Leading Article

Inhaled corticosteroids in pulmonary sarcoidosis

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Introduction

Pulmonary sarcoidosis is a chronic inflammatory disease characterized histologically by granuloma formation within the lung interstitium. Clinically the disease has a variable course. In the majority of patients the inflammation resolves spontaneously, while in 15–20% of patients the granulomata persist and lead to irreversible fibrosis with significant respiratory embarrassment. Clear guidelines for treatment in this disease are absent.

Despite substantial advances in the scientific understanding of the basic immune mechanisms responsible for pulmonary sarcoidosis, there is to date a lack of any clear prognostic signs in this disease. This leaves in dispute the question of who and when to treat. Usually therapy is started late, and consists of systemic corticosteroids in varying doses and regimes with variable clinical efficacy. Systemic corticosteroids have been shown to control the local inflammatory response in sarcoidosis by decreasing the CD4/CD8 T cell ratio, with consequent increase in CD8+ T-lymphocyte accumulation at the site of the granuloma.¹ In addition, there is also suppression of local immunoglobulin production, and a reduction in the lymphocytic production of interleukin-2.² Invariably, however, undesirable side effects occur. For this reason systemic steroid therapy is often started too late (or curtailed too soon), with many of the patients already developing pulmonary fibrosis. When this happens the lung damage is irreversible, with steroid therapy often being found to be ineffective both clinically and at the cellular level.^{3,4}

Against such a background, there is clearly a need for a therapeutic regimen that is safe enough to commence early in disease, that can be targeted to the lung, and that can be shown (as with systemic steroids) to modulate the underlying cellular dysfunction occurring in the lungs of sarcoid patients.

Inhaled corticosteroids became available 15 years ago for the treatment of patients with bron-

chial asthma. Early attempts to use inhaled steroids for the treatment of pulmonary sarcoidosis were unsuccessful,⁵ probably because the daily dose was too low and the disease too advanced to be treatable with targeted corticosteroids. With the development of newer generations of inhaled corticosteroids that possess an improved ratio between anti-inflammatory effects and systemic potency, together with a different lung pharmacokinetic profile, the idea for using such therapy in pulmonary sarcoidosis has revived. Preliminary studies⁶ using inhaled budesonide in a dose of 1600 µg per day have shown that it produces clinical benefit with minimal side effects in patients with active pulmonary sarcoidosis. Yet these investigations have not documented whether such therapy would be effective in modulating local immune reactivity, or indeed whether the inhaled mode of administration is effective in depositing the drug at the site of the alveolitis.

Essentially, all previous work on sarcoidosis has invariably focused on lymphocyte activity and its manipulation with therapy. It is now becoming increasingly recognized that both the T-cell activation and the granuloma formation occurring in sarcoidosis are mechanisms controlled by macrophage-like cells.⁷ In support we have conclusively shown that the immune aberrations within the sarcoid lung extend to the non-lymphoid population, involving subpopulations of macrophages with distinctive phenotype and function.^{8,9} In particular, we have observed the emergence of a specific population of cells with the morphological appearance of alveolar macrophages (AM), but co-expressing antigenic characteristics of both mature phagocytes and dendritic antigen-presenting cells. Experiments on the functional capacity of these macrophages with the double phenotype have shown them to suppress autologous and allogeneic peripheral blood lymphocyte reactivity.^{10,11} Of greater significance, such alterations have been found to reflect changes in clinical status.¹² These observations were made possible by the use of monoclonal antibody (MoAb) probes that specifically identify subpopulations of macrophages

within the bronchoalveolar lavage (BAL) of active sarcoid patients.¹³ It appears that the persistent granulomata and fibrosis seen in pulmonary sarcoidosis are features determined as much by AM as by T-lymphocytes. It follows, therefore, that in order for steroids to be properly evaluated as a means of treating pulmonary sarcoidosis their immune-regulatory effect on the macrophage population in the lung must be ascertained.

Studies

Initial placebo-controlled studies were designed to analyse the effects of inhaled steroids on the phenotype and functional capacity of AM obtained by BAL from a homogeneous group of previously untreated active sarcoid patients. The observed local cellular results were correlated with clinical, radiological and physiological parameters. The placebo group consisted of an equal number of active sarcoid patients who seemed to be in the same stage of their disease as the treated group (in so far as clinical status, pulmonary function and radiological grading). The results showed that regimens of inhaled steroids such as budesonide administered via a 750 cm² spacer device in a relatively small dose of 800 µg twice daily achieve approximately 10% alveolar deposition and effective symptomatic relief with no adverse effects.¹⁴ Furthermore, within 4 months the inhaled therapy was shown capable of modulating the tested features of the aberrant immunological reactions existent in the lung in this disease. Inhaled steroids not only produced a significant decrease in lavage lymphocytosis, but concurrently induced a return to normal in the phenotypic proportion of AM subpopulations.¹⁴ As the rising proportions of particular macrophage subsets in sarcoid BAL had been previously found to reflect severity of disease,¹¹ the above results gave the first indicator that inhaled steroids might be able to efficaciously modify the disease process in sarcoidosis. In support, after treatment with inhaled steroid, the induced changes in the proportion of phenotypically distinct macrophage subsets were accompanied by a reversal of the suppressive AM function previously observed in active sarcoid BAL.¹⁴

Although these observations were not associated with any striking improvement in chest X-ray appearance or lung function, in an extended study over 18 months, inhaled therapy succeeded in keeping patients in remission, while maintaining a modulatory effect on the cellular aberrations in their lungs.¹⁵ No similar changes were seen in the placebo control group.

The results prompted the intriguing questions of whether the above observations occurred as a direct effect of inhaled steroid at the cellular level or

a general reflection of local anti-inflammatory action.

To address this question, glucocorticosteroid receptor antibody probes, in combination with well-proven immunocytological methods¹⁶ were used to relate the above changes in AM phenotype and function to steroid receptor expression. Initial results using appropriately treated cytopspins (i.e. fixed in 2% paraformaldehyde and permeabilized with 0.05% Triton X-100) showed a significant increase in the intensity of nuclear GR staining in AM obtained from patients treated with inhaled steroids. This was not seen in the placebo group.

In separate experiments the effect of contact with steroid on cell phenotype and function was determined by setting up cultures of cell suspensions of whole lavage from healthy subjects, into which varying concentrations of inhaled steroid in suspension were introduced under pre-set conditions (established in earlier studies). Parallel control cultures (with no steroid) were also set up. *In vitro* incubation with steroid resulted in significant change in AM phenotype, in particular the down-regulation of the phenotype of dendritic cells, with simultaneous reduction in the proportion of *in situ* antigen-presenting macrophages. A general reduction in Fc receptor expression on AM was also noted. However, in contrast to the above results using cytopspins of unfractionated BAL cells from inhaled steroid-treated patients, the *in vitro* effect of exposure to steroid on the expression of cell steroid receptor was phasic.¹⁷ More recently these results were substantiated by similar *in vitro* experiments carried out on the AM population from patients with sarcoidosis. Again, a *direct* effect of the instilled steroid on sarcoid AM subsets was clearly shown.¹⁸

Conclusion

The above data promote the hypothesis that the altered AM function observed *in vivo* after treatment of patients with active pulmonary sarcoidosis occurs as a result of a *direct* contact of the steroid with AM subpopulations. It would appear that not only do targeted steroid regimes allow the appropriate drug to be delivered to the site of inflammation, but they also effectively modulate the aberrant macrophage-lymphocyte interactions existent in the sarcoid lung without any systemic upset.¹⁵ In fact, the dose of inhaled steroid (budesonide) used in the *in vivo* studies (1600 µg per day) has been shown to be equivalent to 5.0 mg per day of oral prednisolone in terms of ability to suppress cortisol levels.¹⁹

On the basis of the above results, it would seem logical that inhaled steroids deserve a place in the early management of patients with pulmonary

sarcoidosis, either as sole therapy or in combination with lower doses of conventional systemic immuno-suppressive drugs. The rationale of such an approach would be aimed at aborting the potential persistence of granulomata within their lung parenchyma, and the subsequent development of fibrosis. Further *in vitro* evaluation needs to be undertaken to delineate the appropriate dose and frequency of administration of inhaled steroids to increase their clinical and physiological efficacy in sarcoid inflammation. Use of molecular biological techniques may provide the answer to the nature of the macrophage glucocorticoid steroid receptor, and its relationship to the different AM subsets in health and during inflammation. Such information would enable us to increase the efficacy of the inhaled steroid at the cellular level by directing the

drug at particular cell subpopulations (perhaps with the help of liposomes) in order to arrest the evolution of the exaggerated immune response in sarcoidosis, and prevent clinical deterioration. In this context a detailed evaluation of AM subpopulations in the sarcoid lung could also provide criteria for staging disease activity, as well as guiding therapy in these patients.

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