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EDITORIAL

Inhaled steroids for sarcoidosis?

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The clinical entity of sarcoidosis was described a century ago, and many clinical, epidemiological and pathophysiological data on sarcoidosis have been collected since then. Nevertheless, the cause of the disease is not established, and this lack of knowledge contributes to the fact that specific therapy for sarcoidosis is not available. We do know that about 60–80% of patients with sarcoidosis show spontaneous remission or a benign course of the disease [1–4]. Unfortunately, until now, no reliable predictors for the individual prognosis of the disease have been revealed [5–7]. Furthermore, it is well-established that the course and the prognosis of sarcoidosis, as well as the degree of extrapulmonary involvement, differs between different regions of the world [3, 6, 8].

Most patients with sarcoidosis show a beneficial response to systemic corticosteroid therapy [7–10], as was first established in 1952 by SILTZBACH [11], who demonstrated by means of serial tissue biopsies after treatment a resolution of granulomas under the influence of corticosteroids. A short-term effect of systemic steroid therapy on symptoms and radiological signs has been shown in open as well as randomized studies [8, 10, 12, 13]. However, long-term observations after 5.4 yrs [14] and 10–15 yrs [15] found no differences between treated and untreated patients with respect to lung function parameters and radiological stages in controlled, randomized trials with oral prednisolone. Taken together, it is a difficult task to evaluate the various studies on therapy of sarcoidosis, because study design, criteria of patient selection and steroid dosage are often not comparable. Although there is clinical experience regarding the likely course of the disease in an individual patient, there is no marker nor any objective predictor [16]. Therefore, the individual natural course of sarcoidosis is not predictable.

Since 1986, there have been several reports on pulmonary sarcoidosis without extrapulmonary involvement having been treated with inhaled corticosteroids. The published data refer to open or controlled studies with small numbers of patients [17–19]. Presumably, within the clinical setting, some physicians have tried to treat single patients with sarcoidosis by inhaled steroids for quite some years. It appears to be especially difficult to find criteria for the selection of patients who might respond to this form of therapy. Despite this, from pathogenetic and clinical considerations, there appear to be good reasons for the use of inhaled steroids. In 1986, SELROOS [17] published an open study of 20 patients with active sarcoidosis (stages II, III) treated with budesonide instead of oral steroids. It was observed that there was a general improvement of chest radiograph findings and of inspiratory vital capacity (IVC) and, subsequently, an improvement of alveolitis in bronchoalveolar lavage (BAL) [18], dependent on serum and tissue concentration of inhaled steroids [19].

SPITERI *et al.* [20] reported that three out of 10 patients treated with 800 µg inhaled budesonide *via* nebulizer *b.i.d.* for 16 weeks showed an improvement of their radiological findings but not of lung function parameters. The authors speculated on a possible modulation of the immunological response underlying the disease. This was based on the observation that the number of lymphocytes in BAL decreased significantly, and that the phenotype and the functional characteristics of alveolar macrophage populations had changed after 16 weeks of therapy. No similar changes were seen in the placebo group. This would theoretically favour the approach to treating early stages of sarcoidosis, even asymptomatic patients, to prevent further progress of the disease or to facilitate remission. Additionally, inhaled and oral steroids were compared, and it was noted in both groups that the clinical symptoms improved, but improvement was quicker and more pronounced in patients who received oral steroids. SPITERI *et al.* [20] advocated use of inhaled steroids in the management of sarcoidosis either in uncomplicated early cases or in combination with oral steroids to prevent side-effects.

The use of inhaled steroids in sarcoidosis has also been studied by GUPTA [21] in a larger group of subjects. This open study included 113 sarcoidosis patients from India. Patients were treated either with inhaled steroids alone, with inhaled steroids in addition to nonsteroidal anti-inflammatory drugs, or with oral steroids. Patients who were treated with inhaled steroids alone showed a total of 76 episodes requiring therapy, including relapses. The effect of inhaled steroid therapy was judged by symptoms, improvement in spirometric parameters, fall in serum angiotensin-converting enzyme (ACE) levels, improvement of chest radiographs and lowering of hypercalcaemia. The doses of budesonide were 800–1,600 µg daily and were usually given *b.i.d.* GUPTA [21] could not demonstrate significant improvements after three months, except for clinical symptoms, such as cough and dyspnoea.

ALBERTS and co-workers [22] previously presented data from an open study with inhaled steroids in nine patients

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with sarcoidosis. There was resolution of symptoms in all patients, normalization of chest radiograph in three, and normalization of intrathoracic ^{67}gallium uptake in 6 out of 7 patients. IVC increased on average by 6%, and this was statistically significant.

In this issue of the Journal, ALBERTS and co-workers [23] present the results of their multicentre study which has been carried out in a double-blind and placebo-controlled manner [23]. The study comprised 47 patients with newly diagnosed and histologically proven pulmonary sarcoidosis of stages I, II or III. IVC was less than 79% of predicted or transfer factor less than 77% of predicted. Budesonide was given as a single dose of 1,200 µg daily *via* nebulizer and the period of treatment, with either budesonide or placebo, was 6 months. The study revealed a favourable effect of inhaled budesonide on symptom scores assessed by the patients themselves and on IVC when compared to the placebo group. There were no obvious differences between the budesonide and the placebo group with respect to changes in chest radiograph, transfer factor, and serum ACE levels.

Despite the multicentre design, the number of patients enrolled was fairly small compared to the statistical requirements, as determined by the variability of the data. During the course of the study, 11 patients (23%) had to be switched to oral prednisolone, and this did not depend on whether patients had received inhaled budesonide or placebo. The finding that transfer factor and chest radiograph were not significantly influenced by inhaled budesonide clearly shows the limitations of this therapy. These limitations were also obvious from the study by GUPTA [21], where inhaled budesonide was ineffective in the treatment of relapses. It is generally assumed that about 25–30% of patients with pulmonary sarcoidosis have to be treated with oral steroids and this is indirectly confirmed by the data of ALBERTS and co-workers [23] who found that 23% of patients had to be switched to oral prednisolone.

It is, therefore, questionable whether there is a place for inhaled steroids in sarcoidosis. This question is difficult to answer, because there could be a subgroup of sarcoidosis patients yet to be identified, who could benefit from this therapy with reasonable probability. Following the results of ALBERTS and co-workers [23], it could be speculated that this subgroup comprises patients with marked symptoms but without lung function impairment in stages I and II, as well as all patients with newly diagnosed sarcoidosis, in order to prevent the development and worsening of the disease.

Several studies have demonstrated an increased bronchial responsiveness in patients with sarcoidosis (up to 30%) [24–26] and this appears to be true in newly diagnosed and in chronic sarcoidosis [27]. It can be speculated that patients who respond to inhaled steroids have bronchial hyperresponsiveness. This could explain the improvement of clinical symptoms, such as cough and dyspnoea and, perhaps, also IVC.

In conclusion, based on our current knowledge and the scientific evidence provided, it appears that it is not generally justifiable to recommend inhaled steroids for the treatment of sarcoidosis. Studies like the present one by ALBERTS and co-workers [23] are important to maintain a critical view of the local anti-inflammatory therapy for a systemic disorder of unknown aetiology. The data once more demonstrate the difficulties encountered with any study on a complex disease, which has a large variability in its natural course.

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