.9)	0.14
HAQ	1.4 (0.9-2.1)	1.8 (1.3-2.9)	1.4 (0.8-2)	0.03
SF-36 (0-100)	36.5 (26.2-53.4)	25.4 (19-46.1)	37.4 (28-54.2)	0.006
Patients with erosive disease, n (%)	17 (9.7)	4 (26.7)	13 (8.1)	0.04
Comorbid conditions				
Patients with ≥1 comorbid condition, n (%)	97 (55.1)	9 (60)	88 (54.7)	0.79
Number of comorbidities/patient*	1 (1-2)	2 (1-3)	1 (1-2)	0.09
Charlson score	1 (1-1)	1 (1-1)	1 (1-1)	0.58
Treatment				
Patients with DMARDs, n (%)	92 (52.3)	7 (46.7)	85 (52.8)	0.79
n of DMARDs/patient*	1 (1-2)	1 (1-2)	1 (1-2)	0.92
Patients with corticosteroids, n (%)	69 (39.2)	6 (40)	63 (39.1)	1
Combined DMARDs and corticosteroids, n (%)	41 (23.3)	4 (26.7)	37 (23)	0.75
Years of follow-up	5.9 (2.7-8.7)	6.8 (2.5-8.5)	5.8 (2.7-8.8)	0.78
Outcomes at last follow-up				
n (%) of deaths	2 (1.1)	1 (6.7)	1 (0.6)	0.49
n (%) of patients lost to follow-up	19 (10.8)	0	19 (11.8)	0.67
n (%) patients ≥ 1 comorbidity	119 (67.6)	10 (66.7)	109 (57.7)	1
Number of comorbidities/patient*	1 (1-2)	2 (1-3)	1 (1-2)	0.23
Charlson score	1 (1-1)	1 (1-2.8)	1 (1-1)	0.001
n (%) of patients with latent tuberculosis	38 (21.6)	4 (26.7)	34 (21.1)	0.74
DAS 28	1.7 (1-2.9)	2.4 (1.8-3.8)	1.6 (0.9-2.9)	0.03
HAQ	0 (0-0.13)	0.5 (0-1)	0 (0-0.13)	0.002
SF-36 (0-100)	84 (72.5-92.7)	72.3 (63.4-86.7)	85 (73.9-92.9)	0.02
n (%) of patients with erosions	85 (48.3)	10 (66.7)	75 (46.6)	0.18
n (%) of patients with corticosteroids	87 (49.5)	8 (53.3)	79 (49.1)	0.79
n of DMARDs/patient	2 (1-2)	2 (1-2)	2 (1-2)	0.55

Data presented as median (Q25-Q75) unless otherwise indicated.
*In the patients with the characteristics.

Table III. SIE distribution and RA follow-up to presentation.

SIE categories	n (%) of SIE	(mean±SD) years of follow-up to SIE
Complicated urinary tract infection (urosepsis or pyelonephritis)	8 (23.5)	5.0 ± 4.5
Pneumonia	8 (23.5)	5.2 ± 3.8
Soft tissue infection	7 (20.6)	4.5 ± 4.9
Disseminated herpes zoster	3 (8.8)	3.6 ± 4.2
Complicated upper respiratory tract infection	2 (5.9)	4.08 ± 5.59
Periodontal infection	2 (5.9)	4.9 ± 4.4
Intra-abdominal infection	1 (2.9)	0.5
Invasive pneumococcal disease	1 (2.9)	3.9
Infectious meningitis	1 (2.9)	8.5
Bacteremia (E.coli)	1 (2.9)	9.7

at baseline, cumulative disease activity and treatment (up to SIE in cases or up to equivalent follow-up in controls), serologic variable (at SIE in cases and up to equivalent follow-up in controls) and comorbidity. Based on the number of outcomes of interest (n=13), 3 to 4 variables were included.

All statistical tests were 2-sided and evaluated at the 0.05 significance level. Statistical analysis was performed using the SPSS/PC programme (v.17.0; Chicago IL).

Results

Study population characteristics (Table II)

Patients entering the EAC were primarily middle-aged females, with (mean±SD) 11±3.9 years of formal education. A minority of them were current smokers. Patients had short disease duration on entering the cohort and as expected, had high disease activity, high disability and poor function. The majority of the patients were RF+ and ACCP+ meanwhile few had erosive disease. More than half of the patients had at least one comorbid condition. Regarding treatment at referral to the clinic, 52.3% of the patients were indicated at least one DMARD and 39.2% oral corticosteroids.

Up to February 2015, (median, 25-75 IQR) population follow-up was 5.9 years (2.7-8.7); 2 patients had died, one because of acute abdominal pain and the other one because of an intestinal perforation of unknown etiology. Nineteen patients were lost to follow-up: 5 patients within the 1st year, 5 within the 2nd year, 6 within the period from 3rd to 5th year of follow-up, and the 3 patients left after a follow-up ≥5 years. Up to last follow-up, 85 patients (48.3%) had erosive disease, the majority of them had remission to low disease activity, and improvement of disability and function; all were receiving DMARDs and 49.4% oral corticosteroids; finally, (median, 25Q–75Q) number of DMARDs/patients was 2 (1-2), (Table II).

Description of SIEs

Up to February 2015, the cohort contributed to 948 patient-years of follow-up. There were 34 SIEs in 15 patients (8

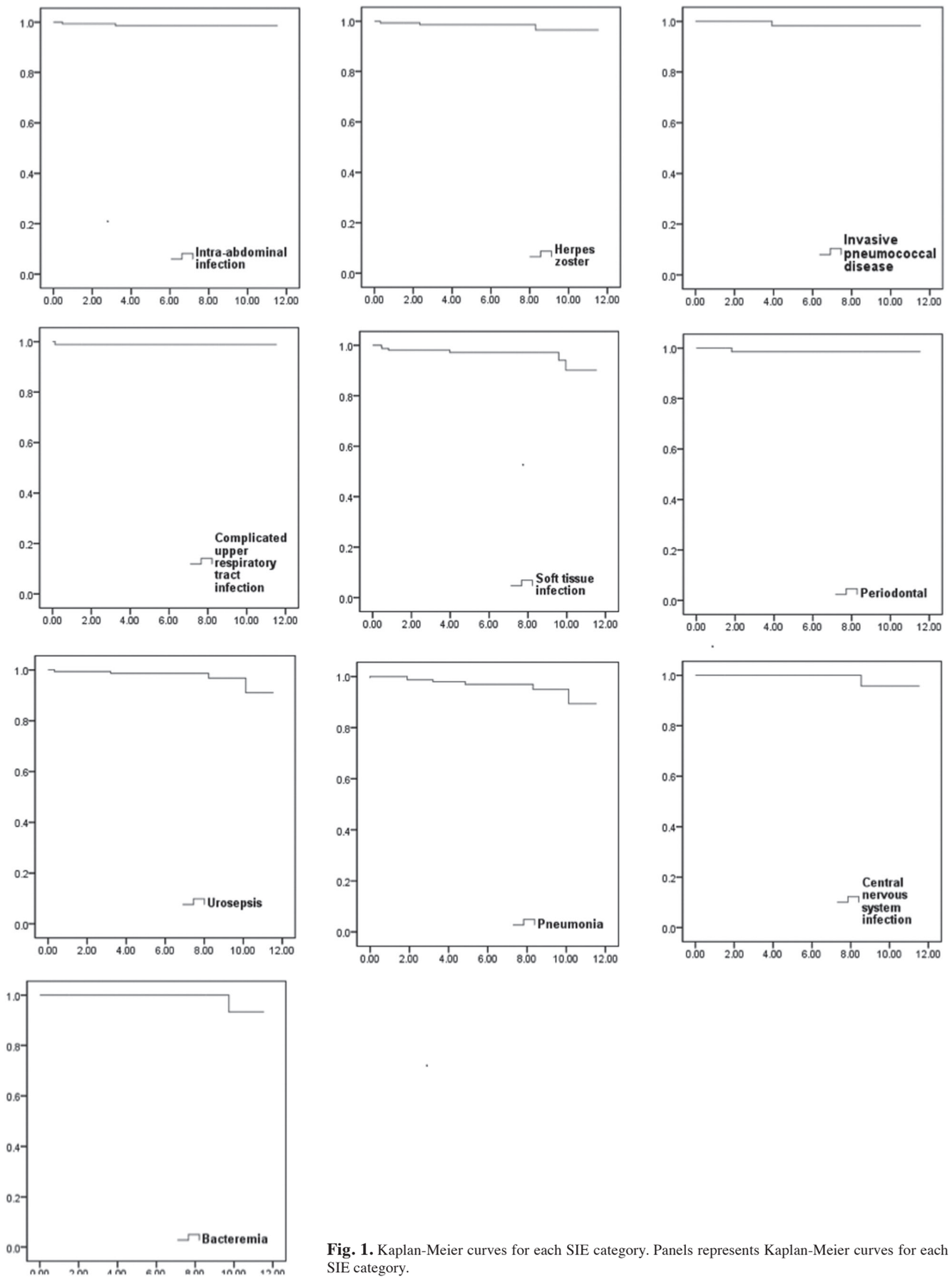

Fig. 1. Kaplan-Meier curves for each SIE category. Panels represents Kaplan-Meier curves for each SIE category.

patients had one single SIE during follow-up, 2 patients had 2 SIEs, 3 patients had 3 SIEs, 1 patient had 4 SIEs and 1 patient had 9 SIEs), at a (mean±SD) follow-up of 5±4 years; 2 SIEs were co-incidental to RA diagnosis and were not considered to calculate incidence rate of SIEs which was 8.7 infections per 100 patient-years. Twenty-four isolated SIEs were present in 14 patients; the remaining 10 SIEs were distributed in 5 clusters occurring in 4 patients.

The most frequent SIE were urosepsis (complicated lower urinary tract infection) (n=8) and pneumonia (n=8) and soft tissue infection (n=7) as shown in Table III. Some SIE categories such as *intra-abdominal infection* occurred earlier during the disease course than others as infectious meningitis and bacteremia (*E. coli*-related). Table III summarises the categories of SIEs and their (mean±SD) follow-up to each SIE category. Figure 1 represents Kaplan-Meier curves for each SIE-category.

Interestingly, no cases of active tuberculosis were described during follow-up; on entering the cohort, 38 patients (21.6%) were diagnosed with latent tuberculosis: asymptomatic patients with PPD induration ≥10mm and conventional chest radiography without abnormal findings. None of them received prophylaxis with isoniazid and after a (median, 25IQ–75IQ) follow-up of 7.9 years (3.2–9.8) there were no cases of active tuberculosis.

Patients with SIEs description and comparison with patients without SIEs

There were 15 patients with SIE whose sociodemographic characteristics, disease characteristics, treatment and comorbidity at baseline were compared to those from patients who never presented a SIE during follow-up. As shown in Table II, patients from the former group were lesser educated, had more disability and erosive disease, and poorer function; among the subgroup of patients with comorbid conditions, those with SIE tended to present a higher number of comorbidities/patient. After a median (range) follow-up of 5.9 years (2.7–8.7), cases had higher disease activity, disability and Charlson score and poorer function.

Table IV. Comparison of baseline and cumulative disease characteristics between patients with incidental SIEs and their counterparts.

Characteristics	Patients with incidental SIEs, n=13	Patients SIE-free, n=161	*p*
Socio-demographic (on entering the clinic)			
Female gender, n (%)	10 (76.9)	145 (90.1)	0.16
Years of age, mean±SD	40.5 ± 14.5	38.3 ± 12.6	0.56
Years of formal education, mean±SD	8.1 ± 3.7	11.3 ± 3.8	0.004
Current smokers, n (%)	2 (15.38)	14 (8.7)	0.34
Cumulative disease characteristics*			
Disease duration on entering the clinic, months	4.2 (2.9-6.2)	5.3 (3.5-6.8)	0.22
Patients with RF on entering the clinic, n (%)	11 (84.6)	134 (83.2)	1
Patients with ACCP on entering the clinic, n (%)	12 (92.3)	137 (85.1)	0.69
DAS 28*	4.1 (2.8-4.8)	2.4 (2-3.3)	0.002
HAQ*	1 (0.4-1.4)	0.2 (0.1-0.4)	0.000
SF-36 (0-100)*	63.3 (39.4-70.1)	68.9 (53.7-79.9)	0.123
Patients with erosive disease, n (%)*	4 (30.8)	25 (15.5)	0.235
Cumulative comorbid conditions			
Patients with ≥1 comorbid condition, n (%)	8 (61.5)	88 (54.7)	0.775
Number of comorbidities/patient	2 (1-2.8)	1 (1-2)	0.29
Charlson score	1 (1-2)	1 (1-1)	0.001
Cumulative treatment			
Patients with DMARDs, n (%)	13 (100)	161 (100)	1
n. of DMARDs/patient	2 (1-2)	2 (1-2)	0.593
Patients with corticosteroids, n (%)	6 (46.2)	79 (49.1)	1

*Data are presented as median (Q25-Q75) unless otherwise indicated.

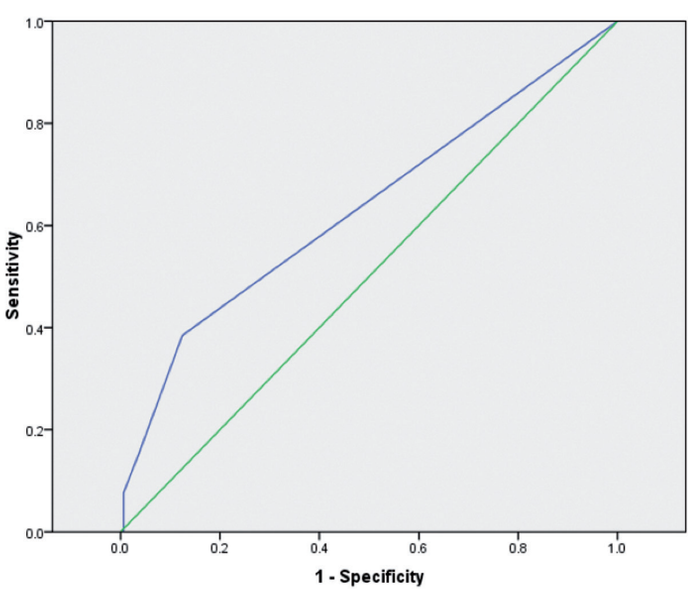

Fig. 2. ROC for Charlson score cut-off to predict SIE. ROC curve to define the best cut-off for Charlson score to predict SIEs.

Finally, patients with latent tuberculosis were compared to their counterparts, and they were older (42.3±11.8 *vs*. 37.6±12.9, *p*=0.04) and lesser educated (9.9±3.4 years of formal education *vs*. 11.4±3.9 years); no other differences were observed.

Predictors of SIE

We first compared baseline and cumulative characteristics (previous to first incidental SIE or up to last follow-up in RA patients incidental-SIE-free) between 13 patients who presented incidental SIEs (2 were discarded as their SIE was diagnosed concomitant to RA diagnosis) and their counterparts (n=161); results are summarised in Table IV; patients from the former group were lesser educated and had higher cumulative disease activity, disability and Charlson score.

Table V. Comparison of items selected from Charlson score between patients with and without SIEs (only those ever scored are listed).

n (%) of patients with Charlson score item	Patients with incidental SIE (n=13)	Patients incidental SIE-free (n=161)	*p*
Moderate to severe liver disease	1 (7.7)	1 (0.6)	0.14
Moderate to severe renal failure	0	1 (0.6)	1
Neoplasia	0	4 (2.5)	1
Leukaemia	1 (7.7)	0	0.075
Myocardial infarct	0	2 (1.2)	1
Chronic pulmonary disease	0	3 (1.9)	1
Mild liver disease	1 (7.7)	1 (0.6)	0.14
Diabetes	2 (15.4)	11 (6.8)	0.25

Based on the number of outcomes of interest, we selected a priori 3 variables to enter Cox regression analysis: cumulative DAS 28 (correlated to cumulative HAQ: rho=0.62, *p*=0.000, and correlated to cumulative DMARDs: rho=0.15, *p*=0.05), years of formal education and Charlson score; higher Charlson score (OR: 2.04, 95%CI: 1.001–4.164, *p*=0.05) and higher cumulative DAS28 (OR: 3.08, 95%CI: 1.91–4.98, *p*=0.000) were predictors of SIE.

In order to define cumulative disease activity level above which there was an increase in SIE risk we entered the following dummy variables into the model previously described, based on EULAR proposal (21): (cumulative) remission (93 patients [53.4%]), low disease activity (31 patients [17.8%]), moderate disease activity (40 patients [23%)] and high disease activity (10 patients [7.6%]); cumulative remission was considered the comparator; cumulative Charlson score (OR: 1.66, 95% CI:1.03–2.69, *p*=0.04), cumulative moderate disease activity level (OR: 16.4, 95% CI: 3.17–84.86, *p*=0.001) and cumulative high disease activity level (OR: 116.23, 95% CI: 6.69–2020, *p*=0.001) were predictors of incidental SIE.

Finally, we used ROC curves to define the best cut-off for Charlson score to predict SIE and found 2 (Fig. 2), sensitivity: 0.39, specificity: 0.88, AUC: 0.53. Table V compares most frequent items selected from Charlson score applied at last follow-up, between patients with SIEs and SIE-free.

Impact of SIEs on disease outcomes

In order to test whether SIEs impacted patient's outcomes, (mean) DAS28, HAQ and SF-36 scores during the following year of a SIE (or equivalent time) from the 13 patients with incidental SIEs (cases) were compared to those from 13 patients SIE-free (controls). Cases and controls were paired as previously described; no significant differences were seen between cases and controls either between (mean) outcome's scores or when the percentage of patients with remission, HAQ=0 and SF-36≥80 were compared; nonetheless, some tendencies were observed favouring better outcomes in RA patients SIE-free: 11 (84.8%) patients SIE-free achieved and maintain DAS28 remission *vs*. 8 (61.5%) patients with SIE, *p*=0.2. Similar results were obtained when last follow-up outcomes were compared. Analysis was repeated in 8 patients (accordingly paired) with isolated incidental SIE and similar results were obtained.

Discussion

In 1998, Hernández-Cruz *et al*. (23) determined factors associated with development, recurrence and severity of infections in RA patients attending the outpatient clinic from our centre. Patient´s gender, age, comorbidity and disease duration were similar to that from the present cohort; their incidence of infections was almost twice ours (17 *vs*. 8.7 per 100 patient-years), although distribution was similar; risk factors associated to infections in their study were treatment-related (cumulative dose of methotrexate, duration taking steroids and daily dose of D-penicilamine) meanwhile cumulative moderate to high disease activity and higher Charlson score were predictors in ours; not surprisingly, patients from the present report had higher cumulative and daily doses of DMARDs (data not shown) reflecting the current standard of therapy and a validated and continuous disease activity evaluation, reflecting the "treat-to-target" era.

Studies performed in developed countries have shown that disease activity increases the risk of SIEs; Au *et al*. (9) evaluated a large cohort of RA patients from the Consortium of Rheumatology Researchers of North America (CORRONA) registry; DAS28 was associated to increased hospitalised infections in patients on stable medication that included corticosteroids, DMARDs and TNF inhibitors; moderate disease activity showed the greatest incidence rate. Emery *et al*. (24) found a linear association between DAS28 and the risk of serious infection in 1365 RA patients treated with conventional DMARDs (and 3470 patients receiving etarnecept). Weaver *et al*. (10), showed that both, disease activity (as measured by CDAI) and disease severity contributed independently to increased risk of serious infections in 4084 RA patients enrolled between 2001 to 2003; patients with CDAI of mild, moderate and severe disease activity experienced increased risk of SIE. Similar to other published studies, we did not find DMARDs (1, 25, 26) and/or corticosteroids (25, 27) as predictors; there was a low correlation between DAS28 and number of DMARD/patient (rho=0.15, *p*=0.05); when cumulative DAS28 was switched into the model to cumulative DMARD, treatment was no longer a predictor; some of the published studies that recognised DMARD and corticosteroids as predictors lacked data on RA disease activity and severity and could not appropriately separate the effects of medications versus disease severity on infection's risk. Data from the present study suggest that dampening of inflammation achieved with DMARDs overwhelmed their intrinsic immunosuppressive effects associated to the increased risk for serious infections.

In addition to cumulative moderate to high disease activity, higher Charlson score was found a predictor of SIEs; comorbidity as pulmonary and cardiovascular disease has been associated to increased risk (1, 2, 9, 25); Doran *et*

al. (2) found comorbidity (in addition to age and corticosteroids) to increase infection rate; interestingly, they also found erythrocyte sedimentation rate, as the only measure available of disease activity associated to increased infection risk. Recently, Crowson *et al*. (28) developed and validated a risk score to predict the 1-year risk of serious infection in RA patients; comorbidities in addition to disease characteristics accurately assessed the risk of SIEs in their population. We used Charlson comorbidity index (29) to identify and score comorbid conditions; it is a diagnosis based index that has additionally been validated in patient populations with various diagnosis and undergoing various surgical procedures (30). With such approach, the best cut-off for Charlson score to predict SIEs was 2; it may be suggested that having any of the 18 comorbid conditions listed into the index, added to having RA, increased the risk. The rate of hospitalised infections in the present study was half of that found by Hernández-Cruz *et al*. (23) at the same Centre 3 decades ago although in the present study combined DMARDs were more frequently used; rate of SIEs felt within the range of 0.3 to 9 per 100 patient years described in the literature (6, 9, 10, 26, 31, 32); differences between studies may be explained based on population's characteristics, cases ascertainment (medical records vs. administrative data bases), period of time and treatment evaluated; distribution of SIEs was similar to other descriptions (1, 2, 9, 33). SIEs were detected at a mean follow-up of 5 years although variations were found within categories; this length of time up to the first SIE favours disease activity as a major predictor instead of treatment as we did not observed increased risk during the first year after DMARDs were initiated, as it seems to be the evidence with some biologics (34).

It is well known that long-term morbidity and mortality are increased in RA patients when compared to the general population and infections partly explain such negative outcomes (6, 35-39). Interestingly, SIEs did not affect disease-related outcomes as disease activity, disability (evaluated per HAQ) and health-related quality of life (evaluated per SF-36) during the following year after SIE or at last follow-up. Disease-specific treatment (but corticosteroids) is frequently withhold in most instances during a SIE and reinstalled after patient is discharged; we additionally controlled for such variable in the corresponding analysis.

Finally, 20% of our patients had latent-tuberculosis; although none received prophylaxis with isoniazid, there were no cases of active tuberculosis up to last follow-up. There is evidence that tuberculosis infections in RA patients were in fact increased before new therapies (as biologics) became available (40, 41) but current guidelines recommend screening for latent tuberculosis only before anti-TNF are initiated (42).

Limitations of the study need to be addressed. The study was performed in a particular population with specific characteristics and this limits the generalisability of the results. We described a short follow-up considering that RA is a lifelong disease. Only infections requiring hospitalisation were included but acknowledge that not all cases of infections are hospitalised; nonetheless, our approach based on charts review and patient's interview allowed confirmation of both RA diagnosis and any serious infection event that required hospitalisation. We adjusted for a limited number of risk factors for infections available in our databases but could still unknown confounders. Charlson comorbidity score index was developed to predict hospital mortality and its performance for predicting SIEs may be questioned. An important potential source of bias is "channeling", whereby drug exposure occurs differentially according to pre-existing risk for the outcome (SIE); we attempted to control for this; main exposure of interest was disease activity and we studied a homogeneous population with respect to such variable; patients entering the cohort had high disease activity. We also excluded patients with a recent history of SIEs at cohort entry and considered those with incidental SIEs. It may be argued that patients with higher disease activity received a more intensive treatment with DMARD, confounding by disease activity and severity. Finally, power of the study was limited by the occurrence of the first SIE (n=13); however, 3 potential predictors (apart from age and gender) were included in the analysis; this meant a number of events-per-variable of 4-5, pointing to acceptable power.

In conclusion, in this cohort of Mexican Mestizos patients intensively treated with conventional DMARDs according to a treat-to-target strategy, SIE was of 0.8 events per 100 patient-years. Cumulative moderate-to-high disease activity and comorbidity were predictors of SIEs, meanwhile disease-specific treatment was not; SIEs did not impact immediate RA outcomes. Treat- to-target era has modified RA patient's therapeutic decisions and follow-up. Achieving remission may have additional benefits to those related to RA outcomes, as preventing SIEs.

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