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Original article

The changing face of septic arthritis complicating rheumatoid arthritis in the era of biotherapies. Retrospective single-center study over 35 years

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ABSTRACT

Objectives: To see whether the frequency and features of septic arthritis (SA) complicating rheumatoid arthritis (RA) have changed over the last 35 years.
Methods: This retrospective single-center study included all patients hospitalized at the rheumatology department for SA bacteriologically documented by synovial fluid and/or blood culture samples. The periods 1979–2002 (before biotherapies) and 2003–2013 (the era of biotherapies) were compared.
Results: Between 1979 and 2013, 64/514 (12.5%) SA presented with a RA – 21/157 (13.4%) in the 2003–2013 period and 43/357 (12.0%) in the 1979–2002 period. Over the past decade, median age of RA SA patients increased (61 vs. 68 years; $P < 0.02$) and predominant gender became males (52% vs. 40%). The features of the RA remained unchanged: history (18 vs. 16 years), rheumatoid factor (95% vs. 87%), and corticosteroids (91% vs. 81%). Over the last decade 24% (vs. 0; $P < 0.003$) of the patients received a biologic DMARD: etanercept ($n = 2$), adalimumab ($n = 1$), rituximab ($n = 1$), tocilizumab ($n = 1$). Proportion of polyarticular infection had decreased strongly (9.5% vs. 37%; $P < 0.02$). Proportion of *Staphyloccus aureus* infections remained stable, but there was a higher incidence of MRSA infections (31 vs. 6%; $P < 0.05$). Blood cultures less often tested positive (29% vs. 47%; NS). Case fatality rate had fallen slightly in RA SA (5% vs. 9%; NS), but not in non-RA SA cases (7% vs. 6%; NS).
Conclusion: This study brings reassuring findings – in the era of biotherapies, the rate of septic arthritis amongst patients with RA has not increased, and the most severe septic polyarticular forms are on the decline.

Rheumatoid arthritis (RA) is a risk factor for septic arthritis (SA) first identified by Kellgren et al. back in 1958 [1]. An estimated 10–15% of patients with SA have RA, but frequency rates vary widely from series to series [2,3]. The risk of SA in an RA patient is increased by 4–15-fold [4–6]. This increased risk is explained by the arthropathies and their joint local treatments, and by both disease-related immunocompromise and treatment-related immunocompromise, largely from corticosteroids and immunosuppressive drugs. The RAs complicated by SA are longstanding and far-developed conditions that, in over half of cases, are treated by corticosteroids [2]. The SAs complicating RA are characterized by the frequency of polyarticular disease, *Staphylococcus aureus* infection, and high mortality [2].

The 2000s marked a sea change in treatment for RA, spurred by the advent of biotherapies. Biotherapies increase infection risk, and in the British Society for Rheumatology Biologics Register, anti-TNF therapy use in RA doubled the risk of SA [7]. However, the hope is that better control of RA and less use of corticosteroid therapy should balance the risk of SA.

We had previously reported our experience on SA in patients with RA seen between 1979 and 1993. Here, we re-reviewed the full register of all SA patients hospitalized at CHU Clermont-Ferrand, rheumatology department to see whether the frequency and features of SA complicating RA have changed over the last 35 years.

1. Methods

This retrospective single-center study included the full register of all patients hospitalized at the rheumatology department of CHU Clermont-Ferrand between 1979 and 2013 for septic arthritis. All

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Table 1
Comparison of septic arthritis in RA patients versus non-RA patients.

	Total $n=514$	RA $n=64$	Non-RA $n=450$	*P*-value
Age, median [IQR]	67 [54–76]	65 [55–71]	67 [53–77]	0.31
Gender – males, *n* (%)	294 (57.2)	28 (43.8)	266 (59.1)	0.02
Multifocal joint site, *n* (%)	57 (11.1)	18 (28.1)	39 (8.7)	<0.001
Shoulder	94 (18.4)	11 (17.2)	83 (18.7)	0.72
Elbow	16 (3.1)	10 (15.6)	6 (1.3)	<0.001
Wrist	27 (5.3)	8 (12.5)	19 (4.2)	0.005
Hand	9 (1.8)	4 (6.3)	5 (1.1)	0.02
Hip	81 (15.8)	8 (12.5)	83 (18.4)	0.24
Knee	212 (41.2)	31 (48.4)	181 (40.2)	0.21
Ankle – tarsus	30 (5.8)	5 (7.8)	25 (5.6)	0.47
Foot	27 (5.3)	9 (14.1)	18 (4.0)	0.003
Prosthetic joint, *n* (%)	75 (14.6)	16 (25.0)	59 (13.1)	0.01
Microorganisms				
Staphylococcus, *n* (%)	328 (63.8)	52 (81.3)	276 (61.3)	0.002
S. aureus, *n* (%)	275/328 (83.8)	45/52 (86.5)	230/276 (83.3)	0.57
Multiresistant *S. aureus* (MRSA)	38/275 (13.8)	6/45 (13.3)	32/230 (13.9)	0.92
Streptococcus and *enterococcus*, *n* (%)	92 (17.9)	4 (6.3)	88 (19.6)	0.009
Gram-negative bacilli, *n* (%)	65 (12.7)	6 (9.4)	59 (13.1)	0.40
Other microorganism, *n* (%)	36 (7.0)	3 (4.7)	33 (7.3)	0.44
Synovial fluid culture, *n* (%)	464 (90.3)	62 (96.9)	402 (89.3)	*0.06*
Blood culture, *n* (%)	177 (34.4)	26 (40.6)	151 (33.6)	0.27
Iatrogenic, *n* (%)	40 (7.8)	4 (6.3)	36 (8.0)	0.63
Diabetes, *n* (%)	75 (14.6)	6 (9.4)	69 (15.3)	0.21
Cancer, *n* (%)	47 (9.1)	1 (1.6)	46 (10.2)	0.03
Death, *n* (%)	32 (6.2)	5 (7.8)	27 (6.0)	0.57

patients were clinically diagnosed to have SA with positive microbiology results from a synovial fluid and/or blood culture samples. The following data were collected and compiled: age, gender, year of initial diagnosis, causal agent and mode of identification, joint site, infectious risk factors, including diabetes, cancer, immunosuppressive therapy, and death during hospitalization. For patients with RA, we further specified: time since diagnosis, rheumatoid factor status, corticosteroid therapy and (if yes) dose, and the DMARD at the SA episode. All the patients met the ACR–87 diagnostic criteria. The features of SA complicating RA were compared against the features of non-RA SA cases. The first generation of biologics emerged in the year 2000. Allowing for slow initial diffusion of these innovative treatments, we compared the features of SA cases in the last ten years (recorded between 2003 and 2013) against earlier SA cases (recorded between 1979 and 2002).

Statistical analysis was performed using Stata 13 software (StataCorp LP, College Station, TX, US). The tests were two-sided, with a type I error set at $\alpha = 0.05$. Subject's characteristics were presented as mean (± standard-deviation) or median [interquartile range] for continuous data (assumption of normality assessed using the Shapiro–Wilk test) and as the number of patients and associated percentages for categorical parameters. Comparisons between the independent groups (RA and non-RA, 1979–2002 and 2003–2013) were performed using:

- Chi^2 or Fisher's exact tests for categorical variables;
- Student *t*-test or Mann–Whitney test for quantitative parameters (assumption of homoscedasticity studied using Fisher-Snedecor test).

2. Results

Over the period 1979 to 2013, the rheumatology department hospitalized 514 patients for SA. The patient characteristics are shown in Table 1. Sixty-four patients had RA (12.5%). We had previously reported 24 of these case observations [2]. Proportion of SA complicating RA has not varied over time (Fig. 1), at 13.4% (21/157) over the period 2003–2013 and 12.0% (43/357) over the period 1979–2002.

2.1. Features of SA complicating RA

Median patient age of SA cases complicating RA is 65 (55–71) years, i.e. comparable to non-RA SAs. There was a larger proportion of women in the RA group and a larger proportion of men in the non-RA group (Table 1). The RA registered had longstanding median history of 16 years, had rheumatoid factor in 90% of cases, and were treated by corticosteroids in 84% of cases at a mean dose of 10 mg/d. Roughly two third have a DMARD, i.e. methotrexate in 15 cases (35%), D-penicillamine (16%), hydroxychloroquine (14%), and a biotherapy agent in 5 cases (etanercept, $n=2$; adalimumab, $n=1$; rituximab, $n=1$; tocilizumab, $n=1$). All patients treated with biologics had associated corticosteroids. There was no significant difference in frequency of diabetes between the RA and non-RA groups (9.4% vs. 15.3%), but cancer was less common in RA group patients (1.6% vs. 10.2%; $P<0.03$). RA patients had a higher incidence of multifocal joint infection (28% vs. 9%; $P<0.001$) and a higher incidence of prosthetic joint infection (25% vs. 13%; $P<0.01$) of the foot, elbow, wrist, or hand than non-RA patients.

S. aureus infection is more frequent in SA complicating RA (70% vs. 51%; $P<0.003$) whereas streptococcal–enterococcal infections

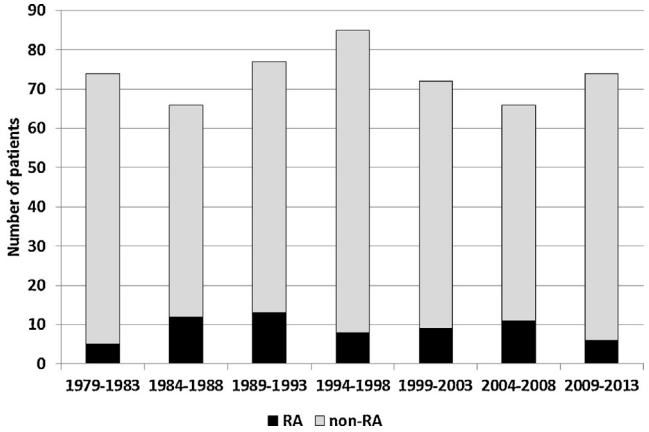

Fig. 1. Frequency of septic arthritis complicating rheumatoid arthritis between 1979 and 2013.