Rate of Infection in Rheumatoid Arthritis Patients

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ABSTRACT

Objectives: Rheumatoid arthritis is an autoimmune inflammatory disorder associated with increased risk of infection. The aim of this study was to evaluate infections frequency in rheumatoid arthritis patients and to report the independent associated risk factors.

Methods: Rheumatoid arthritis patients (n = 200) were retrospectively reviewed at King Abdulaziz University Hospital Jeddah, Kingdom of Saudi Arabia from January 2008 to December 2010. The rate and predictors of infection were evaluated.

Results: The frequency of infection in rheumatoid arthritis patients was (36%). The most common infections were pneumonia, bacteremia and urinary tract infection occurring in 18%, 12%, and 10%, respectively. The strongest and significant predictors for infection were cardiovascular disease (OR = 8.87), renal impairment (OR = 7.12), and steroid use (OR = 1.67).

Conclusions: Infection rate in rheumatoid arthritis patients was high but lower than other studies. Comorbid illnesses (renal and cardiovascular diseases) and steroids in rheumatoid arthritis patients predisposed them to develop infections that may necessitate hospitalization. Comorbid illnesses should be managed early and steroids to be used cautiously in order to reduce infection risk among rheumatoid arthritis patients.

Keywords
Antirheumatic agents, Glucocorticoids, Steroids, Antimalarial, Methotrexate

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ADVANCE TO KNOWLEDGE

This is the first study assessing the risk of infection in Rheumatoid Arthritis patients in Saudi Arabia.

APPLICATION TO PATIENT CARE

This study highlights the importance of recognition on predisposing condition to infection in rheumatoid arthritis patients, specifically cardiovascular, renal diseases and steroids treatment.

INTRODUCTION

Over the past 40 years, the frequency of infections in rheumatoid arthritis (RA) has been reported to be high. Through hospital-based case series, it was known that RA was associated with increased susceptibility to infection particularly in the skin, joint, bone, and respiratory tract[1-3]. It has been postulated that it may be related to the immune effects of the disease itself or to the frequent use of corticosteroids and other immunomodulatory therapies[4-6]. In previously published literature, only few case-control series have been conducted to report the risk of infection in patients with RA. The results in these studies were conflicting as some showed no increased risk[5,6] while others did[7,8]. However, few studies evaluated the risk factors for infection in RA namely; extra-articular manifestations in rheumatoid arthritis (ExRA), leucopenia, comorbidities, and medication such as steroids, non-biologic disease-modifying antirheumatic drugs (DMARDs) and biological therapy[9-12]. The latest was at the Mayo Clinic which reported that glucocorticoids (GCs) use was associated with a dose-related increased risk[13].

Based on our research, no previous study has been conducted in Saudi Arabia to determine the risk of infections in patients with RA. Thus, the aim of our work was to determine the frequency of infections in patients with RA and to report the independent associated risk factors.

SUBJECTS AND METHODS

Patients with RA who were followed at King Abdulaziz University Hospital (KAUH), Jeddah, Kingdom of Saudi Arabia, were retrospectively evaluated for the rate of infection from January 2008 to December 2010.

The study was approved by the Biomedical Ethical Research Committee of the Faculty of Medicine at King Abdulaziz University; June 2011, approval number 550-11.

Patients with RA (n = 200) were identified according to the 2010 American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) classification criteria for RA; however, before 2010 they were identified according to the 1987 American College of Rheumatology classification criteria for RA[14]. Exclusion criteria were age less than 14 years and evidence of minor upper respiratory tract infection, due to the low severity of these infections some patients may not have been able to report them, and therefore, these may not be in the charts.

By definition, any patient with chronic arthritis less than 16 years to be diagnosed as Juvenile Idiopathic Arthritis (JIA), but as 14 is the age limit for adults in many Arab countries they were included.

The following demographic features were obtained from the charts: age, gender, and duration of the disease at the time of the study (in years). The patients’ treatments were reviewed. These included the use of the following: Glucocorticoids (GC), DMARDs namely Methotrexate (MTX), Sulfasalazine, Leflunomide, and antimalarial agents (Hydroxychloroquine [HCQ] or Chloroquine) either alone or in combination with biologics (the newer type of drug treatment for RA).

Activity of the disease was chronicled at the infection period and defined based on the index. Disease Activity Score-28 (DAS28), and high disease activity was defined if the score was > 5.1[15]. Extra-articular features were evaluated based on the predefined criteria[16]. Comorbid illnesses were recorded as follows: Diabetes mellitus (DM), defined according to the WHO as fasting plasma glucose ≥ 126 mg/dl (7.0 mmol/L)[17]; hypertension (HTN), classified according to the World Health Organization-International Society of Hypertension Guidelines as a diastolic blood pressure > 90 mmHg, or if the patient is taking any antihypertensive substances[18]; renal disease (kidney amyloidosis, nephrotic syndrome or chronic renal failure); cardiovascular disease (CVD): Ischemic heart disease, arrhythmias, congestive heart failure and peripheral vascular disease; respiratory disease (chronic obstructive pulmonary disease or preexisting radiographic interstitial infiltrates indicating lung fibrosis or bronchiectasis) and malignancy.

Infection in general was defined as the presence of positive results of microbiologic cultures or radiologic imaging; whether life-threatening, requiring hospitalization, IV, antibiotics, or non-serious cases. The definitions for each infection type were as follows: Bacteremia/ septicemia, the presence of fever (38.0°C) with positive 1 or more blood cultures; septic arthritis, positive culture from joint aspirate fluid; urinary tract infection (UTI), if > 100,000 colony-forming units/ml was isolated from the urine in the presence clinical symptoms or urosepsis or pyelonephritis; pneumonia was diagnosed based on the presence of consolidation seen by chest radiography in the presence of clinical setting; osteomyelitis, confirmed either by radiologic examination or positive bone culture; skin and soft tissue infections included wound infections, abscesses, cellulitis, herpes zoster, and diabetic foot infections; intra-abdominal infections were included based on clinical findings such as acute cholecystitis, ascending cholangitis, suppurrative appendicitis, and peritonitis. The category “other infections” included any episodes of gastroenteritis, sinusitis and tonsillitis that required hospitalization[24].

Statistical Analysis

Data were analyzed using SPSS-V16 (IBM SPSS Statistics Inc. Chicago, IL USA) database program. The mean was determined for quantitative data and frequency for
categorical variables. Chi-squared test was used when comparing categorical variables and "student's" t-test when comparing the age of the 2 groups (RA patients with and without infection). Logistic regression analysis was used to identify the most relevant predictor for infection. A $P$-value < 0.05 was considered significant.

RESULTS

The total number of RA patients identified (N = 200). At the time of inclusion, the mean (± SD) age of the patients with RA was 47 (15.69) years. Females represented 165 (82%) patients. The mean disease duration ± SD was 7.5 ± 6.9 years; the disease duration was < 1 year in 34 (17%) patients, 1-5 years in 63 (31%) patients, > 5-10 years in 43 (22%) patients, and > 10 years in 60 (30%) patients. Ninety-two (46%) RA patients had the high disease activity documented by DAS28 score of > 5.1.

The most common comorbidity observed was hypertension occurring in 53 (27%), and the least common was malignancy occurring in 18 (9%) patients. RA patient have been using the DMARDs either as a single therapeutic agent or combined in 73 (37%) patients. Steroids have added on the top of DMARDs to control disease activity in 81 (41%) patients. All DMARDs did not show any statistically significant association with infection risk. Biologics have been used in 59 (30%) patients combined with DMARDs. The following biologics were used: Adalimumab 43 (21.5%) patients, Etanercept 4 (2%) patients, Infliximab 3 (1.5%) patients, and Rituximab 9 (4.5%) patients. Table 1 shows the demographic characteristic, comorbidities and treatment in the 200 RA patients.

A total of 72 (36%) patients were identified to have infections. The frequency of infection in RA patients are shown in Table 2, more than one infection may exist on the same patient. The 19 patients on biologics who developed infections had the following infections (more than 1 infection may exist on a patient): 11 patients with pneumonia, 7 with sepsis, 5 with UTI, 4 with skin or soft tissue infection and 2 with osteomyelitis. The following organisms were isolated from the sputum: Gram negative bacilli and fungi. From the blood: Gram negative bacilli, diphtheroid species, fungi and Micrococcus luteus. From urine: Escherichia coli and Acinetobacter baumannii. From the skin and wounds; Gram negative bacilli, Staphylococcus aureus, fungi and herpes virus.

On evaluating RA patients with and without infections, the following were associated with significant risk of infection ($P < 0.05$), the presence of extra-articular features (OR = 5.1, 95% CI 2.7-9.5), chronic use of steroids(OR = 3.05, 95% CI 1.68-5.61), the presence of comorbid illnesses (OR = 2.23, 95% CI 1.19-4.15), age more than 60 (OR = 1.88, 95% CI 1.32-2.68), and disease duration more than 10 years (OR = 1.78, 95% CI 1.25-2.55). Certain comorbid illnesses carried higher risk than others; renal disease (OR = 10.8, 95% CI 3.51-33.32), cardiovascular diseases (OR = 10.66, 95% CI 4.35-26.13), respiratory disease (OR = 7.4, 95% CI 2.6-21.08), DM (OR = 4.4, 95% CI 2.14-9.29), malignancy (OR = 4.32, 95% CI 1.28-14.5) and finally hypertension (OR = 3.9, 95% CI 2.04-7.6). All DMARDs did not show any statistically significant association with infection risk. By logistic regression analysis; cardiovascular disease (OR = 8.87, 95%CI 3.47-22.65), renal impairment (OR = 7.12, 95% CI 2.13-23.81), and the steroid use (OR = 1.67, 95% CI 0.85-3.26) were the most significant predictors of infection.

### TABLE 1.

Demographic features of 200 patients with rheumatoid arthritis patients at the time of the study.

| Variables                  | N (%)       |
|---------------------------|-------------|
| Age (years): Mean (SD) range | 47 ± 15.69 (15-75) |
| Age > 60                  | 42 (21)     |
| Gender                    |             |
| Male                      | 35 (18)     |
| Female                    | 165 (82)    |
| Extra-articular features   | 122 (61)    |
| High Disease Activity     | 92 (46)     |
| Disease Duration           | 7.5 ± 6.9   |
| < 1 year                   | 34 (17)     |
| Between 1-5 years          | 63 (31)     |
| > 5-10 years               | 43 (22)     |
| > 10 years                 | 60 (30)     |
| Comorbid illnesses         | 88 (44)     |
| Diabetes mellitus          | 40 (20)     |
| Hypertension               | 53 (27)     |
| Cardiovascular disease     | 35 (18)     |
| Renal disease              | 23 (12)     |
| Respiratory disease        | 23 (12)     |
| Malignancy                 | 13 (6.5)    |
| Treatment                  |             |
| Steroids                   | 81 (41)     |
| DMARDs                     |             |
| Antimalarial               | 88 (44)     |
| Methotrexate               | 164 (82)    |
| Biologics                  | 59 (30)     |

### TABLE 2.

Rate and type of infection in patients with rheumatoid arthritis.

| Infection Typeb | RA N = 200 (%) |
|-----------------|----------------|
| Total Infections| 72 (36)        |
| Pneumonia       | 36 (18)        |
| Bacteremia / Septicemia | 24 (12) |
| Urinary Tract Infection | 19 (10) |
| Skin / Soft tissue | 10 (5)        |
| Osteomyelitis   | 5 (3)          |
| Gastroenteritis | 4 (2)          |
| Meningitis      | 1 (0.5)        |
| Septic Arthritis| 1 (0.5)        |
| Sinusitis       | 1 (0.5)        |
| Tonsillitis     | 1 (0.5)        |
| Intra-abdominal | 0              |

Abbreviations: RA = rheumatoid arthritis

aDate are presented as frequency (percentage) unless otherwise stated.
bMore than one infection may exist in the same patient.
Table 3 summarized the effect of different variables on the frequency of infection in RA patients.

**DISCUSSION**

The present showed three important findings: the rate of infection in patients with RA was (36%), the most common infections observed in the RA group were pneumonia, bacteremia and UTI. Finally the predictors for infection were renal impairment, cardiovascular disease and steroid use.

In this present study, the rate of infection in RA patients was (36%) in all infection types compared to the largest Canadian retrospective study of 27,710 patients with RA in which (92%) had at least 1 mild infection (requiring antibiotic treatment) and (18%) had at least 1 serious infection requiring hospitalization. The risk of infections in our study was less than expected possibly due that most of our patients had a recognizable illness.

Few case-control studies have evaluated infections in patients with RA. The authors reported a higher rate of infection in RA patients when the control group was from the general population, rather than patients with osteoarthritis (OA) and soft tissue rheumatism. Therefore, physicians have to be careful when interpreting such results by looking at healthy control.

Similar to our findings, other studies showed pneumonia, UTI and septicemia to be common in patients with RA. The authors reported a higher rate of infection in RA patients when the control group was from the general population. Therefore, physicians have to be careful when interpreting such results by looking at healthy controls.

Using GC in the first 90 days
represented the highest risk. With regard to the dose of GC, no increased risk of serious infection was detected with low dose use (< 5 mg per day), while high doses of steroids (20 mg or more per day) were associated with a 6-times higher risk of serious bacterial infection (RR = 5.48; 95% CI 3.29 – 9.11), with sepsis being the highest risk (RR = 6.83, 95% CI 3.29 – 9.11) followed by pneumonia (RR = 6.69, 95% CI 3.29 – 9.11). Although a significant association between GC use and infection was observed in this study; however, analysis of duration and the exact dosage of GC was not possible to determine due to the retrospective nature of the patients (increasing the dose of steroids temporary whenever the disease was active).

DMARDs were another considerable predictor for infection in RA patients but not as high as the GCs. As demonstrated in the largest retrospective study that included 27,710 RA patients, GCs but not DMARDs were associated with an increased risk of infections (both mild and serious). For patients on anti-TNF biologics, the risk of infection was lower than the DMARD when 858 anti-TNF-treated patients where compared to 601 DMARD-treated controls in a German study.

The present study showed a no significant increase risk of infection in patients who used MTX or HCQ. Studies were conflicting regarding the risk of infection with MTX use in patients with RA as some showed an associated risk, while others did not.

Regarding comorbid illnesses, in the Mayo cohort study, comorbid conditions were considered as a risk factor. Cardiovascular disease was a significant risk factor for infection and it was twice as common in patients with RA as in the controls. This point should be considered in the future management of patients, which needs the cooperation between the rheumatologist and the internal medicine team, in reducing the infection rate among patients with RA. Furthermore, a strict control for atherosclerotic risk factors (high blood pressure, hyperlipidemia, obesity, and DM) will help to improve patients’ outcome.

The current study has some limitations. Given the retrospective nature of our study, it is difficult to document all infections as some data may have been lost despite our efforts to accurately collect information from patients’ files. In addition, some patients would have their infections managed locally in the peripheral hospitals. However, according to our search, only one study was conducted in Saudi Arabia. The risk of different types of infections in RA patients at our society. It is in this light that we are conducting a study comparing the frequency of infection in RA patients on conventional DMARDs versus biologics.

**CONCLUSION**

This present study demonstrated that the rate of infection in patients with RA was high but lower than that reported in other studies. Associated comorbid illnesses and the use of steroids predisposed them to develop infections that may necessitate hospitalization. Although, clinicians are aware of the risks associated with steroid use in RA, more effort is required to reduce the infection risk by titrating the steroids to the lowest possible doses and managing associated comorbid illnesses.

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 معدل إنتشار نسبة العدوى في مرضى التهاب الروماتويدي المفصلي

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المستخلص:
الأهداف:
التهاب المفاصل الروماتويدي هو إضطراب التهابي مناعي ذاتي ترتبط به زيادة في الالتهابات المعدية و الهدف من هذه الدراسة هو تحديد وثوابت الإصابات بالالتهابات المعدية في مرضى التهاب المفاصل الروماتويدي وتقديم تقرير عن المخاطر المتعلقة بهذه الأمراض المعدية.

الطريقة:
تمت مراجعة ملفات مرضى التهاب المفاصل الروماتويدي بتأخر رجعي في مستشفى جامعة الملك عبد العزيز (عدد 200 حالة) خلال الفترة من يناير 2008، إلى ديسمبر 2010، واستنتاج معدلات العدوى والتبني بها.

النتائج:
كانت نسبة شيوخ أمراض العدوى في مرضى التهاب المفاصل الروماتويدي (36%)، أكثرها كان الالتهاب الرئوي، وجرثومه الدم، والتهاب المسالك البولية، بنسبة 12%، 11% على التوالي، وقد كان أكبر وأقوى إرهاصات التنبؤ بالأمراض المعدية = (OR = 12.67)، واستخدام هرمون الإستروئيد (OR = 4.87) · استخدام هرمون الإستروئيد (OR = 4.87)

الاستنتاجات:
إن معدل الإصابة بالأمراض المعدية في مرضى التهاب المفاصل الروماتويدي عالية، ولكن أقل من غيرها في الدراسات الأخرى، وتنبيه من هذه الدراسة أن أمراض القلب والأوعية الدموية و الكلى والعلاج بهرمون الإستروئيد يمثلون عوامل مخاطر الإصابة بالالتهابات المعدية والتي قد تتطلب العلاج في المستشفى.