Trends in Serious Infections in Rheumatoid Arthritis

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ABSTRACT. ***Objective.*** To examine trends in the rates of serious infections among patients diagnosed with rheumatoid arthritis (RA) in 1995–2007 compared to rates previously reported from the same geographical area diagnosed 1955–1994.

Methods. A population-based inception cohort of patients with RA in 1995–2007 was assembled and followed through their complete medical records until death, migration, or December 31, 2008. All serious infections (requiring hospitalization or intravenous antibiotics) were recorded. Person-year (py) methods were used to compare rates of infection.

Results. Among 464 patients with incident RA in 1995–2007, 54 had ≥ 1 serious infection (178 total). These were compared to 609 patients with incident RA in 1955–1994 (290 experienced ≥ 1 serious infection; 740 total). The rate of serious infections declined from 9.6 per 100 py in the 1955–1994 cohort to 6.6 per 100 py in the 1995–2007 cohort. Serious gastrointestinal (GI) infection rates increased from 0.5 per 100 py in the 1955–1994 cohort to 1.25 per 100 py in the 1995–2007 cohort. Among patients with a history of serious infection, the rate of subsequent infection increased from 16.5 per 100 py in 1955–1994 to 37.4 per 100 py in 1995–2007. There was an increase in the rate of serious infections in patients who received biologic agents, but this did not reach significance.

Conclusion. Aside from GI infections, the rate of serious infections in patients with RA has declined in recent years. However, the rate of subsequent infections was higher in recent years than previously reported. (First Release April 1 2013; J Rheumatol 2013;40:611–16; doi:10.3899/jrheum.121075)

Key Indexing Terms:
RHEUMATOID ARTHRITIS INFECTION BIOLOGIC AGENTS

Patients with rheumatoid arthritis (RA) have increased susceptibility for infections[1]. Reasons for increased infection risk in patients with RA are multifactorial. Probable causes include the underlying immunologic disturbance associated with the disease process, immunosuppressive therapy used for treatment of RA, and other coexisting risk factors for infection that may be more common in patients with RA[2]. Concern for risk of infection has been heightened in recent years as clinicians have struggled to evaluate the possible influences of the introduction of biologic agents for treatment of many rheumatological conditions[3,4,5,6]. In addition, the approach to management of RA has moved toward more aggressive therapy to prevent disease progression and complications. It is unclear whether these trends have had an effect on infection risk.

This has led to recent publications by ourselves and others examining the risk factors for infection in patients with RA and providing scoring systems to evaluate the risk of infection in these patients[7,8,9]. However, recent trends in the rates and types of infection among patients with RA have not been evaluated. The objective of our study was to compare the rates and types of serious infection among patients diagnosed with RA in 1995–2007 to rates previously reported among patients with RA from the same geographical area who were diagnosed in 1955–1994.

MATERIALS AND METHODS

Study population. We performed a retrospective longitudinal cohort study comparing infection rates in residents of Olmsted County, Minnesota, USA, aged ≥ 18 years with incident RA in 1995–2007 with our previous cohort of residents with incident RA in 1955–1994[1]. Patients in both cohorts fulfilled 1987 American College of Rheumatology (ACR) criteria for RA[10]. Patients with incident RA were identified as described[11]. All study subjects were followed through their entire inpatient and outpatient medical record, until death, migration from the county, or the date of study end (December 31, 1999, for the 1955–1994 cohort and December 31, 2008, for the 1995–2007 cohort).

These RA cases were identified using the data resources of the Rochester Epidemiology Project (REP), a diagnostic indexing and medical records linkage system that affords access to medical records from all sources of care for community residents[12].

This study was approved by the institutional review boards of the Mayo Clinic and the Olmsted Medical Center.

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Data collection. Data on all episodes of serious infection requiring hospital admission or intravenous (IV) antibiotics occurring after the RA incidence date were collected according to a prespecified and pretested detailed protocol. Data for the 1995–2007 cohort were collected by an abstractor who collected data for the 1955–1994 cohort.

The operational definitions for each infection type were as follows: bacteremia/septicemia, isolation of a pathogenic microorganism from 1 or more blood cultures, with fever (> 38°C); septic arthritis, positive microbiologic culture from joint aspirate fluid in the presence of suggestive clinical features; urinary tract infection, including pyelonephritis and urosepsis, isolation of > 100,000 colony-forming units/ml of urine in the presence of suggestive clinical features; pneumonia, presence of new infiltrates, consolidation, or effusion seen by chest radiography and suggestive clinical features; and osteomyelitis, clinical suspicion with confirmation by definite radiologic findings or positive bone culture. Lower respiratory tract infections, skin and soft-tissue infections, and acute gastrointestinal (GI) infections could be included on the basis of a physician's diagnosis and relevant clinical findings alone, but microbiologic culture results were recorded if available. Skin and soft-tissue infections included cellulitis, abscesses, wound infections, herpes zoster, and diabetic foot infections. GI infections included gastroenteritis, diverticulitis, infective colitis, *Clostridium difficile*, and vancomycin-resistant enterococci. Opportunistic infections included cytomegalovirus, cryptococcus, mycobacterium tuberculosis, nontuberculosis mycobacterium, vancomycin-resistant enterococci, histoplasmosis, blastomycosis, coccidioidomycosis, cryptococcosis, endemic mycosis, nocardiosis/actinomycosis, listeriosis, toxoplasmosis, pneumocystis, legionellosis, salmonellosis, aspergillosis, candidemia, progressive multifocal leukoencephalopathy, and optic neuritis. Intra-abdominal infections could be included on the basis of clinical findings alone, and comprised acute cholecystitis, ascending cholangitis, suppurative appendicitis, and peritonitis. The category "other infections" included episodes of otitis media and sinusitis that required hospitalization, eye infections, male and female genital tract infections, and acute hepatitis. Data on urinary tract infections (other than those classified as urosepsis/acute pyelonephritis) were not recorded. Patients who fulfilled criteria for more than 1 infection simultaneously were classified in both categories, except in the case of septicemia, which was classified in a single category referred to as septicemia with a notation of the accompanying infectious condition (e.g., pneumonia with septicemia, urinary tract infection with septicemia).

Information was ascertained on potential confounding factors for infection [rheumatoid factor positivity, diabetes mellitus, leukopenia, smoking status, alcoholism, chronic lung disease, cancer, and extraarticular manifestations of RA (ExRA)], along with dates of onset. Leukopenia was defined as white blood cell counts < 4000/ml on 2 or more occasions. Manifestations of severe ExRA included pericarditis, pleuritis, Felty's syndrome, glomerulonephritis, vasculitis, peripheral neuropathy, scleritis, and episcleritis[13,14]. Data were also collected on start and stop dates of medication used at any point during followup, including commonly used disease-modifying antirheumatic drugs (DMARD) such as methotrexate, hydroxychloroquine, other DMARD (gold, sulfasalazine, azathioprine, cyclophosphamide, cyclosporine, D-penicillamine, or leflunomide), biologic agents, and corticosteroids.

Data on vital status were also collected. Case fatality was defined as a death within 30 days of a serious infection.

Data analysis. Baseline characteristics of the study population were summarized using descriptive statistics. Cumulative incidence adjusted for the competing risk of death was used to compare the occurrence of characteristics between cohorts appropriately accounting for differences in length of followup[15]. Cumulative incidence rates were compared using the methods of Gray[16]. Incidence rates for infections were calculated by dividing the total number of events by the number of person-years (py) of followup. Rate ratios (RR) were obtained by dividing infection incidence rates in patients with RA in the 1995–2007 cohort by those in patients with RA in the 1955–1994 cohort, and 95% CI for these RR were calculated. Because of the differential length of followup in the 2 time periods, cumulative incidence rates were also computed for infections to provide comparison of infection rates at the same length of followup in the 2 time periods.

Comparisons of infection rates between time periods were also performed after adjustment for infection risk factors. Adjustment for risk factors was performed by first calculating the infection risk score we previously developed at the RA diagnosis and at the beginning of each subsequent year of followup for each patient[7]. The Andersen-Gill adaptation of the Cox model allowing inclusion of multiple events in the same patient was used to compare the rate of development of serious infections between the time periods after adjustment for the risk score[17]. The risk score adjustment was performed using a time-dependent covariate to represent the risk score, which changed at the beginning of each yearly interval throughout followup.

The rate of infections during biologic treatment was calculated as the number of infections that occurred between the start and stop dates of biologic treatment divided by the length of followup from the start to the stop of biologic treatment. Infection rates in patients with biologic exposure included the infections and followup after the stop of biologic treatment in patients who were exposed to biologics.

RESULTS

The cohort of patients with incident RA in 1995–2007 comprised 464 patients. These patients were compared with 609 patients with incident RA in 1955–1994. The mean age at RA incidence for the early cohort was 58.0 years (73% female) and for the later cohort 56.0 years (69% female; Table 1). The mean followup time was 12.7 years for the early cohort and 5.9 years for the later cohort, corresponding to 7730 total py and 2715 py, respectively. Rates of smoking and comorbidities were similar in the 2 time periods, except for diabetes mellitus, which occurred more frequently among patients in the 1995–2007 cohort compared to the 1955–1994 cohort. The risk score for serious infections was significantly higher among patients with incident RA in 1995–2007 compared to those with incident RA in 1955–1994 ($p = 0.015$).

More patients in the 1995–2007 cohort received the nonbiological DMARD methotrexate and hydroxychloroquine and biologic agents, and more patients were exposed to corticosteroids, compared with patients in the 1955–1994 cohort. However, patients in the 1995–2007 cohort were less likely to receive other nonbiologic DMARD than patients in the 1955–1994 cohort.

In the 1995–2007 cohort, 54 patients had ≥ 1 serious infection (178 total infections) and in the 1955–1994 cohort, 290 patients experienced ≥ 1 serious infection (740 total infections). The rate of all serious infections in patients in the 1995–2007 cohort was 6.6 per 100 py, which was less than the rate of 9.6 per 100 py that was seen in patients in the 1955–1994 cohort (RR 0.69, 95% CI 0.58, 0.80; Table 2). The rate of first infection was also lower in the 1995–2007 cohort (2.0 per 100 py) compared to the 1955–1984 cohort (3.8 per 100 py). Similar differences in rates were noted comparing the cumulative incidence of first serious infection at 10 years after RA [15.6% (95% CI 11.2%–20.0%) for 1995–2007 vs 34.5% (95% CI

Table 1. Characteristics of 609 incident patients with rheumatoid arthritis (RA) diagnosed in 1955–1994 and 464 incident patients with RA diagnosed in 1995–2007. Except where indicated otherwise, values are the number (%) of patients. Percentages for "ever during followup" are estimates of cumulative incidence at 10 years of followup.

Variable	RA 1955–1994, n = 609	RA 1995–2007, n = 464
Age, mean ± SD yrs	58.0 ± 15.1	55.6 ± 15.5
Female	445 (73)	320 (69)
Length of followup, mean ± SD yrs	12.7 ± 9.4	5.9 ± 3.5
Rheumatoid factor positivity	392 (65)	306 (66)
Infection risk score at RA incidence	2.6 ± 2.1	3.3 ± 3.0
Ever-smoker	317 (55)	235 (51)
Diabetes mellitus		
At RA incidence	25 (4)	48 (10)
Ever during followup	63 (9)	77 (21)
Chronic lung disease		
At RA incidence	67 (11)	74 (16)
Ever during followup	113 (20)	99 (24)
Alcoholism		
At RA incidence	13 (2)	37 (8)
Ever during followup	42 (6)	41 (9)
Ischemic heart disease		
At RA incidence	20 (3)	25 (5)
Ever during followup	73 (13)	46 (14)
Cancer		
At RA incidence	24 (4)	28 (6)
Ever during followup	72 (13)	63 (20)
Leukopenia, ever during followup	102 (15)	56 (18)
Extraarticular RA*, ever during followup	78 (8)	22 (6)
Medication use, ever during followup		
Methotrexate	133 (18)	299 (73)
Hydroxychloroquine	221 (37)	297 (68)
Other nonbiological DMARD	215 (36)	104 (30)
Biologic agents	3 (0.2)	96 (29)
Corticosteroid (PO or IV)	312 (46)	376 (90)

* Includes pericarditis, pleuritis, Felty's syndrome, glomerulonephritis, vasculitis, peripheral neuropathy, scleritis, and episcleritis. DMARD: disease-modifying antirheumatic drug; PO: by mouth; IV: intravenously.

30.4%–38.6%) for 1955–1994]. Among patients with a serious infection, the risk scores for serious infections for the beginning of the year of followup when the first serious infection occurred were somewhat higher among patients in the 1995–2007 cohort (median 8.4%; 25th percentile, 75th percentile: 3.8%, 36.0%) compared to the 1955–1994 cohort (median 6.5%; 25th percentile, 75th percentile: 3.0%, 23.8%; p = 0.059). Adjustment for the serious infection risk score had no effect on the difference in infection rates between the cohorts.

Bacteremia/septicemia, pneumonias, and skin/soft-tissue infections were the most common types of infections in both time periods. Bacteremia/septicemia rates decreased from 0.78 infections per 100 py in the 1955–1994 cohort to 0.52 infections per 100 py in the 1995–2007 cohort (RR 0.68, 95% CI 0.36, 1.16). The rate of serious pneumonia infections decreased from 3.10 to 1.99 infections per 100 py (RR 0.65, 95% CI 0.47, 0.85). Skin/soft-tissue infections decreased from 2.37 to 1.51 infections per 100 py (RR 0.64, 95% CI 0.45, 0.89). Septic arthritis, osteomyelitis, lower respiratory infections, urosepsis/pyelonephritis, intra-abdominal infections, and other infections all followed a similar decline in infection rates between the 2 time periods.

In contrast, the rates of serious GI infections increased between the 2 groups from an infection rate of 0.49 to 1.25 infections per 100 py, respectively (RR 2.55, 95% CI 1.60, 4.04). The rates of opportunistic infections increased significantly (RR 9.35, 95% CI 3.22. 41.4), as did the rates of *C. difficile* infections (RR 12.34, 95% CI 2.84, 176.5).

The only opportunistic infections that occurred in our cohort were *C. difficile* and vancomycin-resistant enterococci.

The overall rate of all subsequent infections in patients who developed at least 1 previous serious infection requiring hospitalization was increased from 26.3 to 65.1 infections per 100 py (RR 2.48, 95% CI 2.02, 3.01). Similarly, the rate of second serious infection among patients with a first serious infection was increased from 16.5 per 100 py in 1955–1994 to 37.4 per 100 py in 1995–2007. Note that the rate of all subsequent infections (i.e., not including the initial infection) declined when estimated among all patients with RA, not just those with an initial infection: that is, 5.8 vs 4.6 infections per 100 py (RR 0.79, 95% CI 0.64, 0.95).

In the 1995–2007 cohort, 96 patients received biologic agents at some point; about 95% were tumor necrosis factor inhibitors, so analyses of subtypes of biologic agents were not performed. The rate of infections during treatment with biologic agents was 8.2 infections per 100 py (95% CI 4.9, 12.8 per 100 py) compared with 6.4 infections per 100 py (95% CI 5.4, 7.5 per 100 py) for those not receiving biologic agents (RR 1.31, 95% CI 0.78–2.01). Similarly, the rate of infections for patients who were ever exposed to biologic agents (during or after use of biologic agents) was 7.9 infections per 100 py (95% CI 5.3, 11.1 per 100 py) compared with 6.4 infections per 100 py (95% CI 5.4, 7.5 per 100 py) for those who had never used (or prior to use of) biologic agents (RR 1.24, 95% CI 0.82–1.79).

Case fatalities occurred in 90 (12%) of the 740 infections in the 1955–1994 cohort and 7 (4%) of the 178 infections in the 1995–2007 cohort, indicating a substantial decrease in case fatality rates (p < 0.001).

DISCUSSION

The overall rate of serious infections in our population has declined among patients diagnosed with RA in recent years, while the rate of subsequent serious infections in those patients with a history of at least 1 serious infection has increased. The principal sites of infections remained consistent between the 2 cohorts; however, there were significantly increased rates of GI infections and opportunistic infections, predominately *Clostridium difficile* in

Table 2. All infections requiring hospitalization in 609 patients diagnosed with rheumatoid arthritis (RA) in 1955–1994 compared with 464 patients diagnosed with RA in 1995–2007.

Infection Type	Patients, n		Infections, n		Incidence/100 Person-years (all events/person-years)		RR* (95% CI)
	1955–1994	1995–2007	1955–1994	1995–2007	1955–1994	1995–2007	
Total	290	54	740	178	9.57	6.56	0.69 (0.58, 0.80)
Bacteremia/septicemia	53	10	60	14	0.78	0.52	0.68 (0.36, 1.16)
Septic arthritis	20	3	27	3	0.35	0.11	0.36 (0.08, 0.92)
Osteomyelitis	11	0	13	0	0.17	0.00	0.11 (0.00, 0.59)
Pneumonia	155	28	240	54	3.10	1.99	0.65 (0.47, 0.85)
Lower respiratory tract	57	10	89	10	1.15	0.37	0.33 (0.16, 0.59)
Urosepsis/pyelonephritis	27	4	35	5	0.45	0.18	0.44 (0.15, 0.96)
Skin/soft-tissue	109	21	183	41	2.37	1.51	0.64 (0.45, 0.89)
Gastrointestinal infections†	26	13	38	34	0.49	1.25	2.55 (1.60, 4.04)
Intraabdominal	25	5	26	5	0.34	0.18	0.59 (0.20, 1.33)
Other	24	8	29	12	0.38	0.44	1.21 (0.59, 2.26)
Opportunistic infections††	3	6	3	11	0.04	0.41	9.35 (3.22, 41.4)
Clostridium difficile	1	3	1	6	0.01	0.22	12.34 (2.84, 176.5)

* Rate ratio obtained by dividing infection incidence rates in 1995–2007 patients with RA by those in 1955–1994 patients. † Includes gastroenteritis, diverticulitis, infective colitis, *Clostridium difficile*, and vancomycin-resistant enterococci. †† Includes *Clostridium difficile* and vancomycin-resistant enterococci.

the 1995–2007 cohort. We noted a similar burden of comorbidities related to infection risk in the 2 cohorts, except for an increase in diabetes mellitus among patients in the 1995–2007 cohort compared to the 1955–1994 cohort. More patients in the 1995–2007 cohort were exposed to antirheumatic medications including certain DMARD (such as methotrexate and hydroxychloroquine), biologic agents, and corticosteroids. A possible increased rate of serious infections was observed in patients who received biologic agents; however, because of the limited number of patients receiving biologic agents in our study, a definitive conclusion about the use of biologic agents and the rate of serious infections could not be made.

Patients with RA are known to be at increased susceptibility for infections[1,18]. Active inflammatory disease may confer a higher risk of infection[19]. Alterations in the cellular immune system, including alterations in the RA-related T cell functions, likely also contribute to the infection risk[18,20,21]. Other risk factors for infection include advancing age, leukopenia, and comorbidities (chronic lung disease, alcoholism, dementia/Alzheimer's disease, and diabetes mellitus)[2,7]. Treatment options for RA can also place patients at increased risk for serious infections. These include corticosteroids, DMARD, and biologic agents[2,22,23,24]. As well, severity indices of RA such as increased sedimentation rate, ExRA, and rheumatoid factor positivity are all predictive of development of serious infections in these patients[2].

In the past decade, more aggressive use of conventional DMARD as well as the introduction of biologic agents have contributed to better control of RA activity. The decrease in the number of serious infections in patients with RA may potentially be due to decreased inflammation. While we did not directly assess disease activity, we noted that more of the patients who were diagnosed recently had received corticosteroids (90% vs 46%), methotrexate, hydroxychloroquine, and biologic agents compared to the patients diagnosed earlier. This more aggressive treatment is likely associated with a lessened inflammatory burden, but additional associated potential safety risks of such agents.

It is unclear why the rate in GI infections and particularly *C. difficile* infection has risen in patients diagnosed more recently. The rate of *C. difficile* infection in the general community has increased in recent years, likely due to a combination of factors[25]. Therefore, the increased risk of this infection in patients with RA may simply reflect the overall increase in this infection in the general population. There is some evidence of an increased risk of *C. difficile* in patients receiving biologic agents[26,27]; however, further studies are needed to clarify this.

Although the rates of subsequent serious infections in patients who have had a previous serious infection requiring hospitalization were increased, we speculate this was likely a result of overall declines in hospitalization rates[28]. For instance, some of the infections that required hospitalization in the 1960s would not require hospitalization in the 1990s because these infections can now be treated outside the hospital, owing to the development of more potent antibiotics and more accessible diagnostic tests. Therefore, patients in the later cohort who require hospitalization for an initial infection are fewer but generally of poorer health than

those who have been managed in the community, and are hence more likely to develop a subsequent serious infection requiring hospitalization. For this reason, although the rate of subsequent infection appears to be increasing in the subset of patients who had an initial infection, it has actually declined overall. However, the decrease in the overall rate of subsequent infections was smaller than the decrease in the rate of initial infections, which resulted in an apparent increase in the rate of subsequent infections when estimated using the subset of patients who experienced an initial serious infection.

Strengths of our study include the longitudinal population-based study design with extensive followup and the use of complete inpatient and outpatient medical records, providing complete ascertainment of study outcomes for all study subjects. In addition, the data for both time periods were collected using the same criteria, as well as the same abstractors, ensuring comparable data between the 2 cohorts of patients.

Our results need to be interpreted in light of potential limitations. Some ethnic groups are underrepresented in the catchment area of Olmsted County, Minnesota, but results are generally reflective of the US population[5]. The influence of disease activity on infection risk was not assessed, because disease activity scores (e.g., Disease Activity Score–28) were not available. In addition, the followup time in the 1995–2007 cohort was substantially shorter than in the 1955–1994 cohort, which might influence the rates of infection. However, comparisons of cumulative incidence at a specific RA duration yielded similar results. In addition, disease duration was not associated with infection rates in our cohort, so the differences in length of followup between cohorts were unlikely to influence our findings. Finally, the rates of serious infections over time are influenced by secular trends in the threshold for hospitalization, the use of diagnostic tools, the prevalence of antibiotic-resistant strains, and the use of influenza and pneumococcal vaccine and other factors, which could not be accounted for in this observational study.

There has been a decline in the rates of serious infections in patients with RA diagnosed in recent years, despite some increases in comorbidities that could predispose to infection. This decline is most likely due to declining hospitalization rates in the general population over this time period, but better control of the inflammation associated with RA likely also plays a role. The rate of GI infections such as *C. difficile* has risen in recent years, probably related to the increase in this infection in the general population. Further studies to assess the relationship between the severity of inflammation and its influence on serious infections in patients with RA would be beneficial.

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