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Survival and safety of treatment with infliximab in the elderly population

SIR, Anti-tumour necrosis factor α (TNF- α) agents, such as infliximab, represent a major advance in rheumatoid arthritis (RA) and ankylosing spondylitis (AS) treatment. Infliximab is usually well tolerated but has some potential adverse effects, particularly infections [1–6]. The ageing process induces a decline in the function and control of the immune system. Thus, the prevalence of adverse effects of anti-TNF- α agents, and particularly of infections, might be increased in the elderly population. However, being elderly does not appear in most recommendations regarding the prescription of anti-TNF- α agents [7, 8]. This might be due to the fact that, to our knowledge, the elderly population has not been evaluated separately, although we have suggested in previous work that the prevalence of severe pyogenic infections might be greater in older than in younger infliximab-treated patients [6], and the mean age of patients developing severe infections was higher than the mean age of the whole group of patients treated with anti-TNF- α agents in Northern Ireland [9]. The aim of the present study was to evaluate the survival and the safety of infliximab in older patients in comparison with younger patients, using infliximab withdrawal and the reason for withdrawal as an outcome.

The Burgundian network includes the rheumatology departments of nine hospitals around the Burgundy area. All patients treated with infliximab for RA or AS in these departments are included in the cohort. The patients who started infliximab before November 2003 were included in the present study. The population was arbitrary split into two groups. Older patients were defined as those aged 70 yr or more at the date of starting infliximab. The other patients were classified as the younger patients. The endpoint was infliximab withdrawal. The drug survival of the two groups was evaluated using the Kaplan–Meier life table method, with 1 November 2003 as the censoring time, and compared using the log-rank test. Between-group differences were studied using one-way analysis of variance or Fisher's exact test. Similar analyses were performed in the subgroup of RA patients.

Informed patient consent and ethical approval were not obtained since the data obtained in this study were from a standardized follow-up developed in Burgundy in order to improve the quality of treatment and medical decisions.

Eighty-three patients (55 women, 28 men, mean age at start of infliximab 53.9 ± 13 yr) suffering from RA (60 patients) or AS (23 patients) were included. Infliximab was given at the recommended dose. During the follow-up (median = 1 yr), infliximab was withdrawn in 30 patients (36.1%) because of inefficacy (12 patients), adverse effects (12 patients, including four severe infections and

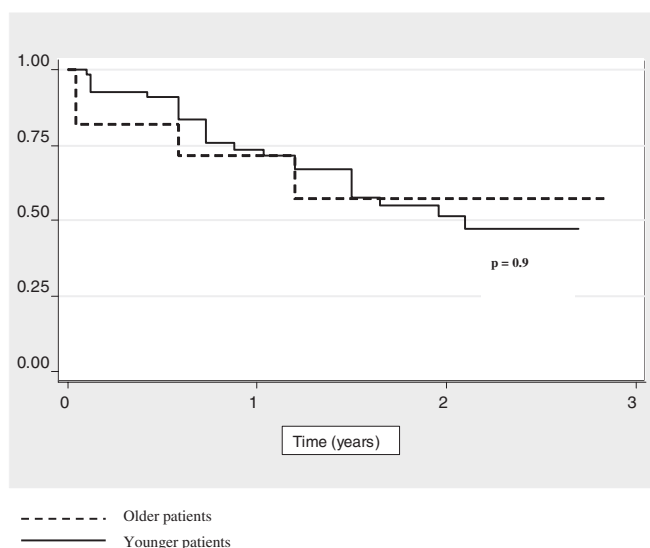


FIG. 1. Infliximab survival curves in older (≥ 70 yr) and younger (< 70 yr) patients.

six allergic reactions) and for miscellaneous reasons (six patients). Among the 83 patients, 11 were aged at least 70 yr (eight women, three men, mean age 75.7 ± 3 yr, range 72–81 yr, all treated for RA). There were no between-group differences in the percentage of patients treated with corticosteroids, the mean prednisone daily dose, the mean methotrexate weekly dose (10.1 ± 5.4 vs 11.9 ± 5.7 mg, $P = 0.4$), the mean duration of follow-up (1.3 ± 1 vs 1.1 ± 0.8 yr, $P = 0.3$), the percentages of patients who stopped infliximab (36.4 vs 36.1%, $P = 1$) and the drug survival curves (Fig. 1). There was no difference in the percentage of patients who stopped infliximab for adverse effects (27.2% of older patients, 12.5% of younger patients, $P = 0.19$), inefficacy (0% of older patients, 16.7% of younger patients, $P = 0.35$) or allergic reactions (9.1% of older patients, 6.9% of younger patients, $P = 0.59$). However, there was a trend towards a greater percentage of patients who stopped infliximab for severe infections in the older patient group (18.2 vs 2.8%, $P = 0.08$). The analyses performed in RA patients were similar to those performed in the whole population.

This study was an observational cohort study, not a randomized clinical trial (RCT), but observational cohort studies are useful in providing information about issues that have not been addressed in RCTs [10]. However, the design of the study does not allow us to eliminate the hypothesis that the results might have been influenced by confounding by indication bias: the rheumatologists might have prescribed infliximab in a particular subgroup of older patients with better general health than the whole older population. Another limitation of this observational cohort is that it had not been set up to answer the specific question of tolerance of infliximab in elderly patients. However, since only the severe adverse effects led to treatment withdrawal, maintenance and reasons for withdrawal represent a valid hard outcome with which to assess the tolerance. The results of this study, which show that the question is not anecdotal, since more than 13% of the treated patients were aged 70 yr or more, might be considered as reassuring since the between-group drug survival and the reasons for withdrawal were similar. However, there was a 6.5-fold higher incidence of withdrawal for severe infection in older patients, close to statistical significance. Since the number of events was low, we believe that this non-statistically significant difference was due to a lack of statistical power. Larger studies are needed to address this issue.

<i>Rheumatology</i>	Key messages
	• Drug survival for infliximab does not differ between older and younger patients. • The 6.5-fold higher incidence of withdrawal for infection in older patients needs confirmation.

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Mycobacterium tuberculosis as a cause of chronic periaortitis

SIR, We read with great interest the comprehensive review of chronic periaortitis (CP) by Jois and colleagues [1]. We wish to highlight another cause of this condition not mentioned in the review, as illustrated by a recent case.

A 36-yr-old Pakistani man resident in the UK for 13 yr presented with a 2-month history of intermittent pain in his epigastrium, myalgia, drenching night sweats and a non-productive cough. He also reported a 2-kg weight loss over 2 months. His previous medical history was of peptic ulcer disease with no known history of tuberculosis (TB). He was a market trader by profession and had not travelled abroad for at least 2 yr. He lived with his wife and two daughters, all of whom were in good health. Clinical examination revealed low-grade pyrexia and minimal epigastric tenderness without organomegaly. Cardiorespiratory and locomotor examinations were normal. His ESR was raised at 93 mm/h with CRP of 48 mg/l (normal range <10 mg/l). Autoantibody profiling showed the presence of anticardiolipin antibodies (IgG 28 IU; normal range 0–16 IU), but was otherwise normal. The following investigations were normal: full blood count, serum glucose and cholesterol, renal, liver, muscle and bone profiles, coagulation, electrocardiogram, chest radiograph, gastroscopy and cultures (of blood, stool and three early-morning urines for acid alcohol fast bacilli). An abdominal ultrasound revealed a fatty liver, but no other abnormality was noted.

MRI of the thorax and abdomen (Fig. 1a) showed circumferential encapsulation of the upper abdominal aorta with secondary aortic narrowing by an abnormal soft tissue mass. This extended 7 cm below the diaphragm and unfortunately was inaccessible for biopsy. A diagnosis of CP was made and the patient was commenced on 40 mg of prednisolone daily. However, following 3 months of treatment with only minor symptomatic improvement, repeat MRI scanning did not demonstrate any resolution of the periaortic mass.

One month later, the patient's persistent dry cough became productive of green sputum. A clinical diagnosis of *Mycobacterium tuberculosis* infection (smear negative) was made and 6 months of quadruple antituberculous therapy (rifampicin, pyrazinamide, ethambutol and isoniazid, with pyridoxine cover) commenced. A dramatic improvement occurred in both his respiratory and systemic symptoms in conjunction with normalization of inflammatory markers. Repeat abdominal MRI scanning (Fig. 1b) showed significant regression of the periaortic soft tissue, and the patient is well at 12 months follow-up.

We propose that this patient's CP be due to infection with *M. tuberculosis*, which, though resistant to corticosteroids, responded to antituberculous therapy. As highlighted by Jois *et al.* [1], chronic inflammation is the primary pathogenetic factor in the development of retroperitoneal fibrosis and periaortitis. A radiological diagnosis of CP is often made but determination of the exact aetiology may prove difficult [2, 3]. Chronic infections such as tuberculosis, actinomycosis and schistosomiasis can initiate this inflammatory reaction and are recognized causes of CP [4]. Even though microbiological confirmation of *M. tuberculosis* could not be made in this case, the patient's clinical history, radiological findings and therapeutic response were consistent with this being the causative organism.