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Inhaled budesonide and pulmonary sarcoidosis revisited

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Abstract. Results of a few controlled clinical studies have been reported with inhaled corticosteroids (ICS) in patients with pulmonary sarcoidosis. Some evidence of efficacy has been observed, but mainly with the ICS budesonide (BUD). These clinically important and statistically significant results are restricted to maintenance therapy with BUD after induction of treatment with systemic corticosteroids for a few weeks or months. Positive results have also been described in patients with relapses after earlier treatment with oral corticosteroids. A possible explanation for BUD's efficacy in patients with parenchymal lesions could be that inhaled BUD is rapidly absorbed into systemic circulation, creating plasma peaks which result in systemic anti-inflammatory activity in both peripheral airways and lung tissue. At airway level this steroid activity is furthermore prolonged because a BUD fraction is intracellularly, reversibly transformed into lipophilic BUD-oleate. These mechanisms have been proposed to explain the theoretically unexpected similar efficacy of BUD compared with more lipophilic ICSs in patients with asthma and COPD. In this review we summarize the results of clinical studies with ICSs in patients with pulmonary sarcoidosis. It is obvious that current ICSs, including BUD, cannot generally be recommended as such for treatment of sarcoidosis. However, using BUD as a model substance further pharmacologic and kinetic studies could possibly define a kinetic profile giving optimal partitioning between airway and systemic activity with less adverse systemic risks. Such a substance could replace or reduce oral corticosteroids in the treatment of airway and pulmonary parenchymal diseases.

Key words: pulmonary sarcoidosis, inhaled corticosteroids, budesonide, pharmacokinetics

Introduction

Sarcoidosis is a systemic granulomatous disease that may affect all organs but preferably lungs and lymph nodes. In many cases lung parenchymal infiltrates represent the major clinical problem. The course of sarcoidosis is unpredictable including the possibilities of spontaneous recoveries and in the other end a spectrum of widespread irreversible lung fibrosis.

Initial expectation after diagnosis without treatment is generally recommended in hope of spontaneous recovery, particularly in patients with pulmonary sarcoidosis, normal lung function and without troublesome extrapulmonary manifestations (1). It is generally agreed that corticosteroids (CS) are the drugs of choice in patients requiring therapy (1-3). Various treatment regimens have been used. There is no general consensus about starting doses of oral corticosteroids (OCS), time for tapering the dose, or duration of treatment (1-3). The indications for starting therapy will not be discussed here.

The great variation in disease prognosis, including spontaneous recoveries, makes controlled clinical trials difficult to perform. This is true of all types of drugs tested in sarcoidosis patients.

Inhaled corticosteroids (ICS) were in the beginning tested in single sarcoidosis patients and in small open studies. The type of patients varied, as the reported results. Subsequently larger and better designed studies were performed. Reviews concluded that, even if not satisfactorily documented, ICS could

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have a place in therapy, particularly in patients with newly detected disease and in those with local airway symptoms, such as cough (3-4). However, more recent summaries, including ERS guidelines, do not mention ICS at all (5). Other authors concluded that ICSs have no place in therapy for patients with pulmonary sarcoidosis (6,7). This fits with the accepted kinetic view that inhaled ICS cannot reach active steroid levels at peripheral airways and lung parenchyma (8).

The most convincing evidence of efficacy of ICS in pulmonary sarcoidosis has emerged from studies with inhaled budesonide (BUD); treatment of relapses in patients earlier treated with OCS (9,10) and in maintenance therapy after induction of therapy with a course of OCS (11). Indeed, the clinical results with BUD are inconsistent and not of the magnitude that this ICS could be generally recommended for use in all type of patients with pulmonary sarcoidosis or other types of parenchymal lung diseases.

The development of ICSs for asthma has gone from compounds with some water solubility towards more and more lipophilic substances, reaching claimed airway selectivity by their protracted intraluminal dissolution. However, clinical studies in patients with asthma and obstructive pulmonary disease (COPD) have shown the same efficacy with the less lipophilic, more watersoluble BUD, compared with e.g. the more lipophilic fluticasone propionate (FP). An explanation could be that BUD`s airway activity is prolonged by another mechanism; a BUD fraction is intracellularly, reversibly transformed into lipophilic BUD-oleate (12). Furthermore, the bulk of inhaled BUD is more rapidly disposed into systemic circulation, creating plasma peaks adding systemic anti-inflammatory activity which then includes peripheral airways and lung tissue (13). These alternative kinetic mechanisms are proposed to explain the theoretically unexpected similar efficacy of BUD compared with eg FP in asthma and COPD (14).

Summary of clinical studies with inhaled corticosteroids in pulmonary sarcoidosis

Clinical studies with inhaled budesonide

The first unexpected result was seen by one of us (OS) in the mid 1980'ies. It was a female patient with pulmonary sarcoidosis of stage II. Her sarcoidosis had been diagnosed six years earlier. She had previously been treated with two courses of oral CS, duration 15 months and 3 year and 9 months, respectively. After these courses her chest radiograph was almost normalized and lung function improved to values within the normal reference range. Now she suffered from a new relapse. A new course with oral CS was recommended but the patient refused the medication due to severe side-effects during previous courses. She also refused treatment with cytotoxic drugs. Treatment with inhaled BUD was initiated, 800 μg twice daily via a pressurized metered dose inhaler attached to a spacer. She tolerated the treatment well. The radiograph became gradually better and better. The dose was reduced to 400 μg twice daily and treatment could be discontinued after a total of 14 months therapy when the chest radiograph appeared normal and lung function as well. She was followed-up for five years without further relapses. Relapsing pulmonary sarcoidosis after treatment with oral corticosteroids does rarely improve spontaneously. Therefor it cannot be excluded that the therapeutic response observed in the abovementioned patient was the result of an effective treatment – inhaled BUD.

Consequently, three open studies were performed (15-17); one in 20 patients with stage II-III pulmonary sarcoidosis treated for 18 months (nine earlier treated with oral CS but not within 6 months prior to study) (15). Further details are given in Table 1. A gradual improvement in chest radiographs was noticed and a normalization of serum angiotensin converting enzyme (SACE). A second open study was performed in 12 patients with relapsing pulmonary sarcoidosis of the same type as in the first patient seen (16). Although not consistent some patient improved in an unexpected way. The third open study was also in 20 patients (17). Ten patients were treated with oral methylprednisolone for 8-12 weeks together with inhaled BUD, 800-1600 μg per day. BUD treatment continued for 18 months. Other 10 patients were treated with OCS throughout the study. No clinically important differences were seen between the groups.

The published studies with inhaled BUD are listed in Table 1 (15-25).

Alberts et al reported the results of a placebo-controlled study in 47 patients. Compared with placebo they found significant differences in favour of BUD for symptoms and inspiratory vital capacity (24).

Table 1. Studies with inhaled budesonide in sarcoidosis patients

Author, year (reference)	ICS	Type of study	Observation period	No of pats	Type of pats	Measurements	Outcome
Selroos, 1986 (15)	pMDI with tube spacer 600-800 μg bid 3-6 mo, thereafter reduction to 400 μg bid	Open	18 months	20	Chest X-ray stage II-III SACE above reference No CS treatment for 6 mo prior to study	Chest X-ray, spirometry, SACE Subjective symptoms	Chest X-ray: after 3,6,12 18 mo: unchanged 13,9,4,3 pts, slightly improved 4,9,6,4, markedly improved 2,2,7,5, deteriorated 1,0,0,2, normalized 0,0,3,6 pts. SACE significantly decreased at all time points. Increase in FVC but not stat significant
Selroos, 1987 (16)	pMDI with tube spacer 1200-2400 μg/ day	Open	1-27+ months	12 pts treated with OC: 5 pats one course (14-75 mo), 4 pats two courses (19-52 mo), 3 pats three courses (21-48 mo)	Previously treated patients with relapse and widespread pulmonary infiltrates	Chest X-ray, spirometry, DL_{CO} SACE, β_2-microglobulin, lysozyme ^{67}Ga uptake (n=3)	Chest X-ray: Deterioration 1 (changed to oral methylprednisolone), 3 unchanged after 6 mo, 6 pts improvement after 6-27+ mo, 2 pts almost normalization. Three patients have had OC added. ^{67}Ga uptake reduced
Morgan et al, 1987 (18)	pMDI 400 μg bid added to same or increased dose of OC	Open	4-26 months, follow-up 11-26 mo	10 pats with disease for >2 years	Parenchymal shadowing	Chest X-ray, spirometry, DL_{CO} SACE	Oral steroid sparing effect in 7/10 patients maintained over the follow-up time
Selroos, 1988 (17)	A.BUD 1600 μg/d + OC 8-16 weeks B. OC, 40-7.5 mg pred throughout the study	Matched controls	18 months	10+10 earlier untreated pats	Resp symptoms, parenchymal infiltrates, DL_{CO} <70% predicted, VC <75% predicted	Chest X-ray, spirometry, SACE	A.6/10 pats treated with BUD alone during maintenance phase. 4 pats received added OC B.5/10 pats treated according to plan. 5 pats received higher doses of OC Development of chest X-rays, VC and SACE was similar in the two groups
Bjermer et al, 1992 (19)	Oral prednisone 60-20 mg/every other day for 3 months. Thereafter A.BUD 1600 μg/d or B.Prednisone 20 mg/ every other day	Randomized, double-dummy after 3 mo run-in on OC	12 months	13 (6+7) The aim was to include 30 consecutive pats not using OC within 6 mo prior to study	Progressive, advanced disease, DL_{CO} <70%, VC <75% pred. BAL lymphocytosis >30%	Chest X-ray Spirometry, DL_{CO}	Three pats in group A discontinued the study, two had lung function and chest radiographic deterioration. "It needs to be clarified whether ICS should be used in higher doses or together with OC"

Table 1 (*Continued*)

Author, year (reference)	ICS	Type of study	Observation period	No of pats	Type of pats	Measurements	Outcome
Zych et al, 1993 (20)	For 6 weeks oral prednisone, 40-20 mg. Thereafter A.BUD 1600 µg/d via Nebuhaler B. 10 mg prednisone	Double-blind, double-dummy, randomized	12 months	20+20 previously untreated patients	Stage II-III pulmonary disease. No regression during 6 months after onset of disease	Chest X-ray, spirometry, SACE	In 10+10 pats regression of chest X-rays were seen during the initial 6-week phase. Thereafter the pictures remained unchanged. In 3 pats in group A and in 7 in group B improvement continued after 6 weeks. Four group A pats and 1 group B pat had progression to initial status during the follow-up. In one pat no change at all was seen Conclusion: ICS may be an alternative to oral steroids during follow-up
Selroos et al, 1994 (21)	8-week run-in on oral methylprednisolone 48-4 mg/day. From week 5 BUD pMDI 800 µg bid.	Open, prospective	18 months treatment. Thereafter 18 months follow-up without treatment	47 (31 stage II, 16 stage III) In 7 cases treatment started immediately after diagnosis. 40 patients had been followed for 6->12 months without signs of recoveries	Chest X-ray stage II-III SACE above reference No previous CS treatment	Chest X-ray, spirometry, DL_{CO} Serum ACE, lysozyme, β_2-microglobulin	Treatment could be discontinued after 18 months in 38/47 pats. 31/38 pats had been treated with BUD alone after run-in. 7 pats had received short courses of OC Chest X-ray: At 18 mo normal 21(1), improved 13(1), unchanged 4(4), deteriorated (3). Figures in brackets show ongoing treatment. Significant improvements in lung function tests.
Tolokh et al, 1994 (22)	6-week run-in on prednisone 40-20 mg. Thereafter oral prednisone 10 mg or BUD 1600 µg daily	Double-blind	12 months	36	Pats with stage II-III pulmonary sarcoidosis	Chest X-ray and spirometry, plasma cortisol	Cortisol levels suppressed in prednisone group, not in BUD group. No difference in lung function values. Chest X-ray and spirometry not reported
Milman et al, 1994 (23)	BUD pMDI via Nebuhaler 1200-2000 µg/d. Later during the study BUD Turbuhaler	Double-blind, randomized, placebo-controlled	12 months, 6 months follow-up	21 untreated pats in groups 1 and 2 8 pats in group 3 16 pats, group 4, Total 45 pats	Group 1. Stage I chest X-ray Group 2. Stage II Group 3. Pats using OC Group 4. Pats from groups 2 and 3 not fulfilling all inclusion criteria	Clinical symptoms, chest X-ray, spirometry, DL_{CO} Biochemical markers including SACE	No stat sign differences between BUD and placebo during treatment and follow-up. Regression in disease activity observed in both BUD and placebo groups (groups 1 and 2) Group 3: no sign differences in clinical variables. Doses of OC and tapering pattern identical. Group 4. Data not analysed.

Author, year (reference)	ICS	Type of study	Observation period	No of pats	Type of pats	Measurements	Outcome
Alberts et al, 1995 (24)	BUD pMDI via Nebuhaler 1200 µg/d	Double-blind, randomized, placebo-controlled	6 months, 6 months follow-up	47	Chest X-ray stages I-III IVC <79% pred normal, TL_{CO} <77% pred. Pats in stage II-III with normal lung function but with BAL lymphocytes >20%	Clinical symptoms (global clinical impression, GCI scale), chest X-ray, spirometry, DL_{CO} Serum ACE	GCI showed a stat sign difference in favour of BUD. IVC showed a sign difference during treatment with 7.9% predicted in favour of BUD. The diff remained during follow-up (9.4% pred). No stat sign differences were seen for development of chest X-rays or SACE. DL_{CO} remained unchanged during the study
Pietinalho et al, 1999 (11)	Oral prednisolone for 3 months (20-10 mg). Thereafter BUD 800 µg/bid via Turbuhaler or placebo	Double-blind, randomized, placebo-controlled, multicenter study	18 months	189	Newly diagnosed patients. Chest X-ray stages I-III Pats with erythema nodosum and pats with lung fibrosis (stage IV) excluded	Chest X-ray, spirometry, DL_{CO} SACE, β_2-microglobulin	No sign difference between the groups was seen in development of chest X-rays. After treatment for 18 months the difference in DL_{CO} was stat significant in favour of BUD treated pats. The biggest difference was seen in patients with initial FVC <80% predicted and DL_{CO} <75% predicted normal
Pietinalho et al, 2002 (25)	Follow-up of patients in study above	Open follow-up without treatment	5 years	149	See above	Yearly follow-ups with chest X-ray, spirometry, DL_{CO} SACE.	Of pats in original placebo group 30 (38%) treated with OC had remaining chest radiographic changes compared with 18 (26%) in BUD group. FVC and DL_{CO} sign higher in BUD treated pats ($p<0.05$ for both). Favourable results were restricted to pats with initial stage II-III findings. No diff in pats with radiographic stage I

Abbreviations: CS: corticosteroids; OC: oral corticosteroids; BUD: budesonide; TA: triamcinolone acetonide; BDP: beclomethasone dipropionate; bid: twice daily; SACE: serum angiotensin converting enzyme; ESR: erythrocyte sedimentation rate; FEV_1: forced expiratory volume in one second; FVC: forced vital capacity; IVC: inspiratory vital capacity; DL_{CO}: diffusions capacity for carbon monoxide; pts: patients; pMDI: pressurized metered dose inhaler; mo: months.

Zych et al performed a double-blind study in 40 patients receiving OCS during a 6-week run-in period (20). Thereafter patients were treated with inhaled BUD or OCS. Improvements were seen in both groups. The authors concluded that inhaled BUD may have a role in maintenance treatment of patients with pulmonary sarcoidosis.

The by far largest placebo-controlled study in more than 100 patients was published by Pietinalho et al (11). After initial treatment with OCS patients

were randomized to inhaled BUD or placebo. After 18 months therapy the difference in DL_{CO} was statistically significant in favour of BUD treated patients. The biggest difference was seen in patients with initial FVC <80% predicted and DL_{CO} <75% predicted normal. The patients were then followed with yearly controls up to 5 years (25). The authors noticed that patients initially randomized to treatment with BUD had significantly better lung function at the 5-year follow-up than placebo-treated patients.

Over all the results with inhaled BUD in pulmonary sarcoidosis are modest but nevertheless existing. Clinical studies with BUD, especially in patients with newly detected disease, have shown clinical efficacy compared with placebo. The most obvious results are seen in the studies starting with a run-in period with OCS for 3-6 months. The long-term maintenance therapy with BUD resulted in clinical improvements compared with placebo (11,25).

Some interesting Japanese case reports with beneficial outcome with BUD have also been published (26-28).

Clinical studies with inhaled corticosteroids other than budesonide

Clinical studies with other ICS than BUD are listed in Table 2 (29-34). Most of the studies are of pilot study type with a few patients.

Gupta (29) reported on experiences during 345 treatment episodes in 113 patients. In the groups of patients with beclomethasone dipropionate (BDP) alone – initial therapy or treatment of relapses – no objective effects were seen. Some effects were observed in the groups treated with BDP together with chloroquine and/or some nonsteroidal anti-inflammatory drug.

duBois et al (32) performed a double-blind, randomized, placebo-controlled study with inhaled fluticasone propionate (FP) in patients with chronic stable pulmonary disease. Approximately 75% of the patients were using OCS. No objective benefit was seen with the addition of FP to the treatment regimen.

Baughman et al (33) also studied FP in a double-blind, randomized, placebo-controlled study in a group of 21 patients on OCS. They monitored the doses of OCS and reported a tapering of OCS in 80% of the patients. They also noticed a reduction in local symptoms such as cough. No difference in changes in lung function was seen between FP and placebo-treated patients.

There are no randomized, placebo-controlled studies with other ICS than BUD in patients with newly detected sarcoidosis requiring treatment.

An interesting case report was published by Milman et al using inhaled BDP (35). The objective was to investigate changes in fluorodeoxyglucose PET scan (FDG-PET) in a patient with pulmonary sarcoidosis prior to and during treatment with ICS followed by systemic corticosteroids. The patient presented with stage I pulmonary sarcoidosis, which 19 months later had progressed to stage II. FDG-PET was performed at 19, 29 and 33 months after presentation. No treatment was given prior to the 1st PET. Subsequently, before the 2nd PET, the patient was treated with inhaled BDP 800 μg/day for eight months. Finally, prior to the 3rd PET, the patient was treated with oral prednisolone 30 mg/day for 3 months. The 1st PET showed a high FDG uptake in the hilar and mediastinal lymph nodes and a high focal uptake in the peripheral parts of the lungs. The 2nd PET showed a slight uptake in a few mediastinal lymph nodes and an unchanged high focal uptake in the peripheral parts of the lungs and the pleura. The 3rd PET showed no abnormal uptake at all. Treatment with oral prednisolone completely depressed the inflammatory activity. The treatment with BDP appeared to have a slight effect on hilar lymph nodes. No effect on parenchymal lesions may be due to a too low daily dose compared with the later dose of prednisolone and the type of inhaler used (QVAR Autohaler).

Effects of inhaled corticosteroids on bronchoalveolar cells

A few studies have investigated the influence of ICS on bronchoalveolar lavage (BAL) content. These studies are listed in Table 3 (34,36-39).

In open studies in small number of patients a reduction in total BAL lymphocyte counts and in T-helper/T-suppressor (T4/T8) cell ratios have been observed irrespective of ICS used (33,36-38).

In a placebo-controlled randomized study Erkkilä et al found reductions in BAL hyaluronan, BAL lymphocytes and T4/T8 ratio in BUD-treated group vs placebo (35). Spiteri et al (37) found a significant decrease in BAL lymphocytes in the BUD group, but not in the placebo group. A significant reduction in macrophages expressing RFD1+ and RFD1+D7+ was also observed in the BUD group.

Table 2. Studies with other ICS than budesonide in sarcoidosis patients

Author, year (reference)	ICS	Type of study	Observation period	No of pats	Type of pats	Measurements	Outcome
Gupta, 1989 (29)	BDP 800-1600 µg/d alone or with NSAID and/or chloroquin	Open, non-randomized	Varying, mostly 6-24 months	113 pats, 345 episodes (ep). A. 42 ep therapy BDP B. 25 ep BDP+NSAID and/or chloroquine C. 34 ep as group A D. 149 ep as group B	Biopsy-proven cases Groups A and B initial therapy; groups B and D treatment of relapses	Lessening of symptoms, lowering of ESR, SACE, hypercalcaemia, -calciuria, increase in VC, improvement in chest X-ray Good result was improvements in at least 4/6 variables	No obvious effect in groups A and C. In groups B and D one third of the patients showed objective improvements. Effects seen mainly on pulmonary lesions, not on extra pulmonary lesions
Tolokh, 1996 (30)	A) BDP 1500 µg/d, or BUD 1600 µg/d, B) prednisolone 40-20 mg/d	Open, non-randomized	6 months	70 pats; group A) 34 earlier untreated, ICS given to 20 pats. Group B) 36 pats had relapses (ICS +prednisolone group). ICS to 24 pats	Pulmonary stages II or III	Variables not mentioned	Improvement in 28 pats (78%) who received ICS; includes both group A and B Diff between BDP and BUD not reported
Niven, 1997 (31)	TA 1800 µg/d as induction therapy	Double-blind randomized, placebo controlled	24 months	11 pats	Earlier untreated	Changes in chest X-ray, DL_{CO} and subjective symptoms	Subj improvements in TA group vs placebo but change not stat sign. No effect on chest X-ray or DL_{CO}
du Bois, 1999 (32)	Fluticasone propionate (FP) 2 mg/d	Double-blind, randomized, placebo-controlled	6 months	44 pats with stable and controlled pulmonary sarcoidosis, appr 75% using OC	Diagnosed at least 1 year before the study	Spirometry and diffusion capacity Symptom scores and SF-36 (health perception assessment)	No objective benefit from FP
Baughman, 2002 (33)	Fluticasone propionate (FP) 880 µg twice daily	Double-blind randomized, placebo-controlled	48 weeks	21 pats	Pats who developed pulmonary lesions requiring treatment	Initial treatment at least 20 mg prednisone (P). Pats were seen every six week and the dose of P was adjusted by an algorithm Need of OC and cough was evaluated	Tapering of OC was followed in over 80% of visits. 8/10 pats on FP improved cough compared to 6/11 on placebo despite they were on OC.
Ludwig-Sengpiel 2005 (34)	BDP 800 µg/d extrafine aerosol	Open, parallell groups	6 months	15 (BDP 6, placebo 9)	Newly diagnosed stage II-III	Chest X-ray, DL_{CO} BAL	Chest X-ray suggested improvement in BDP pats. DL_{CO} improved ($p<0.05$) comp with baseline

Abbreviations: CS: corticosteroids; OC: oral corticosteroids; BUD: budesonide; TA: triamcinolone acetonide; BDP: beclomethasone dipropionate; bid: twice daily; SACE: serum angiotensin converting enzyme; ESR: erythrocyte sedimentation rate; FEV_1: forced expiratory volume in one second; FVC: forced vital capacity; IVC: inspiratory vital capacity; DL_{CO}: diffusions capacity for carbon monoxide; pts: patients; pMDI: pressurized metered dose inhaler; mo: months.

Table 3. Effects of inhaled corticosteroids on bronchoalveolar lavage (BAL) cells counts and proteins in sarcoidosis patients

Author, year (reference)	ICS	Type of study	Observation period	No of pats	Type of pats	Measurements	Outcome
Erkkilä, 1988 (36)	BUD pMDI 800 μg bid via large volume spacer	Double-blind, randomized, placebo-controlled	8-10 weeks	10 BUD 9 placebo	Untreated pats diagnosed <6 months before study.	BAL cell counts, lymphocytes subpopulations Chest X-ray, spirometry. Serum ACE, β_2-microglobulin BAL ACE, β_2-microglobulin, albumin, hyaluronan	No diff in changes in chest X-ray or spirometry. Sign decrease in serum ACE and β_2-M and BAL hyaluronan, BAL lymphocytes and T4/T8 ratio in BUD-treated group vs placebo
Petermann, 1988 (37)	BUD pMDI on average 368 mg during 9 months	Open	9 months	4 BUD 5 OC during 6 months	Treatment of relapse	BAL cell count, lymphocyte subpopulations	Decrease in total lymphocytes, T4-cells and T4/T8 ratio in both groups. "Tendency of normalization considerably slower" in BUD patients.
Spiteri, 1989 (38)	BUD pMDI 800 μg bid via large volume spacer	Open. Non-randomized, placebo-controlled	16 weeks	10 BUD 5 placebo 10 healthy volunteers	Biopsy-proven, earlier non-treated patients. Chest X-ray: parenchymal changes	BAL cell counts, lymphocytes, macrophages Chest X-ray, spirometry.	Sign decrease in BAL lymph in BUD group, not in placebo group. Sign reduction in macrophages expressing RFD1+ and RFD1+D7+ in BUD group
Alberts et al, 1991 (39)	BUD pMDI 1200 μg via large volume spacer	Open	6 months	7 10 healthy control subjects	Biopsy-proven, non-treated patients diagnosed within 1 year	BAL before treatment; repeated in 4 after treatment. BAL proteins analyzed	BAL lymphocytes 14-31% After treatment BAL albumin, IgG, IgM, IgA reduced to normal or almost normal levels
Ludwig-Sengpiel, 2005 (34)	BDP extrafine aerosol 400μg bid	Open,parallel groups, placebo-controlled	6 months	BDP 6 Placebo 9	Newly-diagnosed patients with stage I-III pulmonary lesions	BAL cell counts, cytokine production of lymphocytes. Serum ACE, β_2-M, lysozyme, neopterin Chest X-ray, spirometry, DL_{CO}	Sign decrease in BAL lymphocytes in BDP group, decrease in HLA-DR expression on BAL lymphocytes.

Abbreviations: CS: corticosteroids; OC: oral corticosteroids; BUD: budesonide; TA: triamcinolone acetonide; BDP: beclomethasone dipropionate; bid: twice daily; SACE: serum angiotensin converting enzyme; ESR: erythrocyte sedimentation rate; FEV_1: forced expiratory volume in one second; FVC: forced vital capacity; IVC: inspiratory vital capacity; DL_{CO}: diffusions capacity for carbon monoxide; pts: patients; pMDI: pressurized metered dose inhaler; mo: months.

It is not surprising that local therapy with ICS can influence the content of BAL. However, whether the effect is "the egg or the chicken" is not clear as the deposition of drug on the alveolar level is unknown.

Inhaled corticosteroids and extrapulmonary sarcoidosis

Extrapulmonary sarcoidosis is mostly associated with a chronic type of disease requiring treatment with oral corticosteroids and/or immunosuppressive drugs. Exceptions are lymph node enlargements, iritis/uveitis, arthritis and erythema nodosum which are common findings in the patients with acute/subacute sarcoidosis.

Effects of ICS on extrapulmonary sarcoidosis have not been addressed in controlled clinical studies. In individual patients with non-chronic pulmonary parenchymal manifestations and hilar lymphadenopathy the lymph node enlargement has diminished at the same time as the pulmonary infiltrates have resolved (11,15-17,21).

From a theoretical point of view the pulsatile peak of BUD, as previously described (13,14), seen after absorption from the airways, results in a systemic anti-inflammatory activity which could influence also extrapulmonary lesions in sarcoidosis. But, this effect of BUD is probably not strong enough to be clinically important.

Conclusion about effects of ICS in pulmonary sarcoidosis

As for other inflammatory/immunologic diseases corticosteroids do not cure sarcoidosis. But they suppress inflammatory activity in various organs, including airways, lung parenchyma, lymph nodes and bone marrow. The results of the performed clinical studies in patients with sarcoidosis show that ICS have some effect when used as maintenance therapy after induction with OCS for some weeks or months (e.g.11,25). This is a clinical situation where the inflammatory activity is believed to be low. The systemic effect after inhalation of BUD is probably high enough to keep the inflammation under control.

The other clinical situation where effect of ICS has been shown is treatment of relapses. Relapses are difficult to define and there is little evidence about what predict what is called a relapse (40). The relationship between corticosteroid therapy and relapses is also unclear (41). However, a clinical deterioration after stopping treatment is usually called a relapse and there is some evidence that spontaneous recoveries do rarely occur in this situation. It has also been suggested that CS do not at all influence the course of sarcoidosis. Corticosteroids suppress the inflammation but the disease continues irrespective of treatment until the driving force has ceased (42). When treatment is discontinued the disease goes back to the stage it would have had without "therapeutic" intervention. This could be why ICSs sometime result in anti-inflammatory efficacy high enough to suppress the actual or remaining inflammation.

In patients on treatment with OCS the addition of an ICS has shown oral steroid sparing capacity (17,33).

Proposed mechanism for budesonide's efficacy in pulmonary sarcoidosis

Compared with more lipophilic ICSs, BUD exhibits a more rapid systemic uptake due to its lower lipophilicity and higher water solubility. Figure 1 shows the different plasma profiles in patients and healthy subjects inhaling a single dose of BUD/formoterol 400 μg/12μg (Turbuhaler) or FP/salmeterol 500/50 μg (Diskus), where the former formulation rapidly leads to a high but brief plasma peak of 1 nmol/L BUD while the latter gives a 10-fold lower but steady FP level (13). A BUD concentration of 1 nmol/L is close to its ED50 to saturate the glucocorticoid receptor in vitro (43). The peak duration is long enough to trigger at least some anti-inflammatory effects (44,45).

An early in vitro study with an isolated, perfused and ventilated rat lung model showed that higher concentrations of BUD could be seen in the lung parenchyma after instillation of BUD than after an intravenous injection (46). This was an interesting observation asking for studies in man.

Van den Bosch et al gave a single dose of 1600 μg BUD to 10 patients immediately before thoracic surgery for lung cancer (47). As soon as possible a peripheral specimen of lung tissue was removed and analysed for its content of BUD. Plasma samples were obtained at the same time. The BUD concentration

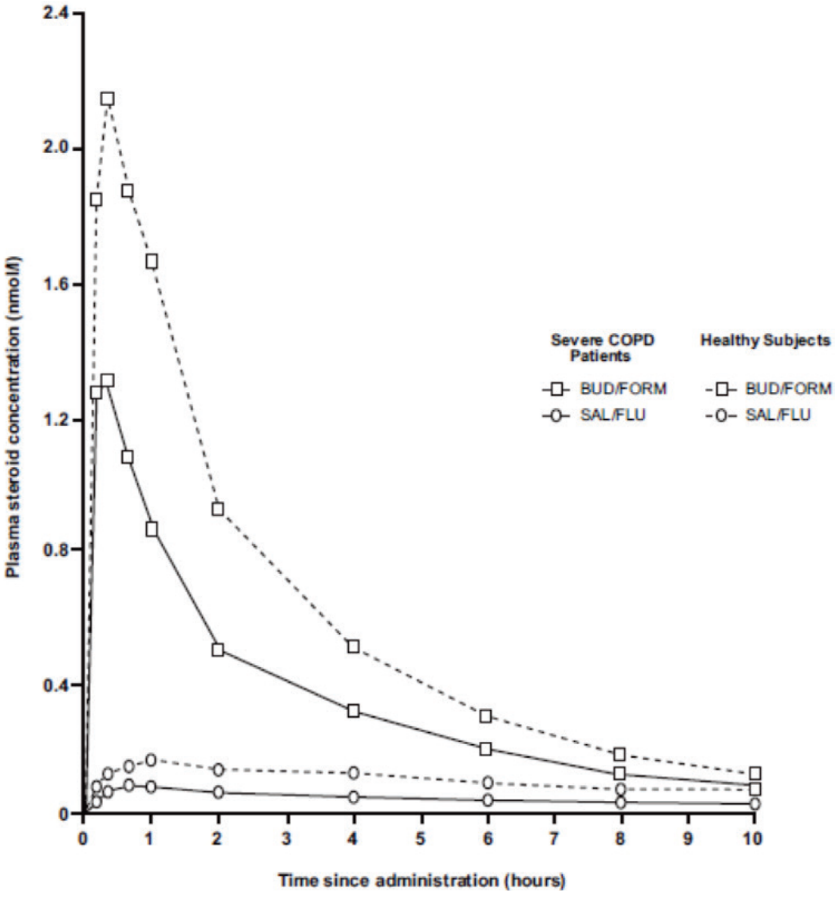

Figure 1. Plasma levels in COPD-patients and healthy subjects inhaling a single dose of budesonide/formoterol Turbuhaler (400/12μg) or fluticasone propionate/salmeterol Diskus (500/50μg) (13). Reprinted with permission from Creative Common Licence Deed.

was eight to 10 times higher in lung tissue than in plasma and high enough to permit good binding to the glucocorticoid receptors.

Maassen van den Brink et al also collected lung and tissue samples for analyses of patients inhaling 1000 μg BUD or FP before lung cancer operations (48). Lung tissue samples were obtained from 22 patients at surgery, 1–43 hours after drug dosing. BUD was detectable from earliest sampling in central and peripheral lung tissue up to 10 h, but BUD oleate for almost two days after inhalation (in 21 of 22 samples). The highest levels of free BUD were 17 and 4 nmol/L at central and peripheral lung tissue respectively, 1 nmol/L in plasma and 3 nmol/L in intercostal muscle (the latter representing systemic tissue compartment). FP reached higher lung levels, 87 in central and 19 nmol/L in peripheral lung tissue, while the systemic levels were much lower (plasma 0.1 nmol/L, intercostal muscle under detection limit). This together with very high bronchial brush levels suggest that the high FP lung levels largely represent microcrystals with a risk to be swept away by mucociliary clearance. These results suggest that BUD, compared with the more lipophilic FP, appears to have a combined local and systemic efficacy profile in patients with airway diseases and probably also in patients with parenchymal lung diseases. However, the presence of FP in lung tissue could be the result of undissolved drug in the airway lumen not accessible to intracellular glucocorticoid receptors.

The difference in kinetics between BUD and FP is also reflected in the difference in risk of systemic side-effects. The high peak concentration of BUD is short and causes less side-effects than FP with persistent higher systemic concentrations over time. The difference in risk of side-effects has been

well documented in comparative clinical studies in patients with asthma or COPD (14).

Clinical prospects of inhaled corticosteroids's efficacy in pulmonary sarcoidosis

Based on the published clinical studies with inhaled BUD in patients with pulmonary sarcoidosis it appears that clinical efficacy can be demonstrable, particularly during long-term maintenance therapy after a run-in period on OCS (11,20,21,25). This was especially true for patients with disease treated within 6-12 months after diagnosis (11,25).

The pharmacokinetic studies in patients undergoing lung surgery have given some information about how BUD might function in patients with pulmonary parenchymal disease. A comparison with airway diseases, such as asthma, is here of interest. After inhalation, patients reach BUD lung tissue concentrations high enough to be of clinical importance (47,48). In patients with pulmonary sarcoidosis inhalation of BUD has shown wanted effects on BAL cellularity and biochemical markers of disease activity (36,38). Similar results were seen in studies with extra fine aerosol of BDP (34,49), leading to faster dissolution and formation of the active metabolite (beclomethasone monopropionate) having similar kinetic properties as BUD.

It thus appears that the less lipophilic BUD can reach lung and blood concentrations high enough for supportive anti-inflammatory actions. Importantly, this is not coupled to concomitant systemic adverse risks as BUD by its lower lipophilicity may exploit a differentiation mechanism programmed for cortisol´s various actions (14). This differentiation prospect can be reached only for ICSs with short plasma half-life. However, further basic pharmacologic and kinetic studies are necessary to define the physicochemical structure which may give an optimal difference between ICS`s lung parenchymal and their systemic adverse effects. Such a substance could replace or reduce OCS in the treatment of pulmonary parenchymal sarcoidosis.

Future research that might shed further light on these issues would include studies of extracellular and intracellular distribution of inhaled corticosteroids and their metabolites or conjugates, together with further study of central and peripheral lung deposition.

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