

Infections in Rheumatoid Arthritis — A New Phenomenon?



Recent case reports of life threatening infections in patients with rheumatoid arthritis (RA) treated with biological therapies have raised concern within the rheumatology community. There have been a number of such reports of serious, and in some cases, fatal, infections in patients with RA taking these new medications. For many years, however, there have been reports of a high frequency of infections complicating RA. In particular, high prevalence rates of pulmonary infections and septic arthritis have been described¹⁻³. Further, reports have suggested, even in the pre-steroid era, that patients with RA may have increased susceptibility to infection⁴. In large series of patients with septic arthritis, RA is the most common predisposing factor to infection and has been present in between 10 and 40% of these patients⁵. Increased mortality rates in RA have also been attributed, in part, to infections — studies from several countries have established that patients with RA have higher mortality due to common infectious diseases, in particular genitourinary and bronchopulmonary infections, compared with the general population⁶⁻¹⁰.

The excess mortality from infection, along with the reports of serious infections, suggests that patients with RA may be predisposed to develop infections in comparison with non-affected individuals of the same age and sex. Another possibility is that infections in RA may run a more severe course than in the general population, leading to more frequent occurrence of severe infections and a higher case fatality rate. It has been postulated that an increased susceptibility to infections may relate to the immune effects of the disease itself, or to the frequent use of corticosteroids and other immunomodulatory therapies. One prospective study of 228 patients with RA documented a relative risk for infection in patients taking methotrexate of 1.52 (95% CI 1.04–2.22)¹¹. Corticosteroid use has also been shown to increase the risk of serious infection¹². More recently, some severe and opportunistic infections have been attributed to immune suppression related to anti-tumor necrosis factor/biological therapies.

Data on the frequency of infections in RA, and on the relative risk for infection and severity of infections compared with the general population, are limited. Therefore, no reliable background rates are available to compare with the rates of infection in RA patients taking biological agents. Hernandez-Cruz, *et al* estimated the incidence of all infections in 195

consecutive patients with RA seen in an outpatient clinic to be 17 new infections per 100 patient-years of followup¹³. Another study by Ramey, *et al* examined the occurrence of serious infections in RA. These investigators found the incidence of infections requiring hospitalization to be 3.1 per 100 patient-years in 5569 patients with RA¹⁴. Unfortunately, both these studies were hospital based and lacked a control group. The absence of a control group makes it difficult to determine whether the observed rates of infection are significantly different from the rates that would be expected among people of the same age and sex in the general population.

Only two case-control studies of infections in RA have been reported. These retrospective studies, which examined self-reported frequency of infections, found that patients with RA are not more susceptible to common infections than controls with osteoarthritis (OA) or soft tissue rheumatism. The first of these, which compared 286 RA patients with controls with OA or soft tissue rheumatism, found no significant difference in frequency of genitourinary infection — odds ratio 0.83 (95% CI 0.57–1.2), and a reduced frequency of bronchopulmonary infections — odds ratio 0.61 (95% CI 0.39–0.96)¹⁵. The second study of 448 RA patients and 185 controls found that a similar proportion of both groups had at least one infection during the preceding year — 101 (23%) RA versus 50 (27%) controls — and that the types of infection in both groups were similar¹⁶. Limitations of these studies include the fact that they were relatively short term, relied on recall for self-reporting of infections by patients, and examined only hospital based series of patients.

We are currently conducting a population based study to compare the frequency and severity of infections in an incidence cohort of RA patients with frequency and severity in a cohort of age and sex matched non-RA controls from the same community. This study design will facilitate both description of the incidence of various infections among RA patients in the community and determination of the risk for each infection in RA cases relative to non-affected controls. We will also examine risk factors for infection in RA. Information such as that forthcoming from our study will indicate whether patients with RA do indeed have increased susceptibility to infections relative to the general population, and whether infections tend to be more serious, as well as the role of medications and other

putative risk factors in the development of infections in RA.

For decades, high rates of infection have been reported among patients with RA. Recent case reports of life threatening infections in patients treated with biological therapies have prompted serious concern regarding the safety of these new agents. While these agents may indeed cause an increased risk of infection, it is also possible that these reports have simply drawn added attention to this longstanding phenomenon. The important problem of infection risk in RA merits careful evaluation; anecdotal reports and case series are inadequate to resolve the questions posed by this issue. Controlled population based studies are needed to determine definitively whether the observed rate of infections among RA patients in the community is indeed higher than would be expected for non-affected persons of the same age and sex from the same community. Only then will clinicians be able to place these recent anecdotal reports in the proper perspective.

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