DRUG POINTS

Fatal exacerbation of rheumatoid arthritis associated fibrosing alveolitis in patients given infliximab

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Tumour necrosis factor α (TNF α) antibodies are increasingly used to treat autoimmune conditions. However, their long term safety is unclear. We report three cases of patients who developed rapid fatal exacerbations of rheumatoid arthritis associated fibrosing alveolitis after taking infliximab (a chimeric monoclonal anti-TNF α antibody; Remicade, Schering-Plough).

Cases

Each patient had longstanding rheumatoid arthritis, was taking azathioprine, and had previously been diagnosed as having asymptomatic fibrosing alveolitis. Sudden onset of breathlessness associated with deteriorating lung function occurred after three or fewer doses of infliximab. Extensive investigations did not find any infection or other cause for the respiratory decline. Details of the patients and investigation are shown in the table.

Comment

As the pathophysiology is unknown, we caution the use of infliximab in patients with underlying lung disease. An infection may have caused the deterioration despite lack of isolation of an organism. Vigilance is needed for all patients on immune modulating drugs. Conversely, progressive lung disease may be falsely attributed to an infection when the cause is an inflammatory or idiosyncratic reaction.

Two further cases of pneumonitis associated with infliximab as monotherapy have been reported: one patient with Crohn's disease, the other in a patient with ankylosing spondylitis.^{1 2} Etanercept (a TNF α receptor fusion protein; Enbrel, Wyeth) has also been linked with lung injury.³ Cases have also recently been described of infliximab precipitating methotrexate pneumonitis.⁴

Associations of pulmonary disease and all three licensed biological agents for rheumatoid arthritis—infliximab, etanercept, and adalimumab (a humanised monoclonal anti-TNF α antibody; Humira, Abbott)—have been reported to the Medicines and Healthcare Products Regulatory Agency.

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Cases of fatal exacerbation of rheumatoid arthritis associated fibrosing alveolitis in patients given infliximab

Case	1	2	3
Age	67	60	75
Sex	M	F	F
Number of infliximab doses (3 mg/kg)	3	2	2
Death after infliximab (months)	1	9	1
Duration of rheumatoid arthritis (years)	4	12	33
Duration of pulmonary fibrosis (years)	2	7	16
Azathioprine dose (mg/day)	200	150	50
Duration of azathioprine before infliximab (months)	12	24	1
Daily prednisolone dose (mg)	15	7.5	5
Chest x ray before infliximab	Mild interstitial shadowing	Mild peripheral reticular nodular shadowing in all zones	Small volume lungs with widespread interstitial pattern
Chest x ray after infliximab	Progressive pulmonary fibrosis	Extensive reticulonodular shadowing	Extensive bilateral reticular shadowing
Computed tomography	Bilateral ground glass and peripheral pulmonary fibrosis	Extensive honeycombing, patchy ground glass opacification, traction bronchiectasis	Not done
Histology results	Active inflammatory fibroproliferative process in keeping with usual interstitial pneumonia (lung biopsy)	End stage lung disease with extensive collagenous thickening of interalveolar septae and honey combing (after death)	Not done