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Current Treatment of Chronic Beryllium Disease

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The current mainstay of management of chronic beryllium disease involves cessation of beryllium exposure and use of systemic corticosteroids. However, there are no randomized controlled trials to assess the effect of these interventions on the natural history of this disease. Despite this limitation, it is prudent to remove patients with chronic beryllium disease from further exposure and consider treating progressive disease early with long-term corticosteroids. The effect of treatment should be monitored using pulmonary function tests and high-resolution computed tomography of the chest. However, once pulmonary fibrosis has developed, corticosteroid therapy cannot reverse the damage.

Keywords beryllium, chronic beryllium disease, corticosteroids

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INTRODUCTION

C hronic beryllium disease (CBD) is a hypersensitivity granulomatous disease that continues to occur in 2 to 5% of beryllium-exposed workers despite efforts to reduce workplace exposures.^(1,2) CBD was first described in 1946 by Hardy and Tabershaw⁽³⁾ in a report on 17 fluorescent light workers who presented with an insidious and debilitating granulomatous lung disease that occurred after exposure to beryllium. Both beryllium exposure and a beryllium-specific cell-mediated immune response are required for the development of CBD.⁽⁴⁻⁶⁾

In addition, there is a genetic component involved in susceptibility to CBD, such as HLA-DP β Glu69 allele.^(7–9) Criteria for diagnosing CBD include the following: (1) evidence of beryllium exposure; (2) evidence of an immune response to beryllium (i.e., positive responses in blood or bronchoalveolar lavage fluid beryllium lymphocyte proliferation tests); and (3) histopathological evidence consistent with CBD.⁽¹⁰⁾

The greatest morbidity in CBD is caused by lung involvement that is associated with progressive declines in lung volumes and diffusing capacity, eventually resulting in pulmonary fibrosis, respiratory failure, and cor pulmonale. Published mortality rates for CBD vary widely, for unclear reasons, from 5.8 to 38%.⁽¹¹⁾

The current mainstay of management of CBD involves cessation of beryllium exposure and use of immunosuppressive drugs. However, there currently exists limited literature regarding the effect of these interventions on the natural history of CBD. All studies are retrospective and observational; no randomized controlled trials have been performed. In addition, the definition of disease has changed over the past few decades. Past studies have frequently defined CBD inadequately—often making the diagnosis without pathological and immunologic confirmation and sometimes erroneously including acute beryllium lung disease.^(12–18) The latter has a very different natural history from CBD; it is more likely to respond to corticosteroids and to spontaneously remit.

Further, with the recent widespread use of screening tests (beryllium lymphocyte proliferation test) and improved workplace exposure conditions, the disease is now being discovered at its earlier stage, often without clinical, physiological, or radiological abnormalities. Although the above limitations do not allow evidence-based therapy recommendations, we have presented the current state of the literature regarding the pulmonary treatment of CBD.

CESSATION OF BERYLLIUM EXPOSURE

S topping beryllium exposure in patients with CBD is usually recommended. Interestingly, initial studies in the $1950s^{(13,14)}$ indicated that disease progression was the general rule even after cessation of exposure. Hardy⁽¹²⁾ in 1955 was among the first to suggest that the natural history of CBD is quite variable and suggested that some patients with abnormal radiographic findings could remain free of "disability."

In 1978, Sprince⁽¹⁹⁾ also reported that chest radiographic and gas exchange abnormalities disappeared in a "great" proportion of untreated patients within 3 years of reduced exposure. Unfortunately, these cases had only limited assessments; only four had biopsy confirmation of disease and no case had immunologic confirmation. In a brief report by Nishikawa⁽²⁰⁾ in 1980, two of eight cases of CBD that were defined by pathological and immunologic confirmation showed radiographic clearing within 1 year of removal from exposure.

In 2004, Sood showed that stopping beryllium exposure was associated with an improvement in pulmonary function in five of six cases; cases being defined by pathologic confirmation and in most cases immunologic confirmation. Although none of these studies evaluated early CBD, the current clinical practice of a strong recommendation to remove CBD patients from exposure is appropriate.^(21–23) Offering it to those with beryllium sensitization may also be prudent.⁽¹⁰⁾

IMMUNOSUPPRESSIVE THERAPY

O ral corticosteroids are the only immunosuppressive drug studied in CBD. The use of corticosteroids in CBD is based on the hypothesis that suppression of the hypersensitivity reaction (i.e., granulomatous process) will prevent the development of fibrosis, quite like pulmonary sarcoidosis.⁽²⁴⁾ Oral corticosteroids are initiated in patients who have evidence of "progressive disease," although "progressive disease" is not well defined.⁽¹⁰⁾ In early CBD without physiological impairment, the general approach is periodic re-evaluation, typically every 1–2 years, to look for clinical, radiological, and physiological deterioration.

The decision to institute treatment with corticosteroids is made case by case.⁽¹⁰⁾ Dosages and regimens of corticosteroids vary, but common recommendations suggest initiating therapy with oral prednisone, from 20 to 40 mg/d (or every other day). Generally, patients are treated for 3 to 6 months followed by a gradual taper to the lowest effective dose.⁽²⁵⁾

Effect of Oral Corticosteroids on Pulmonary Function Tests

In 1958, Ferris studied long-term pulmonary function data on three patients with CBD and one patient with acute beryllium pneumonitis and found a variable and short-lived response to corticosteroids.⁽¹⁶⁾ Ferris explained that an initial response in pulmonary functions in CBD was due to reduced inflammation with a delayed deterioration as irreversible fibrosis set in.⁽¹⁶⁾ Gaensler⁽¹⁷⁾ in 1958 similarly noted two types of pulmonary function response curves in a 3-year follow-up of 11 patients receiving corticosteroids: one that showed an improvement, albeit short-lived, and another that showed no improvement or a slight decline in pulmonary functions. In the seven patients who had serial alveolar-arterial oxygen gradient measurements, no long-term improvement in the gradients was noted. In addition, a number of patients without corticosteroids showed no significant functional deterioration.

In 2004, Sood⁽²²⁾ confirmed Gaenseler's 1958 findings by showing two broad patterns of long-term response (mean follow-up of 10 years) to long-term corticosteroid therapy in CBD. The most common pattern of response in CBD was a short-lived but substantial improvement in pulmonary functions with corticosteroid therapy in four of six patients (mean improvement in forced vital capacity and diffusing capacity for carbon monoxide of 30% and 71%, respectively, from baseline); two other patients showed no improvement in lung function. A 2008 study by Marchand-Adam⁽²⁶⁾ also showed a short-term improvement in lung function with oral corticosteroids in eight patients with a 4–12 month followup (mean improvement in forced vital capacity and diffusing capacity for carbon monoxide by 26% and 20%, respectively). Over a median follow-up of 6 years, diffusing capacity stabilized in six of eight patients and declined in the remaining two patients.

A potential confounding factor in the evaluation of corticosteroid response in CBD may be the timing of the treatment. Corticosteroids are not administered to many patients until the disease is well established. Among 29 of the 44 treated patients (66%) in one review in 1958, ≥ 2 years had elapsed between the onset of their illness and corticosteroid therapy, a period during which significant fibrosis could occur.⁽¹⁵⁾ Sood⁽²²⁾ showed that the median duration from onset of respiratory complaints to start of corticosteroids for the group that showed no improvement in lung function was 9.9 years. In contrast, the corresponding time interval for the group that showed improvement with corticosteroids was 1.1 years. This suggests that early corticosteroid treatment may be more beneficial in improving pulmonary functions than later in the course of the disease.

Effect of Oral Corticosteroids on Radiological Picture

Marchand-Adam⁽²⁶⁾ evaluated the high-resolution computed tomography (CT) picture of eight patients during a 4– 12 month follow-up while on oral corticosteroids (Figure 1). They demonstrated a significant improvement in the active lesion score in all patients; active lesions were defined as ground glass opacities, micronodules, nodules, and alveolar consolidations. There was, however, no change in the fibrosis score; fibrosis was defined as linear opacities, traction bronchiectasis, lobular distortions, bulla formations, cysts, and honeycombing. This was perhaps the first objective evidence that oral corticosteroids are effective in the period before significant and irreversible fibrosis occurs in the lungs.

Effect of Oral Corticosteroids on Clinical Relapse

Most patients show short-term clinical relapses after an initial response, usually while the oral corticosteroid dose is being decreased.⁽²⁶⁾ It is possible that patients with Glu69 homozygosity may be more likely to develop clinical relapses than those without this allele. Clinical relapses are usually accompanied with decrease in pulmonary functions, increase in active lesion score on the high-resolution CT scan, and increase in serum angiotensin converting enzyme level.⁽²⁶⁾ Increase in dose of oral corticosteroids ensured clinical improvement in all short-term clinical relapses in the Marchand-Adam study.⁽²⁶⁾ These results suggest that short-term clinical relapses are linked to reactivation of granulomatous inflammation secondary to corticosteroid dose reduction.

On the other hand, long-term clinical relapses, occurring after the corticosteroids have been stopped, may not show



FIGURE 1. Short-term effects of oral corticosteroids on high-resolution computed tomography scans of eight chronic beryllium disease (CBD) patients. Panels (a) and (b): A representative scan of a patient with CBD (a) before, and (b) during 4 months' steroid treatment. Diffuse ground-glass opacity with some micronodules are visible in (a) but these have disappeared in (b). Panels (c) and (d): Quantification of lesions on scans of eight patients with CBD at baseline and after corticosteroid treatment (4–12 months). Panel (c) shows response to corticosteroids of opacities suggesting active inflammatory granulomatosis (ground-glass opacities, micronodules, and nodules); Panel (d) shows the response of fibrotic lesions (linear opacity, traction bronchiectasis, lobular distortion, bulla formation, cysts, and honeycombing) to corticosteroids. Reproduced with permission of European Respiratory Society Journals Ltd.⁽²⁶⁾

good pulmonary function response with a second course of corticosteroids. Sood⁽²²⁾ suggested that a second course of corticosteroid treatment may be considerably less effective than the first course.

Effect of Oral Corticosteroids on Mortality

There are no good studies to evaluate the effect of corticosteroids on mortality in patients with CBD. Seeler⁽¹³⁾ analyzed the effect of corticosteroids on 382 cases from the Beryllium Case Registry in 1959 and found a favorable effect on mortality among 126 treated patients. In these patients, the mortality was 16% compared with 39% among the 256 untreated patients. Seeler stated that "the interpretation of these data is uncertain in that many of the survivors who have not been treated have lived an appreciably longer time with their disease than those living on steroid therapy."

From the 1958 study of DeNardi,⁽¹⁸⁾ a similar analysis on mortality was made on his 70 patients. The mortality of the treated patients was 10%, while that of the untreated patients was 31%. Seeler rightly commented that these retrospective

studies could not separate apparent therapeutic improvement from patient selection bias.

Additional Limitations of Studies of Oral Corticosteroids in CBD

Studies evaluating the effectiveness of oral corticosteroids in CBD are not limited only by the use of retrospective data that may introduce information bias but also by the use of different pulmonary function laboratories, which may result in increased variability of data; small numbers of patients; and use of variable doses, duration, and tapering schedules of oral corticosteroids at the discretion of different treating physicians. Further, as mentioned above, those with early CBD without radiological and physiological abnormalities have not been studied.

Despite these limitations, it is prudent to consider treating "progressive disease" early with corticosteroids. Therapy may be guided by changes in serial resting and exercise pulmonary function measurements, high-resolution CT scans, and serum angiotensin converting enzyme levels. Unfortunately, lifelong therapy is usually required, since the disease recrudesces with reduction of the corticosteroid dose. Evidence of short-term clinical relapse merits dose escalation. Patients should be monitored for therapy-induced side effects on an ongoing basis. Persistent use of corticosteroids should be avoided if there is no long-term physiological improvement.

ADJUVANT THERAPIES

M odeled on the management of sarcoidosis, oral methotrexate and azathioprine may be used as corticosteroid-sparing agents in CBD.^(27,28) The role of infliximab in CBD is currently under investigation. Adjuvant therapy with bronchodilators and diuretics also should be considered.⁽²⁹⁾ Supplemental oxygen may be necessary to correct hypoxemia associated with CBD.⁽²⁹⁾ Nocturnal polysomnography should be considered in those with overnight oxygen desaturation. Right ventricular failure and its complications are late-stage sequelae. Pneumothorax can also occur.^(24,27)

Supportive therapy may also include pulmonary rehabilitation to maintain muscle strength and tone, vaccinations to prevent influenza and pneumococcal pneumonia, and antibiotics for acute intercurrent respiratory tract infections.⁽²⁹⁾ However, these adjuvant therapies have not been specifically studied in patients with CBD.

CONCLUSION

A lthough CBD is treatable, there is no cure. The goal of treatment is to reduce morbidity and mortality. Cessation of beryllium exposure may be beneficial. Early treatment with corticosteroids may lead to regression of disease and may prevent further progression of disease. However, once fibrosis has developed, therapy cannot reverse the damage.

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