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How to reduce morbidity and mortality from chest infections in rheumatoid arthritis

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ABSTRACT – Morbidity and mortality from pneumonia is increased in patients with rheumatoid arthritis. Factors contributing to this have been recently identified and a number of recommendations have been implemented in an attempt to reverse this trend. The present paper shows that these measures have combined to produce a fourfold reduction in both admissions and case fatality rates. In the study population, immunisation rates against influenza and pneumococcus have improved to 86% and 65%, oral steroid consumption has halved and disease modifying drugs were usually appropriately suspended during acute infection. These measures may now merit more widespread adoption.

KEY WORDS: lower respiratory tract infection, morbidity, mortality, pneumonia, rheumatoid arthritis, vaccination

Introduction

Life expectancy is shorter in rheumatoid arthritis (RA) than in controls.[1] Excess deaths occur in part due to infection, much of which is respiratory in origin.[2–5] Morbidity from sepsis is common and a prevalence as high as 45% over 10 years has been reported.[6,7] An increase in hospitalisation for serious infections among patients with RA has recently been confirmed in a longitudinal cohort where risk factors included the presence of extra articular manifestations and prior use of oral steroids.[8,9]

A high incidence of lower respiratory tract infections (LRTI) in RA patients as compared to controls, with a resulting increased mortality, has recently been confirmed.[4] Factors contributing to these findings included the use of long-term oral steroids and failure to use disease modifying antirheumatic drugs (DMARDs). Several changes were made to our clinical practice following this and the present study was designed to assess the efficacy of these measures. This included a programme of immunisation against both pneumococcus and influenza for all patients with RA independent of their treatment profile. This was combined with specific recommendations to suspend treatment with DMARDs during LRTIs requiring antibiotic treatment and minimisation of the use of long-term oral prednisone.

In addition to this broad approach, two additional recommendations were applied to those patients who appeared at particularly high risk. Initial results had shown an association between low white cell count and mortality from LRTI. As a result, it was agreed to treat all patients with LRTI who failed to mount an adequate white cell response (defined as total leucocyte count under 5×10^6/ml) with folinic acid if they were on methotrexate (MTX), and/or cholestyramine if they were receiving leflunomide. In addition, any patient with severe neutropaenia (neutrophil count under 0.5×10^6/ml) was treated with granulocyte colony stimulating factor (G-CSF) for three days.

This package of measures was instituted following the completion of earlier work in 2004 and the present paper describes the effect of these measures on morbidity and mortality from LRTI within an RA population over the subsequent three years.

Methods

The Queen Elizabeth Foundation Hospital Trust serves a population of 250,000 people in and around Gateshead and receives referrals from another 100,000 outside of the traditional catchment area. This population generates over 3,000 new referrals and 9,000 follow-up attendances to the department annually, with 2,000 RA patients included among the latter. The results of the initial audit were presented internally and the guidelines were developed with respiratory colleagues before being circulated to all physicians within the hospital.

The methodology closely followed that of the initial study.[4] All patients admitted to the Queen Elizabeth Hospital in Gateshead during the three calendar years of 2005 to 2007 as a consequence of acute LRTI[10] with a prior diagnosis of RA[11] were identified from the hospital database. 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 the values of white blood cell count (WBC) and C-reactive protein (CRP) levels on admission. In addition to the demographic data, immunisation history, drug therapy and smoking status on admission were also recorded. The use of folinic acid, cholestyramine and granulocyte-colony stimulating factor was specifically noted. The cause of death in fatal cases 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.

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A cross-check was made at the subsequent clinic review in case patients on the department's RA database had been admitted to a neighbouring hospital with LRTI over the study period. 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 the RA population during these three years. Data were collected from the Rhemos database on the prevalence of DMARD use across the RA population.

All results were then compared to those obtained in the initial work using Student's t test to assess morbidity and mortality in the RA population before and after the above changes were introduced.

Results

A total of 1,822 Gateshead residents with RA (mean age 61 years) had attended the clinic between 2004–5. Among the RA population, a total of 26 admissions occurred as a result of an acute respiratory event during the three-year study period. No admissions from this population to neighbouring hospitals were detected for LRTI during this time, and no deaths from LRTI in the community were identified. Two admissions were found to have been for MTX pneumonitis rather than infection and were therefore excluded from further analysis. The remaining 24 admissions were as a result of LRTI, with all having bacterial pneumonia confirmed on culture or serology. No atypical infections or cases of tuberculosis were detected. One patient had been admitted twice within the three year period and was found to have bronchiectasis.

Table 1 shows that overall mortality was significantly lower than previously thought with only two deaths in three years among the 24 admissions with LRTI. Neither of these patients had received pneumovax and one was on oral steroids. Both had prior chronic obstructive pulmonary disease and had previously smoked. Indeed, the proportion of admissions on oral steroids had risen, as had the mean duration of RA and the prevalence of underlying lung disease.

Fourteen patients (58%) were taking MTX, either as single therapy (n=9) or in combination with one or more other DMARDs (n=5), and five (21%) were taking alternative DMARDs. Two patients were taking anti-tumour necrosis factor (TNF) agents, both with MTX. A further three (13%) patients were taking no DMARD therapy at the time of admission. However, 13 (54%) patients were taking oral steroids for their RA on admission with LRTI and most of these had been on this therapy for over a year. The mean dose of oral prednisone was also higher in those admitted than in those who were not (7.5 mg *v* 4 mg). DMARDs were suspended in all but one patient and they recovered without ill effect.

Data extracted from the treatment database show that, among all patients with RA, 59% were taking MTX, either alone or in combination. The mean dose was 17.5 mg weekly and this was no higher in those admitted with LRTIs than in those who were not. Only 5% of patients with RA were not taking DMARDs. The prevalence of oral steroid consumption among admissions of 54% was significantly higher than in the RA group as a whole (14%, p=0.021).

Table 2 shows that the morbidity from LRTI had fallen significantly in the RA population as a whole. Oral steroid consumption among RA patients in general had fallen, by contrast with those admitted with LRTI. Overall immunisation rates against influenza in the local RA population had improved to 86% and against pneumococcus to 65% – both significant improvements compared to the earlier figures.

Discussion

It appears that specific measures to reduce the morbidity and mortality from LRTI in RA patients are identifiable and effective. Risk factors include use of long-term oral steroids, smoking and prior lung disease. Data also suggest that vaccination against influenza and pneumococcus may contribute to the observed reduction in LRTI. Older age and longer disease duration are also statistically associated with higher risk of infection but are less readily modified. DMARDs were suspended during antibiotic treatment of respiratory infections to ensure an adequate immune response. This may have contributed to the improved outcome and was not associated with any flare in RA disease activity.

The initial data suggested that RA itself, rather than the drugs used to treat it, was primarily responsible for the observed increase in mortality.[4] This work supports the findings of a multicentre study that showed no increase in hospitalisation for pneumonia in patients with RA as a direct consequence of taking DMARDs.[12] This large study demonstrated an increased risk of hospitalisation for pneumonia in patients taking oral steroids, and found that this risk increased with rising steroid dose. This reinforces findings that long-term oral steroid therapy may be a major contributory factor in the development of LRTI. Over half of the patients admitted in the present study were taking oral steroids, as compared to 14% of the RA population in general. It seems prudent to suggest that, wherever possible, flares of disease should be treated with parenteral steroids which are likely to carry less risk.

Table 1. Details of demography and population characteristics among patients with rheumatoid arthritis (RA) admitted with lower respiratory tract infections before and after the introduction of specific guidelines in 2004.

	Calendar year 2003	Calendar years 2004–7	
Mortality rate (%)	22	8	(p=0.037)
Mean age (years)	71	69	(ns)
Males (%)	36	21	(ns)
Oral steroids (%)	42	54	(p=0.035)
Mean RA duration (years)	4	10	(p=0.030)
Prior lung disease (%)	56	83	(p=0.042)
Smoker/ex-smoker (%)	70	75	(ns)

It has previously been shown that vaccination rates improved significantly after a campaign to increase awareness among both patients and primary care providers.[13,14] However, low rates have also been reported.[15,16] Although awareness of the importance of vaccination for RA patients has grown the potential for certain drugs, such as steroids, MTX and anti-TNF therapy, to reduce the efficacy of the vaccination programme has also been recognised.[17] This underlines the potential value of vaccination early in the disease, although further research on the effect of drugs such as MTX on pneumococcal antibody levels in RA patients are needed to inform the development of optimal vaccination schedules.

The relationship between prior lung disease and the development of LRTI was noteworthy in the present study, with 83% of all admissions having established pulmonary morbidity. Smoking contributed significantly to this observation which was supported by earlier findings.[12] Airways obstruction and interstitial lung disease are both common in RA and can contribute directly to the increased associated mortality.[18–20] LRTI frequently complicates these conditions and is more likely to lead to a fatal outcome given the associated reduction in pulmonary reserve. This tendency may be enhanced by the use of long-term oral steroids, often prescribed in these conditions. Immunisation and smoking cessation are particularly important in this subgroup of high-risk patients.

Other factors contributing to LRTI in RA may include bone marrow suppression and hypoalbumineamia.[21,22] Recent evidence suggests that the ratio of CRP:albumin may be of prognostic value in acute exacerbations of chronic disease in the elderly.[23] DMARDs may not cause LRTIs directly but can dampen or delay the immune response.[24] Hence, cessation of DMARD treatment during any LRTI sufficiently severe to require antibiotics is suggested to encourage an adequate immune response to infection. Responsibility for suspending DMARDs during intercurrent infection lies with the prescriber and the patient. This advice can be incorporated into the patient information pack and reinforced at the initial patient education session. Adoption of this approach may have contributed to the fall in mortality from LRTI in RA patients, and is supported by a recently published review of the available evidence.[25]

Table 2. Details of therapy and vaccination rates within the total rheumatoid arthritis population before and after the introduction of specific guidelines in 2004.

	Calendar year 2003	Calendar years 2004–7	
Mean annual admissions	36	8	(p=0.002)
No DMARDs (%)	6	5	(ns)
Anti-TNF therapy (%)	0	2.8	(–)
Oral steroids (%)	28	14	(p=0.021)
Flu vaccination (%)	71	86	(p=0.023)
Pneumovax (%)	43	65	(p=0.017)

DMARDs = disease modifying antirheumatic drugs; TNF = tumour necrosis factor.

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