Acute Lower Respiratory Tract Infections in Patients with Rheumatoid Arthritis

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ABSTRACT. ***Objective.*** To determine whether drugs used in the treatment of rheumatoid arthritis (RA) contribute to the increased risk of respiratory infection or influence its outcome.

Methods. We identified all episodes of lower respiratory tract infection (LRTI) in our RA population over a 12 month period. A detailed drug history was recorded in each case, together with the clinical outcome. Premorbid illnesses and admission data were collected and analyzed to assess the influence of oral steroids and disease modifying antirheumatic drugs (DMARD) on outcome.

Results. The overall annual incidence of LRTI in patients with RA was 2.3% with a mortality rate of 22.5%. Demographic factors predicting LRTI included older age and male sex. Oral steroids and not taking DMARD were also associated with an increased risk of hospital admission with LRTI. Being male and having RA for over 10 years trended to the prediction of death as a result of infection. Taking DMARD was not associated with any adverse outcome.

Conclusion. Respiratory infection is common in patients with RA and carries a high mortality. Oral steroids predispose to infection, while DMARD do not. Increasing age and male sex also predispose to respiratory tract infection. (First Release July 15 2007; J Rheumatol 2007;34:1832–6)

Key Indexing Terms:
RHEUMATOID ARTHRITIS INFECTION PNEUMONIA
MORTALITY METHOTREXATE

Rheumatoid arthritis (RA) follows a variable and undulating course in many patients. Treatment aims to reduce its progression toward structural damage and to maintain daily activities and quality of life[1]. However, RA also shortens life expectancy compared to a control population, and excess deaths are largely caused by accelerated vascular events and an increased propensity to infection, much of which is of respiratory origin[2]. The relationship between infection and RA (cause or effect?) has been questioned[3] and the relative contributions to respiratory infection in RA of the disease itself and the treatment administered to suppress it are unclear.

Doran, *et al*[4] undertook a retrospective longitudinal cohort study comparing infection rates in those with RA with matched controls and found increased mortality in patients with RA and increased hazard ratios for hospitalization due to infection. Risk factors included the presence of extraarticular RA manifestations and prior use of oral steroids[5]. Another study reported no difference in overall infection rates prior to or after the onset of RA compared to other joint diseases[6], but the same group also showed an increase in respiratory tract infections, with increased mortality[7]. Other reports cite a 45% prevalence of sepsis over a 10 year period[8] and confirm increased mortality from infections in RA[9].

British guidelines for the management of RA state patients should be started taking a disease modifying antirheumatic drug (DMARD) within 3 months of diagnosis to reduce disease progression[10]. Methotrexate (MTX) is now the most commonly used DMARD, combining high efficacy with low morbidity[11,12]. However, certain relative contraindications to its use have been suggested, including preexisting lung disease[13], and complications predisposing to infection, such as pancytopenia, have been noted especially in patients with renal impairment[14]. Although some patients may be reluctant to use MTX because of preconceptions about its propensity to cause side effects[15,16], a metaanalysis found a lower rate of treatment termination for this agent than for all other DMARD[12]. The aim of our study was to identify whether patients with RA who develop lower respiratory tract infection (LRTI) do so as a result of their inflammatory arthritis or the drugs used to treat it.

MATERIALS AND METHODS

All patients admitted to the Queen Elizabeth Hospital in Gateshead (a district general hospital with a major commitment to teaching and research) during the calendar year of 2003 with acute LRTI[17] or inflammation who also had a diagnosis of RA[18] were identified from the hospital database. In order to

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Accepted for publication April 27, 2007.

obtain control data, the same analysis was undertaken for patients with psoriatic arthritis (PsA)[19] with peripheral joint disease. The clinical records of these patients were then examined manually and data extracted, specifically for details relating to the acute admission including exact diagnosis, treatment, and outcome, together with data on admission white blood cell count (WBC) and C-reactive protein (CRP) levels. Demographic data on age, sex, and duration of RA, together with all recorded comorbidities, were collected. Specifically, we collected data on symptomatic cardiovascular disease due to proven ischemic heart disease or valvular defects and on respiratory disease due to interstitial lung disorders or fixed airways obstruction. The history of DMARD and oral steroid therapy was noted for each patient, as was the smoking status on admission. The cause of death was ascertained from the medical notes and cross-checked with death certificate data.

Completeness of ascertainment was ensured by comparing database records with those from the Departments of Rheumatology and Chest Medicine. A cross-check ensured that no patient on our database had been admitted to a neighboring hospital with LRTI over the study period at a subsequent clinic review. In cases of "failure to attend" clinic, these data were obtained from the patient's general practitioner, as was the cause of all out-of-hospital deaths in our RA population during this time. A parallel analysis of all patients with inflammatory joint disease was also undertaken using the computerized database (RheMos) that contains clinical details of all patients with RA and PsA and that is the main means by which the efficacy and safety of DMARD therapy is monitored. The number and percentage of patients taking each of the DMARD on combinations of therapy and on no treatment were calculated. This allowed us to compare data from the secondary care population of patients with inflammatory joint disease who did not develop acute LRTI with those patients admitted with acute lung disease.

We confirmed the diagnosis of LRTI[17], excluding those with an alternative explanation, and calculated its annual incidence in the group as a whole and in the patient subsets taking MTX and taking no DMARD. Mortality rates were also calculated for each group. Binary logistic regression was used to make statistical comparison between those admitted with LRTI and those who were not, in order to identify risk factors for infection. We also used logistic regression to compare those who died with those who did not, to try to identify predictors of death.

RESULTS

A total of 1522 Gateshead residents with RA (mean age 61 yrs) were known to our department as a result of having attended clinic within the previous 12 months at the start of 2003. They were drawn from a catchment population of 210,000 people and comprised 1124 women (72%). Demographic data are shown in Table 1. Among the RA population, a total of 43 admissions (involving 36 patients) occurred as a result of an acute respiratory event during the study period. No admissions from this population to neighboring hospitals were detected for LRTI during the study period, and no deaths from LRTI in the community were identified. Seven admissions were for MTX pneumonitis as defined by accepted criteria[20] rather than infection and were therefore excluded from further analysis. The remaining admissions were as a result of infection, with 34 having bacterial pneumonia and 1 each due to infection with cytomegalovirus and *Pneumocystis carinii*; both of these were taking MTX. Increased age and male sex were statistically associated with an increased risk of admission with LRTI. Eighteen patients (50%) were taking MTX, either as single therapy (n = 11) or in combination with one or more other DMARD (n = 7), and 9 (25%) were taking alternative DMARD. A further 9 patients (25%) were taking no DMARD therapy at admission. The overall annual incidence of acute LRTI requiring admission among patients with RA was 2.3%, with the incidence for patients taking MTX 2.8% (p = 0.78). The incidence in those patients taking no DMARD on admission was significantly higher, at 10.6% (p = 0.019). Oral steroid therapy was also associated with an increased risk of admission with LRTI. These data are summarized in Table 2.

Eight patients died from LRTI, giving a mortality of 22.2%, with corresponding figures for patients taking MTX (22.2%; p = 0.78) and no DMARD (33%; p = 0.66) showing no significant difference. There was a trend to increased mortality in men and in those with long disease duration, but these did not achieve significance statistically, as shown in Table 3. Current smoking did not predict probability of either admission with or death from LRTI in our study. Six smokers were admitted, with one fatality from 228 active smokers on the RA database.

By comparison with the RA population, only one patient was admitted with acute LRTI over the same time period from a total of 152 patients with PsA (66% female, mean age 59 yrs) with peripheral synovitis, 86% of whom were taking DMARD, equating to an annual incidence of LRTI of only 0.7%.

Data extracted from the RheMos database show that, among the patients with RA, 41% were taking MTX, either alone or in combination. Salazopyrin (36%) and hydroxychloroquine (28%) were also commonly prescribed. Of the

Table 1. Comparison of demographic characteristics of 1486 patients with RA in the RheMos database not admitted with 36 RA patients admitted as a result of lower respiratory tract infections (LRTI) using logistic regression.

	Nonadmitted Patients, n = 1486	Patients Admitted with LRTI, n = 36	p
Age, mean yrs	61	71	0.013
Male, %	26	36	0.022
Smoking status, %			
Current smoker	29	25	0.91
Ex-smoker	40	47	0.81
Non-smoker	31	28	0.94
RA disease duration, median yrs	6	4	0.88

Table 2. The prevalence of differing drug use of patients with RA who were not admitted compared to the subgroup admitted with lower respiratory tract infection.

Drug	RA Patients Not Admitted, n = 1486, n (%)	Admissions, n = 36, n (%)	Logistic Regression p
Methotrexate	612 (41)	18 (50)	0.78
Other DMARD	798 (54)	9 (25)	0.14
No DMARD therapy	76 (5)	9 (25)	0.019*
Oral steroids	219 (14)	14 (37)	0.041*

* Indicates significantly more admissions of patients than expected. DMARD: disease modifying antirheumatic drugs.

Table 3. Comparison of 8 patients with RA dying in hospital as a result of lower respiratory tract infection with those who survived, using univariate logistic regression.

	Sig.	Odds Ratio	95.0 % CI for Odds Ratio	
			Lower	Upper
Age > 65 yrs	0.378	0.338	0.030	3.779
Male	0.389	2.726	0.279	26.653
Current smoker	0.999	0.000	0.000	
RA > 10 yrs	0.559	2.259	0.147	34.819
Methotrexate	0.783	1.655	0.046	60.006
Any DMARD	0.688	0.474	0.012	18.111
Prednisolone	0.330	0.308	0.029	3.297
WBC < 4.0	0.999	0.000	0.000	
Prior lung disease	0.790	1.363	0.140	13.301

DMARD: disease modifying antirheumatic drugs; WBC: white blood cell count.

patients with RA, 548 (36%) were taking combination therapy with 2 or more DMARD. At the time of our study only 1.8% of our RA population were receiving therapy with anti-tumor necrosis factor (TNF) drugs, and none of these patients required admission for LRTI during the study period. No significant drug interactions were recorded. Only 5% of patients with RA were not taking DMARD.

Prior comorbidity was ascertained for both symptomatic cardiovascular and pulmonary disease. The prevalence of these in the non-admitted RA population was 14% and 8%, respectively, compared to higher values of 20% and 14% in those admitted with LRTI (p = 0.031). In addition, a higher proportion of patients with prior cardiac or pulmonary disease died (5/12) than those in whom no such problems were recorded (3/24), although this did not reach conventional statistical significance. Three of the fatalities occurred in patients receiving daily low-dose oral prednisolone (all below 10 mg). A further 11 patients taking low-dose steroids admitted with LRTI survived. The prevalence of oral steroid consumption among admissions was 37%, which is significantly higher than in the RA group as a whole (14%; p = 0.041).

The mean CRP on admission was 163 mg/l (range 33–553) and the mean WBC was 10.8×10^6 cells/ml ($3.1–29 \times 10^6$ cells/ml). Corresponding mean values for the fatal cases were CRP 233 mg/l (p = 0.71) and WBC 7.3×10^6 cells/ml (p = 0.61). Although these differences were not statistically significant, there was a trend toward lower initial WBC and higher CRP in fatal cases. This apparent disproportion between CRP and WBC was independent of whether the patient was taking DMARD or not. However, neither low WBC (under 4.0) nor elevated CRP (over 200) predicted death on logistic regression analysis.

DISCUSSION

Our study has confirmed a high incidence of LRTI in patients with RA and also showed a relatively high mortality rate compared to community-acquired pneumonia in patients without RA[21]. These findings support previous publications showing increased frequency of infection[7,8] and associated higher mortality[7,9]. Risk factors for admission with pneumonia in our study included taking oral steroids and not taking DMARD, in addition to male sex and older age. There was some evidence that a fatal outcome was predicted by male sex, long disease duration, and prior pulmonary disease, although the small number of fatalities reduced the statistical power of these observations.

The finding that 2.3% of the RA population were admitted with an acute LRTI over the course of one year was striking. This was much higher than that in the age-matched population with PsA who were taking equivalent doses of DMARD,

although their use of oral steroids was negligible and they had less prior lung disease. Patients who were taking no DMARD therapy had a higher incidence of infection than those taking DMARD, while those taking MTX had outcomes similar to those of the group as a whole. There was no evidence to suggest that MTX was associated with an increased risk of LRTI, and this should provide important reassurance to patients[15]. We also found no evidence to implicate drugs as a contributory factor toward adverse outcome. Our data suggest that RA itself, rather than the drugs used to treat it, is primarily responsible for the observed increase in mortality, and the possible link with disease duration would support this.

However, our failure to assess disease severity is a limitation, as this may also be an important factor in the development of LRTI and might account for some of the laboratory findings. The mean CRP was higher in those patients who died, suggesting more severe infection, while mean WBC was lower than in those who survived. This apparent disproportion suggests a reduced immune response may have contributed to poor outcome. However, it is both relevant and reassuring to note that the British Society for Rheumatology's Biologics Register, which has collected outcome data from several thousand patients with RA taking anti-TNF agents, has failed to show any increase in LRTI associated with these agents, which are reserved for those patients whose disease activity remains high in spite of aggressive use of standard DMARD (D. Symmons, personal communication).

Our work supports the findings of a recent multicenter study that showed no increase in hospitalization for pneumonia in patients with RA as a consequence of taking DMARD[22]. Their large study did not examine mortality and did not have a control group, but did show similar links between pneumonia and prior comorbidity. Wolfe, *et al* also showed increased risk of hospitalization for pneumonia in patients taking oral steroids, and found that this risk increased with increasing steroid dose.

Untreated RA is associated with a number of factors that might predispose to infection. They include relative immobility, hypoalbuminemia[23], increased risk of systemic disease, and bone marrow suppression. The absence of any significant difference in incidence or outcome of LRTI between patients taking different DMARD, and the observation that patients taking no DMARD did worse, suggests that these agents do not increase the risk of acute LRTI. However, individual patients receiving MTX who show diminished WBC or who fail to mount an adequate response to established infection do need prompt action to prevent drug-related morbidity and mortality[24]. Folinic acid reversal and bronchoalveolar lavage should be considered, as opportunistic infections are common in this setting.

There were several reasons that some patients with RA were not taking DMARD. These included intolerance, inefficacy, and refusal to accept treatment. In a small number of cases, severe comorbidity may have persuaded the clinician or patient that treatment with DMARD carried unacceptable risks, but we found no evidence to suggest that patients not taking DMARD had longer duration RA or more comorbidity than the group as a whole (data not shown). Several of these patients were treated with low-dose steroids. The possible role of oral steroids in contributing to infection has been highlighted in other studies[5,22]. Our data showed an increased risk of infection in patients taking low-dose steroids, but this was not reflected in mortality rates, which were similar to those for patients taking DMARD alone. Being male was also a risk factor, both for infection and for a fatal outcome. This is consistent with previous work[25,26] and may reflect that men, while less likely to develop RA, are more at risk of systemic involvement, especially of the lungs[27,28].

Changes have been made to our clinical practice as a consequence of the findings of our study. In addition to initiating DMARD early in all patients with RA, we actively pursue annual vaccination against influenza and pneumovax injections every 5 years in all patients, independent of their treatment[29]. Older patients with long disease duration are now actively encouraged to commence DMARD therapy rather than oral steroids, although drug selection may be influenced by the presence of coexistent cardiac or pulmonary disease.

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