EXTENDED REPORT

Risk and predictors of infection leading to hospitalisation in a large primary-care-derived cohort of patients with inflammatory polyarthritis

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Background: The increased mortality observed in patients with rheumatoid arthritis is partly due to an increased occurrence of serious infections. A retrospective study from the Mayo Clinic found that infection risk is increased in rheumatoid arthritis. In particular, serious infection was associated with severe disease and use of corticosteroids. Robust estimates are required from prospective studies of incident cases.
Objective: To examine the risk of infection leading to hospitalisation and potential factors associated with this risk in an unselected population of patients with inflammatory polyarthritis.
Design: A prospective cohort study comparing infection incidence in new-onset patients with inflammatory polyarthritis with local population experience.
Patients and methods: 2108 patients with inflammatory polyarthritis from a community-based register were studied and followed up annually (median 9.2 years). The rate of hospitalisations for serious infection was compared with the rate of hospitalisations in the regional population. The contribution of potential predictors was assessed by undertaking a within-cohort analysis.
Results: Overall, the incidence of infection was more than two and a half times that of the general population (varying by site). History of smoking, corticosteroid use and rheumatoid factor were found to be significantly independent predictors of infection-related hospitalisation. Patients with inflammatory polyarthritis with all three factors were more than seven times as likely to be hospitalised compared with the rest of the cohort.
Discussion: These findings provide background data on the risk of infection associated with rheumatoid arthritis, and are of particular interest given the current awareness of the risk of infection associated with anti-tumour necrosis factorα treatments.

Several studies have shown that patients with rheumatoid arthritis have an approximate 1.5–2 times increased age-adjusted all-cause mortality.[1–8] In cohorts of patients with rheumatoid arthritis, infection is typically the second or third most common cause of mortality.[1 7 9–11] As a consequence, rates of infection-related mortality are increased by almost 4–6 times that of the general population.[2 6 8 11]

Although patients with rheumatoid arthritis who develop a severe infection may have an increased case fatality, it is also likely, that this increased mortality risk is partly due to an increased infection incidence. So far, only two studies have compared the incidence of infection in rheumatoid arthritis with that in the general population. A case–control study found no increased risk of self-reported infection between rheumatoid arthritis patients and population controls.[12] Such an approach may be associated with both recall errors as well as recall bias, limiting the interpretation.

A study from the Mayo Clinic, Rochester, Minnesota, USA using retrospective case-note review, compared the incidence of infection in patients with rheumatoid arthritis, recruited between 1955 and 1994, with that in a group of patients without inflammatory arthritis.[13] Any mention of infection was detected 45% more often, and records of hospitalisation for infection were 70% more common, in patients with rheumatoid arthritis compared with the selected controls. By restricting the analysis to those with laboratory-confirmed infection, the risk was increased by more than 80%. In a further report, comorbid conditions and corticosteroid use were the main predictors of increased risk.[14] In this retrospective study, it was not possible to adjust for all possible predictors given the difficulty in using routine records in standardising data collection.

There are several reasons why rheumatoid arthritis may be associated with an increased rate of infection. Firstly, disturbance of the immune system could reduce the ability to resist infection.[14–17] In addition, rheumatoid arthritis is often treated with powerful immunosuppressive agents that, in themselves, result in a reduction of the immune system's effectiveness.[15 18–20] Finally, rheumatoid arthritis is associated with smoking,[21 22] which is a known risk factor for infection.[23–25]

We therefore report a prospective study that aimed to identify the magnitude of any increased risk of severe infection in an unselected cohort of patients with inflammatory polyarthritis and to ascertain the role of disease and other factors in leading to such a risk.

PATIENTS AND METHODS

Summary of design

We took advantage of a prospective study following up a large primary-care-based incident cohort of patients with inflammatory polyarthritis. The number of hospitalisations for serious infection was compared with the number of expected hospitalisations, calculated using population rates, for the same region. Within the inflammatory polyarthritis cohort, the role of a number of potential demographic and disease-related risk factors in the risk of infection was assessed.

Abbreviations: ACR, American College of Rheumatology; DMARD, disease-modifying antirheumatic drug; HAQ, Health Assessment Questionnaire; NOAR, Norfolk Arthritis Register; TNF, tumour necrosis factor

Patients

The cohort used in this analysis comprised patients enrolled with the Norfolk Arthritis Register (NOAR), based in Norwich, UK. The methods of recruitment are described in detail elsewhere.[26] To summarise, between 1990 and 1999, patients aged ⩾16 years, attending their primary-care physician within the study area with recent-onset synovitis of >2 joints lasting at least 4 weeks, were referred to NOAR. Trained research nurses conducted structured interviews and physical examinations at baseline for all the patients. Serum was taken for analysis of rheumatoid factor, and the baseline Health Assessment Questionnaire (HAQ)[27] was completed by all patients. Finally, patients were classified as past, current or never smokers on the basis of a self-reported history of cigarette smoking.

Follow-up

Patients were followed up annually by a research nurse who collected details of all prescribed drugs in addition to the clinical data on disease activity and severity. Those patients who were diagnosed with another definite rheumatological disorder that explained their symptoms were subsequently excluded. The 1987 American College of Rheumatology (ACR) criteria for rheumatoid arthritis[28] were applied cumulatively over the first five assessments, and patients were categorised as having rheumatoid arthritis if they ever satisfied the criteria, and the remaining patients were categorised as having undifferentiated inflammatory polyarthritis.

Patients were *x* rayed and the hand and feet radiographs scored for the presence of erosions as described elsewhere.[29] In addition, patients completed the HAQ, and an overall mean was computed across all assessments.

Ascertainment of hospitalised infections

Patients were linked to the electronic admissions system of the region's only major hospital. These data provided the International Classification for Diseases-10th Revision (ICD10) coded cause and date of any admissions occurring from 1995 onwards. The major infection sites were grouped using the ICD10, as follows: respiratory, B58–B59, J12–J18 and J20–J22; urinary tract, N30 and N39.0; skin, L01–L08; septicaemia, A40–A41; infectious arthritis, M00–M02. Hospitalisation rates/1000 person years were calculated for the entire cohort and stratified by sex for each infection site of interest and all sites combined. Follow-up time was calculated from onset of inflammatory polyarthritis or January 1995 (whichever was latest) until death, emigration or 31 March 2004 (the end of the study period).

The same electronic admissions data source was used to derive age, sex and calendar year and specific incidence rates of hospitalisation for infection in the regional population covered by NOAR. For both the NOAR and the comparison cohort, only the first infection in any calendar year was included so as to minimise the chance of double counting single infectious events—that is, patients could contribute more than one event as long as each consecutive infection in the same grouping did not occur within the same calendar year.

Analysis

Incidence rates in the NOAR population were compared with expected rates calculated from 10-year age, sex and calendar-year-specific hospitalisation rates obtained from the regional population. Relative risks with their 95% CI were calculated using negative binomial regression for each site as well as all sites combined.

Within the cohort, negative binomial regression was used to model the univariate relative risks of serious (overall) infection. This type of regression is often used as an alternative to the Poisson regression (which is commonly used in situations where the outcome of interest is a count or a rate). Whereas these two models are very similar in practice, the negative binomial model allows relaxation of the assumption that the distribution mean and variance are equal (as in a Poisson distribution). It seemed likely that the variance was greater than the mean of the infection risk (referred to, mathematically, as overdispersion). In such a case, it is advisable to use the negative binomial regression model, which, like the Poisson regression, enables the calculation of relative risks.

Risk was assessed for the following predictors: cumulative rheumatoid arthritis status (ACR criteria, see above) after 5 years (yes vs no), rheumatoid factor status (positive vs negative), current or past history of smoking (vs never smoking), current only smoking history (vs never smoking) and the use of steroids and or disease-modifying antirheumatic drugs (both ever vs never). In addition, as markers of cumulative severity of disease, the HAQ score assessed at baseline, at 5 years and the overall mean (dichotomised into <1, ⩾1) and the presence of erosive joints (ever vs never) were also modelled. A backwards, stepwise regression was then conducted to identify those factors that could be considered significant independent predictors of infection-related hospitalisation (after adjustment for age at inflammatory polyarthritis diagnosis and sex). The least significant predictors were excluded sequentially from each progressive model until only those factors with p values of < 0.1 (to allow for wide CIs resulting from the relatively small numbers after stratification) remained.

For convenience, the risk of hospitalisation was measured against a score based on a model of those predictive factors identified with the stepwise regression (ie, those significant predictors remaining in the model) attributable to each patient. Relative risks were calculated for each score total (compared with those patients without any predictive factors), and the trend per point was also measured.

RESULTS

Between 1990 and 1999, 2318 patients were recruited by NOAR. Of these, 158 were subsequently diagnosed with a condition other than rheumatoid arthritis or psoriatic arthritis (that explained their symptoms) and were thus excluded. Seven patients with missing year of death were also excluded. Linkage with the hospital electronic admissions system was possible for all but 45 patients who had died before 1995. Table 1 provides the demographic data of the remaining 2108 patients.

Table 1 Demographic and clinical data of the patients

Age at IP onset, years, mean (SD)	55 (16)
Sex: female (%)	1410 (67)
Met cumulative ACR RA criteria after 5 years, yes (%)	1239 (59)
Ever positive for rheumatoid factor, yes (%)*	681 (35)
Smoking history at first assessment, current smoker (%)†	521 (26)
Smoking history at first assessment, past (only) smoker (%)†	772 (39)
Steroid use before first admission, ever (%)	530 (25)
DMARD use before first admission, ever (%)	979 (46)
Erosive joints, ever (%)‡	695 (48)
Initial HAQ, mean (SD)	0.85 (0.74)
Fifth assessment HAQ, mean (SD)	0.84 (0.71)
Mean HAQ, mean (SD)	0.84 (0.72)

ACR, American College of Rheumatology; DMARD, disease-modifying antirheumatic drugs; HAQ, Health Assessment Questionnaire; IP, inflammatory polyarthritis; RA, rheumatoid arthritis.
*Based on 93% complete data.
†Based on 94% complete data.
‡Based on 68% complete data.

Patients were followed up for a mean (SD) of 7.8 (2) years, with a total follow-up of 16, 503 person-years. During this period, 200 infections leading to hospitalisation were observed in 168 patients. Table 2 provides the hospitalisation rates for the range of infection sites considered. The most common site of infection was the respiratory tract (accounting for almost 50% of admissions), followed by those affecting the urinary tract (approximately 25%).

Table 3 shows the relative risks of infection leading to hospitalisation (compared with the expected regional hospitalisation rates) for all infections combined as well as by site. The 95% CI excluded unity for respiratory, urinary, skin and septic infections. The site-specific increased risks of infection ranged from 1.9 (for skin infection) to 4.0 (for septicaemia) times that of the general population.

Analysis within the NOAR cohort showed several predictors. Table 4 shows the observed differences between patients hospitalised and those who were not. Compared with the overall cohort, patients hospitalised for an infection were older and less likely to be female. Further, patients admitted with an infection were more likely to meet the ACR rheumatoid arthritis criteria, be positive for rheumatoid factor, have radiological erosions and have a history of corticosteroid use. However, little difference was observed in HAQ scores at baseline, fifth assessment and overall mean as well as for DMARD use between hospitalised and non-hospitalised patients.

After multivariate analysis (table 5), there was a modest but significant, independent, increased risk from presence of rheumatoid factor, cigarette smoking and steroid use. On the basis of the multivariate model, a risk score (range 0–3) was created from the presence or absence of these three variables. Table 6 shows the relative risks and the overall trend for this score. As the patients' scores increased, the risk of hospitalisation for infection increased, such that those patients with all three factors were at least seven times more likely to be hospitalised compared with those having none.

DISCUSSION

In this unselected cohort of patients with inflammatory polyarthritis, the rate of hospitalisation for infection was increased from almost 2 to 4 times when compared with the general population, depending on the site of infection. Overall, the rate of hospitalisation for infection was at least two and a half times that of the general population. Age- and sex-specific analyses were not a major part of this study, so as to avoid the loss of power attributable to further stratifications of the data. Examination of risk of infection by three age groups ($<$50, 50–69 and $\geqslant$70 years), however, showed no consistent difference between the age groups. Similar results were also seen in both sexes. Age and sex were, however, included as factors in all multivariate models as it is clearly important to account for the underlying higher risk seen in ageing populations. Whereas this study was not designed to identify all possible risk factors, three simply acquired variables, steroid use, rheumatoid factor positivity and current cigarette smoking, particularly in combination, identify the group most at risk, whereas the other disease-related variables added little to the prediction.

This study has several strengths. This is the first study of the risk of infection in a primary-care-derived cohort of patients with inflammatory polyarthritis. Thus, the possible bias often associated with the use of hospital or clinic-based patients does not apply to these findings. Furthermore, this cohort was truly prospective and, therefore, unlike studies based on retrospective record review, data collection (particularly of the possible predictive disease characteristics) was standardised. Linkage with the local hospital for admissions data was virtually complete, with only 45 patients (2.1%) excluded from follow-up (as they died before 1995). For the remaining patients, follow-up was complete, and the 16 000 person-years of follow-up generated sufficient exposure time for robust estimates of infection risk as well as for examining the effect of putative factors on such risk. Finally, the ascertainment of infection rates in the comparison cohort was essentially identical in nature to that used for the inflammatory polyarthritis group, and, being based on electronic data capture, was free of observer bias.

However, there are some methodological issues that need consideration. The cohort considered was patients with undifferentiated inflammatory polyarthritis rather than people who met the ACR classification criteria for rheumatoid arthritis at baseline. The use of such patients results in the inclusion of those with generally less severe disease than that reported from hospital-derived cases. Thus, the increased risk in the second group may be even higher. The application of the ACR criteria at baseline is unstable in early arthritis.[30 31] However, in the group examined, approximately 60% met the ACR criteria for rheumatoid arthritis during the first 5 years of follow-up. Interestingly, 5-year cumulative rheumatoid arthritis status was associated with an 80% increased risk of hospitalisation for serious infection, although it was not found to be an independent predictor of infection risk.

Analyses were repeated restricting inclusion to patients meeting the 5-year cumulative rheumatoid arthritis criteria, and indeed there were no overall differences in results. The overall increased risk of infection (relative risk (RR)) was 2.8 (95% CI 2.1 to 3.7), and this is obviously slightly higher than that seen in the overall group, partly because of the relationship between rheumatoid factor and the diagnosis of rheumatoid arthritis. Furthermore, the stepwise regression model identified essentially the same multivariate model of infection risk (the same three factors were found to be independently significant and the respective RRs for each were slightly increased).

For hospital admission, we relied on the records of the only long-stay hospital service provider in this region where, because of its relative geographical isolation, the choice of alternative hospitals is very limited (one of the major reasons for basing the Register in this area[26]). Although the same data were used

Table 2 Incidence of serious infections by site

	Incidence/1000 person-years, mean (95% CI)		
	Men	Women	Total
Respiratory tract	8 (5.7 to 10.8)	5 (3.8 to 6.5)	5.9 (4.8 to 7.2)
Urinary tract	2.1 (1to 3.7)	3.1 (2.2 to 4.3)	2.8 (2 to 3.7)
Skin	2.8 (1.6 to 4.7)	1.5 (0.9 to 2.4)	1.9 (1.3 to 2.7)
Septicaemia	1.5 (0.7 to 3)	0.6 (0.3 to 1.3)	0.9 (0.5 to 1.5)
Infectious arthritis	0.8 (0.2 to 1.9)	0.4 (0.1 to 1)	0.5 (0.2 to 1)
All combined	15.2 (12 to 18.9)	10.7 (8.9 to 12.8)	12.1 (10.5 to 13.9)

Table 3 Relative risk of serious infections by site

	Age- and sex-adjusted RR (95% CI)
Respiratory tract	3.5 (2.3 to 5.4)
Urinary tract	2 (1.2 to 3.4)
Skin	1.9 (1.1 to 3)
Septicaemia	4 (2 to 7.8)
Infectious arthritis	2.2 (0.4 to 12.5)
All combined	2.7 (2 to 3.4)

for both the NOAR and comparison population, we would have missed cases of serious infection that might have resulted in patients attending a different hospital. To deal with the magnitude of this, in addition to the electronic data linkage, we had access to patient self-reports. In NOAR, as part of their annual follow-up, all patients are interviewed and asked to recall all serious illnesses including those leading to hospitalisation in the previous 12 months. These data were not used in the primary analyses above, as they are less reliable and are not available for the comparison cohort. Interestingly, no additional cases were detected using these data.

Hospitalised infection was relied on as the main outcome for two principal reasons: firstly, to focus on those infections of a severe, rather than trivial, nature; more importantly, by using this approach it was possible to capture the infection rate in an identical manner in both the arthritis and the comparison cohort. In many respects this should have ensured that no selection bias was present with regard to the comparison of infection between the two groups, although clearly our results may not be extrapolated to the relative risk of non-hospitalised infections. In addition, if individuals with rheumatoid arthritis were selectively more, or even less, likely to be admitted to hospital with the same infection, then this would either overestimate or underestimate the relative difference between the two groups. This needs to be borne in mind in interpreting the results.

Interestingly, the risk of infection requiring hospitalisation in our cohort is actually substantially larger than that seen in the Mayo Clinic study[13] (RR = 1.9, 95% CI 1.7 to 2.1), despite the Mayo Clinic patients being likely to have substantially more severe disease than that of the NOAR cohort. Some differences were present in the groupings of infections studied, and, as the Mayo clinic study included a broader range of infections, the results might not be entirely comparable. Further, the risk factors identified in the current investigation, particularly steroid use, are very similar to the findings of the follow-up to the Mayo cohort.[14]

Probably, the risk of infection was modified by the severity of the disease. It is difficult to adequately capture measures of disease activity in a study that pools experience over an extended period. In an attempt to deal with this issue, we used HAQ scores at baseline, at 5 years and the overall mean to indicate disease activity. Interestingly, none of these were found to be significant predictors of serious infection, although there was a suggestion of a positive association with mean HAQ score.

There has recently an increased interest in understanding the incidence of, and risk factors for, serious infections in patients with rheumatoid arthritis given the concern about infection risk with the use of anti-tumour necrosis factor (TNF) agents. Tuberculosis seems to be increased in such patients.[32–34] Further, given the role of TNF in combating infection,[35] the possibility is raised that the use of these drugs may increase the risk of other infections. A recent study compared the incidence of infection in patients starting treatment with etanercept, infliximab or anakinra with a group of patients who had changed their current DMARD regimen.[36] Infection risk was increased in the anti-TNFα-treated groups, even after adjustment for severity of disease using propensity modelling. However, patients using biological agents had typically used many more DMARDs and thus there may have been residual confounding. Conversely, a more recent study which investigated the risk of pneumonia in patients treated for rheumatoid arthritis found that only prednisone and leflunomide use (after adjustment for age, sex, disease activity and comorbidities) predicted hospitalisation. All other treatments (including several anti-TNFα agents) were not significantly associated with hospitalisation for pneumonia.[37]

Indeed it is possible to make sense of post-marketing reports of infection risk in ''real world'' patients only by having an understanding of the background risk in conventionally treated patients. During the course of this study, anti-TNF agents had not been in widespread use and only seven patients had been so treated. A recent study from the German National Biologic Register by Listing *et al* [36] showed an increased risk of infection in patients using biological agents compared with biologically

Table 4 Distribution of predictors between patients hospitalised for infection and remainder of cohort

Predictor	Hospitalised for infection	Controls
Age (years), mean (SD)	62 (16)	55 (16)
Sex: female, n (%)	104 (62)	1306 (67)
RA status: met ACR criteria, n (%)	125 (74)	1114 (57)
RF: positive, n (%)	81 (51)	600 (33)
Erosions: ever, n (%)	68 (56)	627 (48)
DMARD use: ever, n (%)	78 (46)	902 (46)
Corticosteroid use: ever, n (%)	82 (49)	439 (23)
Baseline HAQ, mean (SD)	0.84 (0.69)	0.85 (0.74)
HAQ at fifth assessment, mean (SD)	0.96 (0.81)	0.95 (0.82)
Overall HAQ, mean (SD)	0.87 (0.71)	0.83 (0.72)

ACR, American College of Rheumatology; DMARD, disease-modifying antirheumatic drugs; HAQ, Health Assessment Questionnaire; RF, rheumatoid factor.

Table 5 Factors predicting occurrence of serious infection (all sites combined)

	Univariate	Multivariate
Factor	RR (95% CI) adjusted for age and sex	RR (95% CI) adjusted for age and sex
RA cumulative at 5th assessment:		
Yes vs no	1.8 (1.2 to 2.6)	1.1 (0.6 to 2)
Rheumatoid factor*		
Ever positive vs negative	2.2 (1.5 to 3.4)	2.0 (1.3 to 3.0)
Baseline smoking history†		
Current or past vs never	1.5 (1.0 to 2.4)	1.2 (0.7 to 2.1)
Current only vs never	1.7 (1.2 to 2.6)	1.6 (1.0 to 2.5)
Steroid use		
Ever vs never	2.3 (1.6 to 3.5)	2.2 (1.5 to 3.4)
DMARD use		
Ever vs never	1.3 (0.9 to 1.9)	1.0 (0.6 to 1.6)
Erosive joints‡		
Ever vs never	1.3 (0.9 to 1 .9)	1.0 (0.7 to 1.6)
Baseline HAQ		
⩾1 vs <1	1.0 (0.7 to 1.5)	0.6 (0.3 to 1.1)
Five-year HAQ		
⩾1 vs<1	1.0 (0.7 to 1.5)	1.2 (0.8 to 2.0)
Mean HAQ		
⩾1 vs <1	1.3 (0.9 to 1.8)	1.9 (1.0 to 3.4)

DMARD, disease-modifying antirheumatic drug; HAQ, Health Assessment Questionnaire; RA, rheumatoid arthritis.
*Based on 93% complete data.
†Based on 94% complete data.
‡Based on 68% complete data.

Table 6 Risk of serious infection (all sites combined) by risk score

Risk score	RR (95% CI)
0	1
1	1.6 (0.9 to 2.6)
2	3.5 (1.9 to 6.3)
3	7.4 (3.3 to 16.8)
Trend	1.9 (1.5 to 2.5)

naïve patients. This was, however, somewhat reduced after adjustment for each patient's likelihood of needing biological treatment.

The factors found in this study, positive rheumatoid factor, cigarette smoking and steroid use, particularly the latter two, were not surprising. This study has shown that these factors in combination define a group at much greater risk and on whom more attention should be focused. Several reports suggest that cigarette smoking is associated with a worse arthritis outcome,[38] and the current study adds to the specific hazards of smoking in patients with rheumatoid arthritis.

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