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Rheumatoid arthritis: extra articular manifestations and comorbidities☆

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ABSTRACT

Introduction: Rheumatoid arthritis (RA) can present extra-articular manifestations (ExM) and comorbidities such as infections, cardiovascular events, and malignancies, which have been associated with increased morbidity and mortality.
Methodology: analytical, observational, retrospective, 2012–2019. Extra-articular manifestations and comorbidities were studied in patients with established RA, attended in the EAS service of Maciel Hospital, in Montevideo, Uruguay.
Results: 83 cases, mean age 59.1±11, 87% female sex. RA overlapping 30%, 84% of cases with positive RF, 73% with positive anti-CCP, seronegative RA 10.8%. Extra-articular manifestations: 38%, ILD was the most frequent. A higher proportion of those who developed extra-articular manifestations had RF and positive anti-CCP. Infections: observed in 55.4%, 41.3% serious, 95.7% were non-opportunistic infections. The most frequent were urinary and respiratory. The most common causal microorganism was Escherichia Coli. Six patients with opportunistic infections were observed (pulmonary tuberculosis and Herpes Zoster). The use of corticosteroids was a risk factor for infections (p = 0.008), OR: 3,974 (CI: 1.39–11.36). SFZ was a protective factor (p = 0.033), OR: 0.313 (CI: 0.104–0.943). Cardiovascular events: evidenced in 6 patients, 50% had high activity. No increased risk was found with the drugs received. Neoplasms: 5 cases were found, there was no significant association between the risk of malignancy and the drugs used.
Conclusions: Extra-articular manifestations and comorbidities are frequent in RA patients, adding great morbidity. The risk of infections is multifactorial, influencing glucocorticoids and disease activity. Suspicion is important to carry out a search and timely treatment

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Artritis reumatoide: manifestaciones extraarticulares y comorbilidades

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RESUMEN

Introducción: La artritis reumatoide (AR) se asocia con manifestaciones extraarticulares (MEx) y comorbilidades tales como infecciones, eventos cardiovasculares y neoplasias, las cuales se han relacionado con una mayor morbimortalidad.
Metodología: analítico, observacional, retrospectivo, 2012−2019. Se estudiaron las MEx y las comorbilidades en pacientes con AR establecida, asistidos en servicio de enfermedades autoinmunes sistémicas (EAS) del Hospital Maciel, Montevideo, Uruguay.
Resultados: 83 casos, media de edad 59,1±11 años, 87% sexo femenino; 30% de AR solapadas; 84% de los casos con FR positivo; 73% con anti-CCP positivo; 10,8% de AR seronegativas. Manifestaciones extraarticulares: 38%, la EPI fue la más frecuente. Una mayor proporción de los que desarrollaron MEx presentaron FR y anti-CCP positivo. Infecciones: se observaron en el 55,4%, 41,3% graves, 95,7% fueron infecciones no oportunistas. Las más frecuentes fueron las urinarias y las respiratorias. El microorganismo causal más habitual fue*Escherichia coli*. Se observaron 6 pacientes con infecciones oportunistas (tuberculosis pulmonar y *herpes zoster*). El uso de corticoides fue factor de riesgo para las infecciones (p = 0,008), OR: 3,974 (IC: 1,39−11,36). La SFZ actuó como factor protector (p = 0,033), OR: 0,313 (IC: 0,104−0,943). *Eventos cardiovasculares:* se evidenciaron en 6 pacientes, el 50% presentaba una alta actividad. No se halló aumento del riesgo con los fármacos recibidos. *Neoplasias:* se hallaron 5 casos, no hubo asociación significativa entre el riesgo de neoplasia y los fármacos utilizados.
Conclusiones: Las MEx y las comorbilidades son frecuentes en pacientes con AR, lo cual conlleva una gran morbilidad. El riesgo de infecciones es multifactorial, y en ello influyen los glucocorticoides y la actividad de la enfermedad. Es importante su sospecha para realizar una búsqueda y un tratamiento oportunos.

Introduction

Rheumatoid arthritis (RA) is a chronic inflammatory disease that mainly affects the joints, but can present multiple extra-articular manifestations (ExM) with different severity. It has been evidenced that the severity of the ExM is directly related to the time of evolution and the disease activity.[1,2]In the different cohorts there is a wide variability in their frequency, ranging between 18 and 41%.[3–5] The importance of recognizing the ExMs in the framework of clinical practice is linked to the increase in morbidity and mortality in this population. In a prospective cohort study conducted in the United States, with a 40-year follow-up, it was shown that patients with RA have higher mortality than the general population, and the presence of ExM was found to be a strong predictor of mortality, with a HR of 4.4.[6] Other studies have shown a decrease in survival associated with a higher frequency of infections and cardiovascular (CV) diseases in patients with ExM.[7]

On the other hand, the risk of having ExM is related to: disease activity, smoking habit, especially in patients with vasculitis, positivity and titers of rheumatoid factor (RF) and anti-cyclic citrullinated peptide (anti-CCP) antibody, as well as with genetic factors (HLA-DRB1 allele). The HLA-DRB1 allele is associated with Felty's syndrome and vasculitis; however, it would be a protective factor against interstitial lung disease (ILD).[8–11]

The role of biologic drugs, particularly anti-TNFs, in the risk of occurrence of ExM is controversial. Unfortunately, some studies show an increased risk of developing vasculitis and ILD.[11–13]

Infections in RA (opportunistic and non-opportunistic) are more frequent than in the general population; the risk is twice as high in the case of non-opportunistic infections. The factors that increase the risk of severe infection are: advanced age, ExM, comorbidities (COPD, ILD, chronic kidney disease [CKD]), disease activity and immunosuppressive drugs (glucocorticoids, synthetic disease-modifying drugs [DMARDs] and biological DMARDs).[1,14] Infections differ in degree of severity, with mild forms being the most commonly seen. The most frequently affected sites are the respiratory and urinary systems, as well as the skin and soft tissues.[1,14]

An increased risk of infections with the use of glucocorticoids, even at low doses, has been documented in the different international registries, and the risk doubles if they are used at high doses. One of the benefits of the use of synthetic or biological DMARDs is the mitigation of the risks associated with glucocorticoids.[14,15]

Regarding the use of biological therapies, the British data registry (BSRBR) refers to a risk of infections that is multiplied by 4, especially in the first 3–6 months of their use.[14] Within the opportunistic infections, tuberculosis is the most commonly associated. The German database registry shows that the risk of incidence of infections with biological DMARDs is higher than with non-biological DMARDs. In turn, it clearly shows

that the increased risk of infections grows in direct proportion to the increase in the dose of glucocorticoids in both groups.[16]

With regard to cardiovascular events (CVE), patients with RA have a 50% higher risk than the general population. This is explained by an increase in classical CV risk factors, the disease activity and chronic inflammation. Thus, having RA determines an increased atherogenic risk similar to that of diabetes mellitus (DM).[1,17] It has been demonstrated that the vascular risk indices applied to the general population underestimate the CV risk for RA. This has motivated the scientific community to create risks adapted to this population. The latest Eular recommendations state that the traditional cardiovascular risk should be multiplied × 1.5 or the Q RISK2 score should be used.[17]

A meta-analisis[18] published in 2011, which includes 66,000 patients, shows methotrexate (MTX) as a protective factor against CVE, with a risk reduction of 21% in the cases treated with this drug. This has been attributed to the reduction of the chronic inflammatory state associated with the disease. Very similar data were found with hydroxychloroquine (HCQ). Anti-TNFs demonstrated a significant reduction in risk, especially in patients who respond to these therapies. In contrast, corticosteroids and nonsteroidal anti-inflammatory drugs (NSAIDs) increase the risk of CVE.[18,19]

Finally, we cannot disregard the risk of neoplasms associated with this disease. The literature reviews show an increased risk that is related to the greater activity and the time of evolution of the disease, as well as to the treatments received. It has been observed that the risk of lymphomas is higher than in the general population, in such a way that 2/3 of these corresponds to diffuse B cell lymphoma. Likewise, there has been evidence of a slight increase in the risk of bronchopulmonary carcinoma and a lower risk of colorectal (due to the consumption of NSAIDs), prostate, breast, ovarian and endometrial cancer. As for the role of biological therapies in neoplasms, many clinical trials have demonstrated that there are no statistically significant differences in the risk of malignancy when compared to controls. However, a Swedish registry base shows a 50% increased risk of developing melanoma in patients treated with biological agents.[1]

There are no review works or epidemiological studies in Uruguay regarding ExM, nor about comorbidities, which has motivated the interest of the authors in addressing this issue.

The general objective was to study the ExMs and the comorbidities of RA in patients treated in the outpatient clinic for systemic autoimmune diseases (SAD) of the Maciel Hospital, in Montevideo, Uruguay. The specific objectives were to characterize and assess the frequency of ExM; correlate the ExMs with the disease activity and the serological phenotype; study the frequency of infectious complications, as well as of CVEs, and assess their association with the disease activity and the treatments received; in addition, to analyze the frequency of neoplasms and their relationship with the treatments received.

Materials and methods

An analytical, observational retrospective study was conducted in the period between December 1, 2012 and December 1, 2019. The study population consisted of patients with established RA, treated in the outpatient clinic of the SAD service of the Maciel Hospital, in Montevideo, Uruguay. 83 patients who met the criteria for RA were selected from a total of 339 patients with immune-mediated diseases seen in the outpatient clinic. Patients with RA defined by the 2010 classification criteria of the American College of Rheumatology and the European League Against Rheumatic Diseases (ACR/Eular), who had at least 2 consultations in said center, were considered cases.[20] The inclusion criteria were: patients who met the classification criteria for RA, while the exclusion criteria were: patients who attended the consultation on less than two occasions and those who presented other non-immunological causes that explained the ExM. The following variables were defined:

- ExM: rheumatoid nodules, respiratory manifestations such as pleuritis, ILD (defined by computed axial tomography [HRCT] and respiratory function test with DLCO), pneumothorax and bronchiectasis (defined by HRCT), pericarditis, vasculitis (confirmed by biopsy), neuropathy (confirmed by electrical study), ocular manifestations (scleritis, episcleritis) confirmed by ophthalmologist, hematologic manifestations (inflammatory anemia, neutropenia, thrombocytopenia), Felty's syndrome and fever of unknown origin (FUO), defined by the Durack and Street's criteria.[1–5,21]
- Cardiovascular events: transient ischemic attack (TIA) and non-fatal cerebrovascular attack (CVA), non-fatal acute myocardial infarction (AMI), cardiovascular death.
- Malignant neoplasm: diagnosis confirmed by pathological anatomy.
- Serious infection: infection that required hospitalization and intravenous medication, or that caused the death of the patient.[14,22,23]
- Opportunistic infection: caused by specific pathogens or presentations that suggest the probability of immunological alteration in the context of the administered therapy.[22,24]

The calculation of the average dose of glucocorticoids was made based on an average in the last 6 months prior to the infection, cardiovascular event or neoplasm. The data were collected by 4 internists who provide assistance in said consultation. They were assigned a random code in order to safeguard confidentiality.

Data such as age, sex, AHT, DM, consumption of tobacco, CKD, ExM, RF and anti-CCP, DAS28 (at 3 moments: prior to the diagnosis of the disease, after 6 months of treatment with non-biological DMARD and after 6 months with biological DMARD), infectious comorbidities ((non-opportunistic/opportunistic), neoplasms, CVE (TIA/CVA, AMI) and treatments received during the comorbidity, were obtained from the registry of electronic medical records.

In patients without comorbidities (infections, CVE, neoplasms), the treatment received at the time of data collection was recorded. In patients with comorbidities, the treatment received at the time of the comorbidity was recorded. The patients were treated according to our usual clinical practice, following the recommendations of the Eular's treat-to-target strategy.[25]

Statistical analysis

A descriptive analysis of the results and nonparametric hypothesis tests was performed to assess the association between variables. The qualitative variables were represented in tables, using absolute frequencies and percentage relative frequencies, as well as in stratified bar graphs (2 variables simultaneously). The quantitative variables were represented using the mean and its standard deviation as summary measures (normality had previously been studied using the Kolgomorov–Smirov or Shapiro–Wilk tests). The Student's t-test was used for the contrast of qualitative variables, while the chi-square test was used in the qualitative variables, and in the case of expected values lower than 5, the Fischer's exact test was used. The odds ratio (OR) was calculated for the variables of interest, and those that resulted significant were included in the multivariate binary logistic regression model. *P*-values < 0.05 were considered significant. The software used was Microsoft Excel and IBM SPSS version 22.0.

Ethical aspects

The research was conducted respecting the current Uruguayan legal framework, according to the ethical standards consistent with the Declaration of Helsinki updated in 2013. The patients voluntarily consented to participate in the study and the data were handled in a confidential manner.

Results

83 cases of established RA from a population of 339 patients with SAD seen in the outpatient clinic were included. RA was the second most frequent disease in that population after systemic lupus erythematosus (SLE). 87% (72) corresponded to the female sex and 13% (11) to the male sex. The mean age was 59.1 years and the standard deviation was ±11, within a range between 27 and 80 years. The mean duration of the disease before starting the first treatment with DMARDs was 8 months ±18.4, with a follow-up mean of 10±9.7 years. Overlapping with other SADs was found in 30% (25) of the cases. The most commonly associated diseases were SLE, with 48% (12), and Sjögren's syndrome (SS), with 40% (10).

With respect to the disease activity measured by means of the DAS28 in the different phases of treatment, 5% (4) had mild activity, 35% (29), moderate activity, and 52% (43), high activity at diagnosis, with a mean DAS28 of 5.36±1.47. At 6 months of treatment with non-biologic DMARDs, 10% (8) were in remission, 11% (9) had mild activity, and moderate activity was seen in 28% (23), while in 32% (27) there was high activity. After 6 months of treatment with biological DMARDs, 16% (13) were in remission, 11% (9) had mild activity, moderate activity was reported in 10% (8) and in 7% (6) there was high activity. The mean DAS28 was 4.54±1.69 and 3.43±1.77 for the treatment phases with synthetic and biological DMARDs, respectively.

In relation to the serological phenotype, 84% (65) of cases with positive RF and 73% (38) with positive CCP were found, while 10.8% (9) were catalogued as seronegative RA.

Table 1 – Frequency and type of ExM in rheumatoid arthritis.

Extra-articular manifestation	Absolute frequency
ILD	11
Polyneuropathy	6
Inflammatory anemia	5
Serositis or pericardial/pleural effusion	4
Rheumatoid nodules	4
Episcleritis or scleritis	3
Neutropenia/Felty's syndrome	3
Bronchiectasis	2
Rheumatoid vasculitis	2
Thrombocytopenia	1
Pneumothorax	1
Fever of unknown origin	1

ILD, interstitial lung disease.

The most frequent comorbidities were: AHT, which corresponded to 47.0% (39); smoking, 16.9% (14); DM, 12% (10); dyslipidemia, 12% (10); obesity, 8.4% (7); COPD, 4.8% (4), and CKD, 3.6% (3).

Regarding the treatments, 49.4% (41) received glucocorticoids; 45.8% (38), HCQ; 68.7% (57), MTX; 20.5% (17), leflunomide (LFU), and 21.7% (18), sulfasalazine (SFZ). Biological therapies were indicated in 34.9% (29), distributed as follows, in order of frequency: 10.8% (9), tociluzimab; 10.8% (9), rituximab; 8.4% (7), adalimumab, and 4.8% (4), etanercept. 56.6% (47) of the cases received combined treatment with 2 or more drugs (HCQ was excluded from the analysis). The mean dose of glucocorticoids for the general population was 10.3±4.4; 10.2±4.4 for the infected patients, and 10.4±5.1 for the uninfected.

Extra-articular manifestations

They were observed in 38% (32) of the cases. The most common was ILD, with 11 patients, followed by polyneuropathy, with 6 cases. 6 patients with 2 or more concomitant ExMs were evidenced (Table 1). When analyzing only the RA not associated with other SAD, no association was found between the disease activity and ExM (p = 0.473).

It was observed a higher proportion of cases with positive RF —90.5% (29)— and positive anti-CCP —82.4% (26)— that developed ExM, with respect to the subgroup without ExM —81.8% (42) and 75% (38), respectively—, although this was not statistically significant.

In the cases with ExM, 7 patients were active smokers; no statistically significant association was found between the two variables (OR: 2.667; 95% CI: 0.827–8.6; p = 0.093).

The presence of ExM was related to the different comorbidities, with the following results: 19 patients became infected (p = 0.408), only one case had CVE (p = 0.667), and 3 patients presented neoplasms (p = 0.142).

Infections

Infections were observed in 55.4% (46) of the cases. In 95.7% (44), they were non-opportunistic infections, with a single infection in 45.5% (20), while the rest of them presented 2 or

Table 2 – Comparison between the infected and non-infected subgroups.

	Infected $n=46$	Uninfected $n=37$	p
Age, years	59.4±11.3	58.7±12.5	0.813
Female gender	43 (93.5%)	29 (78.4%)	0.055
AHT	22 (47.8%)	17 (45.9%)	0.865
DM	4 (8.7%)	6 (16.2%)	0.329
Dyslipidemia	7 (15.2%)	3 (8.1%)	0.5
COPD	3 (6.5%)	1 (2.7%)	0.625
Obesity	4 (8.7%)	3 (8.1%)	1
CKD	1 (2.2%)	2 (5.4%)	0.583
Smoking	9 (19.6%)	5 (13.5%)	0.464
Hydroxichloroquine	19 (41.3%)	19 (51.4%)	0.361
Methotrexate	28 (60.9%)	29 (78.4%)	0.087
Leflunomide	6 (13.0%)	11(29.7%)	0.061
Sulfasalazine	6 (13.0%)	12 (32.4%)	0.033
Glucocorticoids	20(43.5%)	6 (16.2%)	0.008
Biological agents	14 (30.4%)	15 (40.5%)	0.337
Combination of drugs	28 (60.9%)	19 (51.4%)	0.384
Active disease	21 (45.7%)	12 (32.4%)	0.221

DM, diabetes mellitus; COPD, Chronic obstructive pulmonary disease; CKD, chronic kidney disease; AHT, arterial hypertension.

more non-opportunistic infections. The most frequent infections corresponded to urinary tract infections in 41.3% (19), and respiratory tract infections in 37.0% (17), followed by skin and soft tissue and gastrointestinal infections.

Opportunistic infections occurred in 6 patients and corresponded to pulmonary tuberculosis (2) and herpes zoster (4). The patients with pulmonary tuberculosis received treatment with MTX, glucocorticoids, and etanercept. The cases of herpes zoster received treatment with corticosteroids, MTX, HCQ and rituximab. In all cases of opportunistic infections, the patients received a combination of drugs.

Of the total number of infected (non-opportunistic and opportunistic infections), 4 cases presented concomitant viral and bacterial infections.),

The causative microorganism was identified in 24.1% (20) of the cases, the most frequent being *Escherichia coli* (9), *Haemophilus influenzae* (4), *Streptococcus pneumoniae* (2), *Enterobacter cloacae* (2), *Pseudomonas aeruginosa* and *Enterococcus* spp. (2).

There were 41.3% (19) of patients who presented serious infections, 13 patients on one occasion and 5 patients on 2 opportunities.

Of the total number of patients, 39.8% (33) had active disease; of them, 45% (21) had infections and 32% (12) were not infected.

When comparing the subgroups with infection (at the time when they presented the comorbidity) and without infection, a significant difference was found in the use of corticosteroids, and the risk of infections increased with respect to those who did not receive them (OR: 3.974; 95% CI: 1.39–11.36; p = 0.008). SFZ acted as a protective factor by reducing the risk (OR: 0.313; 95% CI: 0.104–0.943; p = 0.033) (Table 2). In addition, it was observed a trend (although not statistically significant) towards a lower rate of infections in patients treated with DMARDs than in those who were not.

Cardiovascular event

CVE was evidenced in six patients; it is noteworthy that 100% of the cases corresponded to non-fatal AMI. No increased risk of these events was found in association with the drugs received. The six patients who presented CVE had received glucocorticoid treatment at some point during their disease; however, the relationship between both variables was not shown to be significant (p > 0.1). Of the patients who had CVE, three had high disease activity. No association was found between the disease activity and CVE (p = 0.59).

Neoplasms

It was found that 5 patients had a malignant neoplasm. The types of neoplasms found and their histology were: lips (epidermoid carcinoma of the lip), ovary (epithelial ovarian carcinoma, serous subtype), cervix (squamous cell carcinoma of the cervix), colorectal (adenocarcinoma of the colon) and skin (basal cell carcinoma of the skin, at the level of the face). None of the patients who presented neoplasms had received biological therapy, 2 received treatment with glucocorticoids and MTX, and 3 of them received SFZ. There was no statistically significant association between the risk of neoplasms and the different drugs used.

Discussion

During the period of our study, RA was the second most frequent SAD in the total number of patients treated in a referral center for SAD of a general hospital. The majority of cases corresponded to women, with a mean age of 59 years. 84% of the patients presented positive RF, while 73% had positive anti-CCP. We found a high percentage of missing data, probably due to difficulties in accessing serological techniques in our center.

The DMARD most widely used for treatment was MTX, followed by SFZ and LFU, the latter two very similar in frequency. HCQ was used with high frequency, given the high percentage of patients who presented overlap with SLE and SS. Glucocorticoids were used in nearly 50% of the cases. The most widely used biological therapies were anti-TNFs. More than 55% of the patients presented a combination of drugs, many of them corresponding to a biologic drug plus a conventional DMARD, in order to reduce the mechanisms of immunogenicity generated by the biological drugs.

Extra-articular manifestations

Multiple studies reveal a great variability in the frequency of ExM, which is due to the geographical area, the ethnicity and the definition of ExM used by the different authors.[3–5] In this study, 38% of the cases presented ExM, being similar to what was found in international series.[1,2] As for the type of ExM, ILD was the most frequent (3%), more than what was found in the literature. In this sense, a frequency of 0.75% in a Mexican cohort of 617 patients[3] and of 6.3% in an Italian cohort with a

sample size of 587 people[4] stands out. The higher frequency of ILD in this series could be due to the fact that the hospital is a reference center in pneumology and interstitial diseases. Rheumatoid nodules presented a low percentage, compared to other series, probably due to underreporting of non-severe ExMs.[3–5]

In the analyzed series, a trend was observed according to which the greater the activity of the disease, the greater the risk of presenting ExM, although this was not statistically significant, probably due to the small sample size. For this analysis, we only included pure RAs, given that a high percentage of the population overlapped another SAD (SLE, SS), and these diseases have manifestations at the joint and laboratory levels (CRP, ESR) that could be a confounding factor. A higher percentage of patients with positivity for RF and anti-CCP developed ExM, which is in line with what was found in other cohorts.[10]

Some works suggest that the ExMs are associated with smoking, mainly for vasculitides.[9] Even though no statistically significant association between being an active smoker and ExM was found in our series, the two patients who presented rheumatoid vasculitis were smokers.

The ExMs have higher mortality, which some authors explain by the higher risk of infections and CV disease in these patients.[6,7] In our series, 59% of the patients became infected, and only one patient presented a CVE. It is noteworthy that although it was not significant, 2/3 of the patients with neoplasms had ExM.

Infections

Infections are frequent in patients with RA. In the present study, they were observed in 55%, similar to what is reported in international series.[1,14] Among these, the vast majority were represented by non-opportunistic infections, and it is noteworthy that more than half of our patients presented 2 or more infections. Likewise, 42% of the infections were serious.[14,22,23]

Urinary tract infections were the most frequent, followed by respiratory, skin and soft tissue, and digestive infections, similar to what was found in other series. Data from other cohorts establish differences in the sites of infection between outpatients and hospitalized patients. Urinary and skin infections are more common in outpatients, while respiratory infections are seen more frequently in hospitalized patients.[1,14,23,26]

Regarding the causative microorganisms, the different series indicate that bacteria are the most frequently isolated, followed by viruses and fungi. Nonspecific microorganisms are similar to those found in the general population.[14,22,23] The causative microorganism was identified in more than half of the cases in our series, the most frequent being *Escherichia coli* and *Haemophilus influenzae*, coinciding with the microbiological profile of the most frequent foci of infection. Six patients with opportunistic infections, which corresponded to pulmonary tuberculosis and herpes zoster, were registered. The works show that the prevalence of tuberculosis is higher in subjects with RA than in the general population. In the majority of cases, the tuberculosis in patients treated with immunosuppressants is due to reactivation of a latent infection. As for the clinical presentation, although pulmonary tuberculosis is the most common form, as in the cases of this series, it has been seen that extrapulmonary forms are more frequent and more serious than in the general population.[27] The patients who presented pulmonary tuberculosis received treatment with MTX, corticosteroids and etanercept. Glucocorticoids and DMARDs increase the risk of tuberculosis.[28] Tuberculosis is the opportunistic infection mostly associated with anti-TNF drugs, and monoclonal antibodies present three times more risk than fusion proteins.[29,30] With regard to anti-TNFs, some studies show that the risk of having an opportunistic infection is significantly high in the first six months of treatment and with the use of more than two immunosuppressive drugs. This relationship became stronger for opportunistic infections caused by intracellular pathogens.[31]

Viral and fungal infections also predispose to higher morbidity and mortality. A meta-analysis[32] carried out at the Mayo Clinic showed that SADs (SLE and RA) present twice the risk of herpes zoster infection than in the general population. This risk was attributed to the SAD itself and to the immunosuppressive drugs. A study conducted by Curtis et al.[33] compared the risk of herpes zoster in three groups: patients treated with tofacitinib monotherapy, tofacitinib plus glucocorticoids, and tofacitinib plus MTX. After performing a multivariate analysis (using tofacitinib monotherapy as reference), the authors conclude that the exposure to glucocorticoids doubles the risk of herpes zoster, without a clear increased risk for MTX. Four cases of herpes zoster treated with glucocorticoids, MTX and biologicals were recorded in our study, which shows similarity with what has been published internationally.[29] No fungal infections were recorded.

It is noteworthy that in all cases of opportunistic infections in our cohort, the patients received a combination of drugs, which entails a higher risk.[31]

These data show the importance of timely screening for infections in patients with SAD and the corresponding prophylaxis (vaccines, search for latent tuberculosis). It is important to be able to define the periodicity with which we must carry out the search for latent tuberculosis in endemic areas such as Uruguay.

The disease activity has been pointed out as an independent risk factor for the development of infectious complications in patients with SAD.[8,14] A higher proportion of infected patients with active disease was found in our cohort, which, although not statistically significant, was probably due to the small sample size.

In our population, when comparing the subgroups of infected and non-infected patients, the drugs that were independently associated with a higher risk of infection were glucocorticoids (four times higher risk). According to international data registries (European and American), the risk of infections varies according to the treatments received. The use of systemic glucocorticoids increases the risk of infections between 1.5 and 2 times, even when they are used at low doses (prednisone 5 mg/day). This risk sometimes increases with the use of prednisone at doses higher than 15–20 mg/day.[16] Each increase in the dose of corticosteroids multiplied the risk of suffering a serious infection, being 7.5 mg/day the average dose for their occurrence.[34] Systemic corticosteroids are a modifiable risk factor for serious infections.

It is noteworthy that in our work the proportions of infected patients with biological drugs and without these were similar. As for the risk of biological drugs and infections, the international series show contradictory results. On the one hand, the Spanish registry of biologicals, Biobadaser, shows that 35% of adverse events are infections.[35] In agreement, the German Rabbit registry shows that the risk of infections with biological drugs is higher than with non-biological treatments, and this risk increases in direct proportion to the increase in the dose of glucocorticoids in both groups.[16] However, more recent studies question this risk, and after adjusting for confounding factors (glucocorticoids, disease activity, age, comorbidities), they do not observe a clear increase in risk compared to non-biological DMARDs.[36–38] The latter is consistent with what was observed in our study.

There was a trend (although not significant) to a lower rate of infections in patients treated with synthetic DMARDs compared to those who were not treated with these drugs. The Corrona registry shows that MTX presents a higher risk of infections compared with other non-biological DMARDs. Despite this, a meta-analysis published in 2017, which compares the risk of infections of biological therapies versus biological therapies with MTX, does not show significant differences in infection rates between both groups.[15] One hypothesis to explain this finding is that we should not forget that there are other factors that influence the increase in risk, one of these being the disease activity. On the other hand, in our work, SFZ acted as a protective factor, reducing the risk of infection by 70%. SFZ belongs to the group of sulfonamides, used in clinical practice as bactericides. Some works postulate it as a protector against infections together with HCQ.[39]

Cardiovascular events

The frequency of CVE was 7.2% and fully corresponded to non-fatal AMI. International registries such as Corrona show a 6.2% of CVEs, a value very similar to that of our study. The increased risk of CVE in these patients is due to the activity of the disease and the drugs received. In this study, increased risk of these events linked with drugs was not found. All patients who presented CVE had received glucocorticoid treatment at some point during their disease. Of the patients who had CVE, half were in therapeutic failure, and therefore they had a high disease activity, and were more likely to present complications of atheromatous plaque.

Neoplasms

Finally, we had a low frequency of neoplasms: none of those found was one of those most commonly associated in the literature with the disease itself (lymphomas), or with the treatment.[1] In the present study, DMARDs were not found to be an independent risk factor for the development of neoplasms.

Our study had weaknesses. On the one hand, those derived from its design, given that it is a retrospective study, which unfailingly leads to an information bias. This probably determined an underreporting of non-serious infections and non-severe ExMs in the medical records. Despite this, we must highlight that the main limitation was the small sample size, one of the great weaknesses of our study. Another limitation to point out is the difficulty in recording the cumulative dose of corticosteroids and the time of administration of the latter.

As for the strengths, we highlight that it is the first study in the Uruguay on ExM and comorbidities in RA. All this constitutes a motivation for deepening knowledge on this topic, the development of new prospective studies and the strengthening of measures to reduce the frequency of infections in this population. Strategies for this last point could be the use of protocols for screening and prophylaxis of infections in patients with RA, prior to the start of immunosuppressive treatment. Finally, the data found were relevant and encourage us to try to reduce the dose of glucocorticoids used in our usual clinical practice.

Conclusions

ExM and comorbidities (infections, CVD, and neoplasms) are common in patients with RA and are associated with increased morbidity. It is possible that the risk of infections and biological therapies has been overestimated over the years. We should not forget in our clinical practice that the risk of infections is multifactorial, and that it is influenced by glucocorticoids (directly proportional to the dose), as well as by the activity of the disease. Finally, the suspicion of ExM and comorbidities is of the utmost importance in order to accomplish a timely search and treatment.

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Conflict of interest

None.

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