Short- and long-term response to corticosteroid therapy in chronic beryllium disease

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ABSTRACT: Chronic beryllium disease (CBD) is a granulomatous disorder that affects the lung after exposure to beryllium. The present study reports short- and long-term evolution of granulomatous and fibrotic components in eight patients with severe CBD receiving corticosteroid therapy.

Eight patients with confirmed CBD were studied at baseline, after initial corticosteroid treatment (4–12 months), at relapse and at the final visit. Beryllium exposure, Glu⁶⁹ (HLA-DPB1 genes coding for glutamate at position β 69) polymorphism, symptoms, pulmonary function tests (PFT), serum angiotensin-converting enzyme (SACE) and high-resolution computed tomography (HRCT) quantification of pulmonary lesions were analysed.

The CBD patients were observed for a median (range) of 69 (20–180) months. After stopping beryllium exposure, corticosteroids improved symptoms and PFT (vital capacity +26%, diffusing capacity of the lung for carbon monoxide +15%), and decreased SACE level and active lesion HRCT score. In total, 18 clinical relapses occurred after the treatment was tapered and these were associated with SACE and active lesion HRCT score impairment. At the final visit, corticosteroids had completely stabilised all parameters including both HRCT scores of active lesions and fibrotic lesions in six out of eight patients.

Corticosteroids were beneficial in chronic beryllium disease. They were effective in suppressing granulomatous lesions in all cases and in stopping the evolution to pulmonary fibrosis in six out of eight patients.

KEYWORDS: Berylliosis, chronic beryllium disease, corticosteroids, Glu⁶⁹, outcome, sarcoidosis

Chronic beryllium disease (CBD) is a granulomatous disorder that mainly affects the lung after exposure to beryllium (Be). Susceptibility to CBD has been associated with variants of the HLA-DPB1 gene coding for glutamate at position β 69 (Glu⁶⁹) [1].

The primary process of CBD is characterised, at the histopathological level, by an interstitial mononuclear cell inflammation and non-necrotising epithelioid cell granulomas in the lung. Over time, areas of fibrosis surround the granulomas. The development of extensive pulmonary fibrosis is a major complication of CBD and the main cause of mortality [2]. Medical literature suggests that, unlike sarcoidosis, once CBD is clinically overt it continues to progress even after a long interruption of Be exposure [3]. This observation

is probably linked to the low-level clearance of Be and its particularly prolonged persistence in the lung [4].

In CBD, the inflammatory responses to Be can establish a state of acquired Be antigen-specific, cell-mediated immunity, as indicated by an abnormal lymphocyte proliferative response to Be (BeLPT) on peripheral blood or bronchoalveolar lavage (BAL) cells [5]. Medical treatment of CBD is aimed at controlling or reducing the immunological reaction to Be. In addition to stopping exposure, corticosteroid therapy is the cornerstone of treatment [6]. Previous clinical series have shown the efficacy of corticosteroids in improving symptoms and pulmonary function [7–14]. However, nowadays, BeLPT is necessary to diagnose CBD, and previous reports may have

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included some cases with diseases different to CBD, such as sarcoidosis.

The aim of the present retrospective study was to investigate the short- and long-term response to corticosteroid therapy on the granulomatosis and fibrotic components of CBD.

METHODS

Patients

Eight patients with confirmed CBD were recruited and followed up by an investigator (D. Valeyre) in the Dept of Respiratory Medicine, Avicenne Hospital (Bobigny, France) between 1988 and 2004. Five of the patients have been reported previously [15]. Demographic data are given in table 1. All patients stopped smoking during the study. The diagnosis was based on the following criteria [16]: 1) occupational history showing exposure to Be; 2) evidence of noncaseating granulomatosis in tissue samples; and 3) positive BeLPT.

Investigations

Symptoms, physical examination, pulmonary function tests (PFT; see online supplementary data), chest radiography and serum angiotensin-converting enzyme (SACE) activity were recorded on the chart of each patient. The Be exposure level (see online supplementary data) and Glu⁶⁹ polymorphism encoded by HLA-DPB1 genes were also recorded.

High-resolution computed tomography scores

All patients underwent high-resolution computed tomography (HRCT) of the lung at baseline, after 4–12 months of corticosteroid therapy and at the end of the study. Opacities such as ground-glass opacities, micronodules, nodules and alveolar consolidations were considered as active inflammatory granulomatosis lesions and quantified in active lesion score; while opacities such as linear opacities, traction bronchiectasis, lobular distortions, bulla formations, cysts and honeycombs were considered as fibrotic lesion expressions and quantified in fibrosis lesion score (see online supplementary data).

Treatment

All patients received oral corticosteroids (prednisone) at mean initial daily dosage schedules of 0.8 mg·kg⁻¹·day⁻¹ (40–70 mg·day⁻¹), with bisphosphonate as prevention of osteoporosis (when authorised for use in therapeutics). Treatment was started within 4 weeks of baseline. Further adjustment of corticosteroid therapy was based on the response of pulmonary symptoms, radiology and PFT. Occupational exposure to Be was ceased for all patients.

Study design

Response to corticosteroid therapy was evaluated according to clinical, radiological, functional and SACE data. Improvement (defined by a clear decrease of abnormal clinical, radiological and functional manifestations) allowed the reduction of corticosteroid treatment. Conversely, corticosteroids were increased again when two of the following criteria were present: worsening of clinical symptoms, chest radiograph opacities or PFT. The results at baseline and at the first improvement following initial treatment (4–12 months) were compared. Finally, data obtained at the final visit were

TABLE 1 HLA-DPB1 polymorphism, exposure to beryllium, bronchoalveolar lavage (BAL), corticosteroid treatment and total survey period of the study patients													
Patient	Age yrs	HLA-DPB1	Glu ⁶⁹	Beryllium exposure		BAL		Period before steroids months	Mean daily dose mg·day ⁻¹			Total survey period months	
				Length yrs	Level	Cell counts 10 ⁵ cells·mL ⁻¹	Ly %		CD4/CD8 ratio	1st yr	2nd yr		5th yr
1	29	0401/0401	-/-	5	High	4	62	4.2	12	42.5	36.6	29.2	64
2	52	0401/0901	-/+	32	Medium	4.3	49	4.2	9	26.3	10.4	9.3	69
3	38	0402/0901	-/+	3	Low	12.9	70	30	10	51.7	15	NA	26
4	37	0201/0201	+/+	4	High	3.5	63	5.5	12	54.2	52.5	22.7	130
5	31	0201/1001	+/+	5	Medium	2.5	13	4	12	43.3	18.3	24.7	110
6	57	0402/1001	-/+	8	High	10.3	84	3.6	36	37.5	25.4	NA	40
7	23	1301/0201	+/+	6	High	8.5	66	19	8	32.9	15	5	180
8	28	0401/0201	-/+	3	High	NA	NA	NA	20	30.8	11.3	NA	50
Glu ⁶⁹ : HLA-DPB1 coding for glutamate at position β69; Ly: lymphocytes; NA: not available; -: absence; +: presence.													

TABLE 2 Pulmonary function tests at presentation

Patient	TLC % pred	VC % pred	FEV1 % pred	FEV1 % pred/FVC %	DL _{CO} % pred	Kco % pred	Pa,O ₂ mmHg	Pa,CO ₂ mmHg
1	63	52	58	90	76	102	78	41
2	76	73	80	84	49	67	64	36
3	70	50	52	82	26	55	54	35
4	71	67	65	82	31	42	78	36
5	41	34	40	91	32	84	70	37
6	73	85	92	86	50	79	69	37
7	62	58	54	78	36	42	70	35
8	65	64	65	88	31	52	66	42

TLC: total lung capacity; % pred: % predicted; VC: slow vital capacity; FEV1: forced expiratory volume in one second; DL_{CO}: diffusing capacity of the lung for carbon monoxide; KCO: transfer coefficient of the lung for carbon monoxide; Pa,O₂: arterial oxygen tension; Pa,CO₂: arterial carbon dioxide tension.

analysed. The relapse study design is available in the online supplementary data.

Statistical analysis

A nonparametric method was used, and all data are expressed as median (range). The Wilcoxon signed-rank test was performed to evaluate the significance of changes after treatment. A p-value <0.05 was considered significant.

RESULTS

Data at baseline

Demographic, clinical, radiological, biological and Be exposure data at baseline are reported in tables 1 and 2. All patients had dyspnoea (level $\geq$ II of New York Heart Association score) and weight loss (-9 (2–13) kg). Four patients had fever ($>38.5^{\circ}\text{C}$) with cough, and three patients had chest pain. Physical examination revealed crackles in six patients and digital

FIGURE 1. Short-term effects of corticosteroids on pulmonary function tests and the serum angiotensin-converting enzyme (SACE) level of eight chronic beryllium disease patients. a) The slow vital capacity (VC), b) the diffusing capacity of the lung for carbon monoxide (DL_{CO}), c) the arterial oxygen tension (Pa,O₂), and d) the SACE level were measured at baseline and at the first improvement following initial treatment (4–12 months). ●: patients with Glu⁶⁹ homozygosity (HLA-DPB1 coding for glutamate at position β69); ○: patients without Glu⁶⁹ homozygosity. —: median. *: p<0.05 compared with baseline.

FIGURE 2. Short-term effects of corticosteroids on high-resolution computed tomography (HRCT) scans of eight chronic beryllium disease (CBD) patients. A representative HRCT of a patient with CBD before (a) and during 4 months' steroid treatment (b). Diffuse ground-glass opacity with some micronodules and hilar adenopathies are visible in (a) but these have disappeared in (b). c and d) Quantification of lesions on HRCT scans of eight patients with CBD at baseline and after corticosteroid treatment (4–12 months). c) Opacities suggesting inflammatory granulomatosis (ground-glass opacities, micronodules and nodules), and d) fibrotic lesions (linear opacity, traction bronchiectasia, lobular distortion, bulla formation, cysts and honeycombing) were scored separately. The severity was scored in six pulmonary areas according to four basic categories: 0=normal, 1=slight, 2=moderate, 3=advanced. ●: patients with Glu⁶⁹ homozygosity (HLA-DPB1 coding for glutamate at position β69); ○: patients without Glu⁶⁹ homozygosity. —: median. *: $p < 0.05$ compared with baseline.

clubbing in two. The tuberculin test was negative in all six patients tested.

Chest radiographs showed bilateral hilar lymphadenopathy in five patients, and diffuse parenchymal ground-glass ($n=6$), micronodular ($n=7$), linear ($n=3$) and alveolar ($n=6$) opacities.

All HRCT scans presented signs suggesting active CBD, including ground-glass opacities ($n=8$), micronodules with blurred outline ($n=4$) and nodules ($n=2$). The active lesion score was 14.5 (5–17) in study patients (figs 1a and c). The confluence and density of ground-glass opacities and micronodules formed some localised alveolar consolidations in five patients. Linear opacities with thickened interlobular septa were frequently found in five patients but signs suggesting fibrosis were rare (fibrosis lesion score: 3.5 (0–14), fig. 1d). However, one patient (patient number 2) had the longest Be exposure, and had already had significant retraction and bulla formation signs at baseline. In six patients, HRCT showed

bilateral hilar lymphadenopathy and no air-trapping at expiration was noted.

Radiographic improvement was observed in all patients. On HRCT, all patients had an improved active lesion score (–10 (–3–15); $p < 0.05$; fig. 1a–c). In contrast, the fibrosis score did not change with corticosteroid treatment (fig. 1d).

SACE level was abnormal in all patients (90 (44–262 IU·mL^{–1}), normal level <41 UI·mL^{–1}). Noncaseating granulomas were found in lung biopsies from seven patients (video-thoracoscopy: $n=5$; transbronchial biopsy: $n=2$) and in a liver biopsy from the remaining patient. Patients had a positive BeLPT in peripheral blood (five out of eight patients) and/or BAL (four out of four patients).

Baseline PFT results are shown in table 2. All patients presented restrictive patterns, with direct impairment of diffusing capacity of the lung for carbon monoxide (DL_{CO} ; 34 (26–76) % predicted) and arterial oxygen tension (P_{a,O_2} ; 69.5 (54–78) mmHg).

FIGURE 3. Long-term effects of corticosteroids on pulmonary function tests and high-resolution computed tomography (HRCT) scans in eight chronic beryllium disease (CBD) patients. a) Variation of diffusing capacity of the lung for carbon monoxide (DL_{CO}) between the first improvement following initial treatment and the end of study. b and c) Evolution of HRCT lesion scores of patients with CBD. b) Opacities suggesting fibrotic lesions (linear opacity, traction bronchiectasia, lobular distortion, bulla formation, cysts and honeycombing), and c) inflammatory granulomatosis (ground-glass opacities, micronodules and nodules) were scored separately. The severity was scored in six pulmonary areas according to four basic categories: 0=normal, 1=slight, 2=moderate, 3=advanced. ●: patients with Glu⁶⁹ homozygosity (HLA-DPB1 coding for glutamate at position $\beta 69$); ○: patients without Glu⁶⁹ homozygosity. —: median.

Evolution after 4–12 months of corticosteroid treatment

The maximal clinical and functional improvement was reached after 4–12 months of corticosteroid treatment. Dyspnoea decreased in all patients (New York Heart Association classification

improved by one level), and all other clinical findings disappeared (fever, cough, and weight loss). Crackles disappeared in four out of six patients.

The slow vital capacity improved in all eight patients by 26 (9–56) % pred ($p < 0.05$, fig. 1a). DL_{CO} also improved by 20% ($p < 0.05$) in all patients, but remained low (54 (41–78) % pred, fig. 2b). The P_{aO_2} increased in all patients except one (20 (0–36) mmHg; $p < 0.05$; fig. 2c). The SACE level decreased in all patients (21 (15–40) IU·mL⁻¹; $p < 0.05$; fig. 2d).

Relapses after decrease of corticosteroids

Results concerning the CBD relapses in the eight patients are available in the online supplementary data.

End of the study period

The patients did not present any serious complications requiring treatment to stop. Cushing's syndrome was noted in patient seven.

The steroid threshold dose decreased with time. All patients were still treated with prednisone (12 (7–60) mg·day⁻¹) for a median (range) period of 69 (20–180) months. The SACE level was normal. DL_{CO} and HRCT scores (fig. 3) were stabilised in all but two patients. By contrast, in patients four and five, DL_{CO} decreased despite corticosteroid treatment (fig. 3a). On HRCT, these patients presented a direct increase of the fibrosis score compared with other patients (fig. 3b). Interestingly, the appearance of their fibrotic lesions was particular with diffuse multicysts and thin reticulation with honeycomb lesions similar to those of idiopathic pulmonary fibrosis (fig. 4).

DISCUSSION

The present study has shown that corticosteroid therapy at high doses makes the control of active granulomatosis inflammation possible and achieves a clear response of symptoms, PFT, HRCT and SACE in severe CBD. Over the long term, steroid treatment prevented the decline of pulmonary function in six patients by preventing fibrosis progression; however, it did not modify the fibrotic lesions pre-dating corticosteroid initiation. In two cases, despite clear short-term responses to corticosteroids, the issue with time was different with the progressive development of serious fibrotic lesions.

Many clinical series and case reports of CBD have indicated that corticosteroids were effective in reducing symptoms and improving lung function [7–14]. However, in these earlier reports, BeLPT tests were not practised, although this immunological assessment leads to a greater specificity of the diagnosis. In addition, the case definition was prone to potential misclassification, and some cases may have followed a different course as they had different aetiology, such as sarcoidosis. In the present study, all patients had confirmed pulmonary CBD, based on a new gold standard [17]. A recent study examined the effect of long-term corticosteroid therapy on the natural history of six patients with CBD confirmed by a positive BeLPT [18]. The current findings are more relevant because of the radiological distinction between granulomatous inflammation and irreversible fibrosis by using both HRCT scores and SACE measurement and a longer survey period. The same classification as sarcoidosis has been used [19], and the lesions separated into two categories: 1) active granulomatosis

FIGURE 4. Patient number 5 with Glu⁶⁹ homozygosity (HLA-DPB1 coding for glutamate at position β 69). a) A computed tomography (CT) scan 8 months after initial treatment showing slight ground-glass opacity. b) A CT scan 9 yrs later, after which time lung fibrosis has appeared with honeycombing, some large cysts and some septal reticulation.

inflammatory lesions (ground-glass opacities, micronodules and alveolar consolidations); and 2) pulmonary fibrotic lesions (linear opacities, traction bronchiectasia, bulla formations and honey-combings).

The current study showed the importance of inflammatory granulomas in the seriousness of baseline presentation and relapses. The disease presentation at baseline was invariably severe and needed steroid treatment. With corticosteroid therapy, the improvement of symptoms and PFT were associated with a decrease of the active lesion score on HRCT and SACE, a marker of macrophage activation. DANILOFF *et al.* [20] have previously shown that HRCT abnormalities (nodule, ground-glass opacities) were correlated with lymphocytosis in BAL and suggested that HRCT was a meaningful index of the inflammatory activity in CBD. The response to corticosteroids was not examined in the present study.

Before corticosteroid initiation, patients presented with initial linear and reticular opacities and bulla formation suggesting early fibrotic lesions. This was probably related to the natural evolution of several granulomas to fibrosis. STOECKLE *et al.* [13] observed that, in patients with CBD, pulmonary nodular and granular densities on chest radiographs tended to be replaced by linear densities and lung retraction. The delay between the onset of the illness and corticosteroid therapy favoured fibrosis emergence [13]. In a recent autopsy study [2], all patients showed end-stage interstitial fibrosis with varying degrees of cystic and honeycomb change. Little is known about the mechanisms that govern the transition from granulomatous inflammation to increasing fibrosis in CBD. In some CBD patients, histology revealed that an increasing number of fibroblasts infiltrated around granulomas [17, 21].

Corticosteroids were more likely to suppress the growth of existing granulomas and to prevent the development of new ones, and were less effective against fibrotic lesions. STOECKLE *et al.* [13] described several clinical cases where treatment

with steroids appeared to have interrupted the progressive fibrosis. The current study patients were followed after steroid onset for a median duration of 69 months. Six of the study patients demonstrated a persistent initial benefit in terms of pulmonary function and radiological opacity. In particular, fibrosis opacities on HRCT did not worsen in these six patients. Corticosteroids seemed to limit the progressive fibrosis.

However, it is known that the rate of progression of CBD is variable [13, 18, 22]. The present data indicate that after initiating corticosteroid treatment, pulmonary fibrosis did not progress in six cases while it clearly developed in the other two. This worsening of fibrosis lesions may be the consequence of an insufficient control of insidious granulomatous lesions. However, it may also be the consequence of an evolution of fibrosis. FERRIS [23] suggested that the nonreversible fibrosis may develop despite suppressed inflammation by steroids. Several parameters may have participated in the progression to pulmonary fibrosis in the two patients. One of these is the total survey period, as patients with progressive fibrosis were surveyed for a longer time. Although these two patients were Glu⁶⁹ homozygous, it was not possible to draw a conclusion about the role of this factor in the progression to fibrosis owing to the small number of patients (fig. 3).

In conclusion, corticosteroid treatment in patients suffering from serious chronic beryllium disease improved symptoms, pulmonary function tests and radiology by acting on inflammatory granulomas. The control of inflammatory granulomatosis limited the fibrotic evolution as long as doses were monitored under the control of clinical examination, serum angiotensin-converting enzyme and high-resolution computed tomography scanning. However, corticosteroids seemed insufficient to stop this poor evolution for some patients. The understanding of the mechanisms that govern the fibrosis in chronic beryllium disease could help to control its emergence in other granulomatosis, such as sarcoidosis.

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