Dear Editor

Quality of life in a cross-over design

As a parameter, quality of life (QOL) has become more common in clinical trials. The focus has been on the reliability and validity of the chosen tests, their ability to discriminate between different groups of respondents, and administrative simplicity. Less attention has been paid to the design and methodology of the study.

Impaired QOL should be a part of the inclusion criteria. The randomized groups should be comparable. The duration of treatment should be long enough to make sure that an effect is possible. In a cross-over study, the washout period should be long enough to remove any carry-over effect. The required washout period can be difficult to predict, and may differ for various parameters of QOL. This is one of our conclusions from a clinical trial (1).

In this cross-over trial, salmeterol was compared with salbutamol controlled release (salb. CR) in 59 asthmatic patients. Carry-over effect was found for QOL, but not for peak expiratory flow rate, symptom score or additional use of salbutamol. Analyses were carried out on three scores derived from the 'Living With Asthma Questionnaire' (LWAQ): (1) the overall score (OS); (2) the problem subscale score (PSS); and (3) the evaluation subscale score (ESS) (2).

When results were analysed without reference to the order of treatment, we found that, for OS and PSS, there was a significant difference between run-in and salmeterol and between run-in and salb. CR, but there was no difference between salmeterol and salb. CR. However, there was also a significant difference between run-in and washout, suggesting either a trial effect or some carry-over effect from the active treatment. In the case of ESS, the only significant difference was between run-in and salmeterol.

When the order of treatment was taken into account, we found that, for OS and PSS, there was a significant difference between run-in and salmeterol showed an improvement on the ESS, but those treated initially with salb. CR did not show an improvement, in fact there was a non-significant deterioration. The reason for this finding is not clear but one possibility could be that the initial treatment with salb. CR, in spite of the washout period, pre-vented the positive effect of salmeterol. This possibility should be treated with caution and, at this stage, should only be considered as an area for further investigation.

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References


Dear Editor

Pulmonary alveolar proteinosis and disseminated Mycobacterium avium infection

Pulmonary alveolar proteinosis (PAP) is a rare disorder characterized by accumulation of phospholipid material in the alveolar space (1), which can be 'idiopathic' or secondary to various conditions, such as malignant haematologic disorders (2). Recently, isolation of Mycobacterium avium intra cellularare (MAI) has been reported in patients with PAP, suggesting that defective alveolar macrophage function linked to PAP contributed to the higher frequency of pulmonary MAI infection (3). As a further contribution, we report a woman with PAP and a MAI bone-marrow and lymph-node infection but without MAI pulmonary involvement.

We have previously reported the case of a 32-year-old female (4) who developed fever, weight loss, cervical lymph nodes and pancytopenia (white blood cells count: 1.8 × 10^9 l^-1 ) with 63% neutrophils, 25% lymphocytes, 5% monocytes, 5% eosinophils; haemoglobin 7.8 g dl^-1 ; platelets 135 × 10^12 1^-1 ). Numerous caseous necrotic granuloma were seen in the lymph nodes and bone marrow with Ziehl-Nielsen positive bacilli. Culture of bone marrow was positive for MAI. Chest X-ray studies showed a miliary pattern. Bronchoalveolar lavage and sputum culture were negative for mycobacteria as well as for other pathogens. No acquired illness or primary immunodeficiency was found that could explain this
opportunistic infection (the patient had been repeatedly sero-negative for HIV-1 and HIV-2; culture and polymerase chain reaction on peripheral blood mononuclear cells and alveolar cells remained negative for HIV; there was no evidence of a proliferative disorder on computed tomographic scan of the thorax, abdomen, and pelvis). No auto-antibodies were detected; adenosine deaminase and purine nucleoside phosphorylase activities, and serum $\alpha$-foetoprotein level were normal. CD4+ lymphocyte count was moderately decreased ($308 \text{ mm}^{-3}$) with a normal proliferative response to mitogens.

One year later, the patient deteriorated with cachexia, persistence of fever and an increasing pulmonary interstitial infiltrate. Repeated bronchoalveolar lavage analysis and cultures were negative for all pathogens. Analysis of bronchoalveolar lavage cells stained by May Grunwald Giemsa and combined periodic acid Schiff (PAS) with alcian blue disclosed basophilic extracellular deposit with enlarged foamy alveolar macrophages. This material, like the cytoplasm of alveolar macrophages, showed a pink PAS-positive aspect. A similar aspect has been observed on open lung biopsy. Specific stains and cultures were negative for pathogens. The patient died 2 months later. Necropsy did not reveal any malignant disease.

We report a case of PAP associated with MAI bone-marrow infection, and no pulmonary involvement. The diagnosis of PAP was established by analysis of bronchoalveolar lavage and open lung biopsy (1,5). This case is different from those reported previously, which associate PAP and pulmonary mycobacterial infection. To our knowledge, no other such case has been reported. This case suggests that patients with PAP must be examined for MAI pulmonary and extra-pulmonary infection.

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References