Treatment of hypersensitivity pneumonitis: Contact avoidance versus corticosteroid treatment

YVON CORMIER MD, MARC DESMEULES MD

Unité de Recherche, Centre de pneumologie, Hôpital et Université Laval, Québec

Y CORMIER, M DESMEULES. Treatment of hypersensitivity pneumonitis: Comparison of contact avoidance with corticosteroid treatment. *Can Respir J* 1994;1(4):223-228.

OBJECTIVE: To compare the early response to oral corticosteroid treatment with contact avoidance in patients with acute hypersensitivity pneumonitis.

DESIGN: Prospective evaluation of patients with hypersensitivity pneumonitis, who chose either contact avoidance or low dose corticosteroid treatment.

STUDY POPULATION: Twenty-eight patients with acute hypersensitivity pneumonitis.

INTERVENTIONS: Each subject had a clinical evaluation, chest radiographs, lung function measurements and a bronchoalveolar lavage at diagnosis and after one month of either form of treatment (contact avoidance or oral prednisone 20 mg daily).

RESULTS: Nineteen subjects (all with farmer's lung) chose the corticosteroid arm and nine chose the contact avoidance arm (three farmer's lung, four humidifier lung and two bird fancier's lung). Initially subjects in both groups had similar disease severity (single breath carbon dioxide diffusion capacity [DLCO] 61.4 ± 3.9 and $60.7 \pm 18.9\%$ predicted, respectively [mean $\pm$ SD], total bronchoalveolar lavage cells 101×10^6 versus 119×10^6). All subjects improved with either treatment, and 10 subjects considered themselves back to normal. DLCO increased from the above values to 74.6 ± 21.9 and 77.1 ± 18.5 , respectively. Bronchoalveolar lavage lymphocytosis remained unchanged after one month of either treatment.

CONCLUSIONS: Both low dose oral corticosteroids and contact avoidance provided adequate initial treatment of acute hypersensitivity pneumonitis. Bronchoalveolar lavage cellular findings remained abnormal despite clinical improvement; this technique did not provide useful clinical information in the follow-up of hypersensitivity pneumonitis.

Key Words: *Bronchoalveolar lavage, Farmer's lung, Hypersensitivity pneumonitis, Interstitial lung disease*

Traitement de la pneumopathie d'hypersensibilité : Comparaison de la suppression de l'exposition avec la corticothérapie

OBJECTIF : Comparer la réponse initiale d'une corticothérapie par voie orale à celle d'une suppression de l'exposition à l'antigène chez des patients souffrant d'une pneumopathie d'hypersensibilité aiguë.

MODÈLE : Évaluation prospective de patients souffrant d'une pneumopathie d'hypersensibilité qui ont choisi, soit de ne plus s'exposer à l'antigène, soit de suivre un traitement par corticostéroïdes à faibles doses.

POPULATION À L'ÉTUDE : Vingt-huit patients souffrant d'une pneumopathie d'hypersensibilité.

INTERVENTIONS : Chaque sujet a subi une évaluation clinique, des radiographies pulmonaires, des épreuves de fonction respiratoire et un lavage broncho-alvéolaire au moment du diagnostic et 1 mois après l'une ou l'autre forme de traitement (suppression de l'exposition ou 20 mg/jour de prednisone par voie orale).

RÉSULTATS : Dix-neuf sujets (tous atteints du poumon du fermier) ont choisi l'aide des corticostéroïdes et 9 sujets ont choisi d'éviter l'exposition (trois atteints du poumon du fermier, quatre de la maladie des humidificateurs et deux de la maladie des éleveurs d'oiseaux). Initialement, la gravité de la maladie était la même pour les sujets des deux groupes (capacité de diffusion du monoxyde de carbone par la méthode en apnée [$TLCO_{sb}$] $61,4 \pm 3,9\%$ et $60,7 \pm 18,9\%$ de la valeur théorique, respectivement [moyenne $\pm$ écart-type], et nombre total des cellules dans le lavage broncho-alvéolaire 101×10^6 cellules contre 119×10^6 cellules). L'état des sujets s'est amélioré avec chacun des traitements, et 10 sujets ont considéré que leur état était redevenu normal. La $TLCO_{sb}$ comparativement aux valeurs antérieures était respectivement de $74,6 \pm 21,9\%$ et $77,1 \pm 18,5\%$. La lymphocytose dans le lavage broncho-alvéolaire est restée inchangée après un mois de l'un ou l'autre des traitements.

CONCLUSION : Les corticostéroïdes administrés oralement à faibles doses et la suppression de l'exposition sont tous deux des traitements initiaux adéquats de la pneumopathie d'hypersensibilité. Les résultats de l'analyse du lavage broncho-alvéolaire restaient anormaux malgré une amélioration clinique : cette technique n'a pas fourni d'informations cliniques utiles pour le suivi de la pneumopathie d'hypersensibilité.

Correspondence and reprints: Dr Yvon Cormier, Hôpital Laval, 2725 Chemin Ste Foy, Ste Foy, Québec G1V 4G5. Telephone (418) 656-4747, Fax (418) 656-4762

HYPERSENSITIVITY PNEUMONITIS IS A DELAYED-TYPE allergic reaction of the lungs in response to the inhalation of a variety of foreign particles, usually organic in nature (1). Acutely, the disease manifests itself by a febrile reaction accompanied by dyspnea, cough and chest tightness (2,3). These symptoms usually occur 3 to 8 h after contact with the offending allergen and subside over the next 24 to 48 h if contact is avoided. When possible, contact avoidance is the obvious treatment of choice for hypersensitivity pneumonitis. However, when the contact cannot be avoided the acute manifestations can be controlled by systemic administration of corticosteroids. Although steroids control acute manifestations, their use does not modify the long term outcome of the disease (4,5). It is our current practice to suggest contact avoidance as the initial treatment of hypersensitivity pneumonitis and, when this is not feasible, we administer short courses of oral corticosteroids to control the disease. It is not known which of these two approaches gives the best initial response, nor their effects on lung cells as assessed by bronchoalveolar lavage (BAL). The present study was done to compare the short term effect of these two forms of treatment on the initial clinical, functional, radiological and BAL cell recovery in acute hypersensitivity pneumonitis. The results show that relatively small daily doses of oral corticosteroids are as effective as contact avoidance in controlling acute disease. However, a marked bronchoalveolar lymphocytosis persists after one month of either form of treatment.

PATIENTS AND METHODS

The study population included 28 cases of acute hypersensitivity pneumonitis of whom 22 had farmer's lung, four had humidifier lung and two had bird fancier's lung. There were 23 males and five females aged 42 ± 12 years (mean $\pm$ SD), range 24 to 67. Of the five females, two were in the prednisone group and three were in the contact avoidance group. Mean ages were similar for each group: prednisone 40 ± 11 years and noncontact 47 ± 13 years. Twenty-six patients were nonsmokers and two were ex-smokers (longer than one year). The diagnosis was based on clinical, radiological, functional, BAL and serological criteria (6). Since some of these subjects could not avoid contact (usually farmers) they were not randomized into either arm of the study. All subjects were encouraged to avoid contact as the only form of initial treatment. Subjects

who could not avoid the offending environment (19 subjects in this study) were given oral corticosteroids (20 mg of prednisone daily for one month); those who could cease contact received no other form of treatment ($n=9$).

All subjects were studied twice: at diagnosis and at the end of one month of either contact avoidance or corticosteroid treatment. At each visit all subjects had a clinical history and physical examination, lung function measurements, posteroanterior and lateral chest films and BAL. Both lung function tests were measured in the same laboratory on the same pulmonary function equipment. Tests obtained included: lung volumes by body plethysmography, forced expiratory flows and single breath carbon dioxide diffusion capacity (DLCO). Results are reported as a percentage of predicted values (7,8). All chest films were read blindly by one of the authors who is a certified B reader. Films were scored as previously described (9). Briefly, lung fields were subdivided into six regions: upper, middle and lower for each lung. Each of these regions was given a score of 0 to 4 for the presence and intensity of infiltrates. With this system, normal lungs have a score of 0 while a score of 24 signifies marked diffuse infiltrates throughout both lung fields. The BAL was done with 300 mL of sterile normal saline injected in six 50 mL aliquots, each instillation followed by gentle aspiration. The lavage fluid was kept on ice until centrifugation on cytopsin. Cells were counted by Diff Quik (Baxter) and differentials obtained on Giemsa and esterase stained preparations.

Statistical analysis: Data were analyzed using the statistical package SAS (SAS Institute Inc, North Carolina). Results were expressed as mean $\pm$ SD for pulmonary function and as mean $\pm$ SEM for the graphical representation of BAL cells. Original data from the BAL cell analysis were transformed into ranks. Thus, for each variable, the observations were replaced by their ranks because no variance stabilizing transformation was encountered. Data from pulmonary functions were compared using an analysis of covariance on transformed values where the concomitant variables are the initial values as they were correlated with their respective changes. The square root of each proportion was transformed to its arcsine. Thus, the resultant data have an underlying distribution that is normal. All reported P values are two-tailed and were considered significant if they were less than 0.05.

TABLE 1

Results of pulmonary functions at diagnosis (initial) and at one month follow-up (mean $\pm$ SD) for subjects treated with oral corticosteroids (prednisone) or by contact avoidance

	TLC	RV	FVC	FEV ₁	DLCO
Prednisone group					
Initial	95.0 $\pm$ 14.6	146.0 $\pm$ 51.5	73.4 $\pm$ 13.1	72.7 $\pm$ 15.9	61.4 $\pm$ 17.1
Follow-up	99.1 $\pm$ 15.8	136.7 $\pm$ 43.6	82.6 $\pm$ 12.9	80.2 $\pm$ 14.5	74.9 $\pm$ 21.3
Avoidance group					
Initial	99.8 $\pm$ 18.9	134.4 $\pm$ 66.2	80.0 $\pm$ 24.4	81.4 $\pm$ 22.9	60.7 $\pm$ 18.9
Follow-up	99.2 $\pm$ 16.6	114.7 $\pm$ 55.1	94.9 $\pm$ 11.1	97.4 $\pm$ 7.1	76.6 $\pm$ 19.5

DLCO Single breath carbon dioxide diffusion capacity; FEV₁ Forced expiratory volume in 1 s; FVC Forced vital capacity; RV Respiratory volume; TLC Total lung capacity

Figure 1) Individual results and means $\pm$ SD for subjects of both treatment groups at diagnosis and one month later. Lung diffusion capacity (DLCO) increased in most subjects and the mean increase was similar for both groups. Prednisone group $P=0.0002$; contact avoidance (off contact) group $P=0.04$

RESULTS

Nineteen subjects received corticosteroid treatment and continued their work on the farm while the remaining nine were treated by contact avoidance only. Subjects in both groups were of similar age, one ex-smoker was in each treatment group, and of the five females, three were in the contact avoidance group and two were in the prednisone group. All subjects improved with either form of treatment and all subjects reported an improvement in their dyspnea. After one month, 10 patients reported that they were now back to normal and no longer dyspneic; five were in the contact avoidance group and five were in the corticosteroid treatment group. All fever and malaise resolved by the second visit. At diagnosis, inspiratory crackles were heard in 24 subjects; after one month these physical signs had disappeared in 17 (10 in the corticosteroid treated group, seven in the contact avoidance group). Results of pulmonary functions at diagnosis and at follow-up are presented in Table 1. Both groups were initially similar. Lung function improved in most subjects with either treatment. DLCO was the lung function parameter that was initially most abnormal. It significantly improved in each group. Figure 1 shows individual changes in DLCO for all subjects who were treated with prednisone and seven of the nine who ceased contact. Follow-up data for this parameter were not available in two subjects. Forced expiratory volume in 1 s (FEV₁) and forced vital capacity (FVC) also significantly improved in the prednisone group ($P=0.004$ and 0.0008 , respectively). The improvement in these parameters for the contact avoidance

Figure 2) Mean $\pm$ SEM data for the total cells and differentials recovered by bronchoalveolar lavage for each group of subjects and both at diagnosis and after one month of treatment with either corticosteroids (Prednisone) or contact avoidance (Off Contact). Both groups were initially similar and the only cell type that significantly changed was the neutrophils in the contact avoidance group. *To obtain total cells, multiply the graphed values by 10^6 . AM Alveolar macrophages; Ly Lymphocytes; N Neutrophils

group did not reach statistical significance (each $P=0.08$). This lack of significance probably relates to the smaller number of subjects in this group. Total lung capacity and

Figure 3) Individual and mean $\pm$ SEM percentage lymphocytes in the lavage fluid for both groups of subjects at diagnosis and after one month of treatment. Note the similarity in both groups and the relative lack of changes in these cells after one month

Figure 4) Mean $\pm$ SEM chest radiograph (XR) scores before and after treatment for the prednisone treated group (P1 and P2) and the contact avoidance group (off 1 and off 2). Chest radiograph infiltrations improved in both groups

residual volume were not significantly changed by either treatment.

A similarity was seen in both groups for the BAL cells (total, lymphocytes and alveolar macrophages) (Figure 2). However, neutrophils were higher in the contact avoidance group. Repeat BAL showed a mild decrease in BAL cells after one month, similar in those who had received prednisone and in those treated by contact avoidance only (Figure

2). Again, the only BAL cell that differed was the neutrophil, with a significant decrease in the contact avoidance group but no changes in the corticosteroid treatment group. Individual values for the percentage of lymphocytes at diagnosis and at follow-up for each group are shown in Figure 3. These cells were not significantly different one month after treatment from the initial values. The percentage BAL fluid return was similar for both study groups at the first ($50 \pm 12\%$ for the prednisone group and $50 \pm 13\%$ for the contact avoidance group) and at the follow-up studies ($57 \pm 11\%$ versus $55 \pm 15\%$, respectively); this difference was not statistically significant ($P=0.07$).

Chest films at diagnosis and at one month follow-up were available for review in 22 subjects. Initial radiographic scores were similar in both groups. One month later scores had decreased significantly and remained similar in both groups (Figure 4). The only correlation between variables was between lung diffusion capacity and chest radiographic (CXR) score at diagnosis ($P=0.0014$) (Figure 5). There were no correlations between any of the BAL cells parameters and lung function or CXR scores at either diagnosis or at one month follow-up, whether tested for the group as a whole or for the two groups separately.

DISCUSSION

The present study shows that relatively small doses of corticosteroids and contact avoidance are both effective in the initial treatment of acute hypersensitivity pneumonitis. Although all subjects improved by either treatment and some had actually returned to normal, BAL, after one month of corticosteroids or contact avoidance, was still markedly abnormal, with a persisting lymphocytic alveolitis. Although

side effects were minimal, one would obviously recommend contact avoidance when possible; however, in certain cases, especially farmers, contact avoidance was often socio-economically impractical. In such circumstances, corticosteroid treatment seems to be a valid alternative. The often quoted recommended daily dose of corticosteroids in the treatment of acute hypersensitivity pneumonitis is higher than the 20 mg per day given in this study (5); in one review the dose is not specified (10). We have not compared the relative effects of two doses of corticosteroids on outcome. However, since 20 mg daily gives a similar improvement in most of the clinical parameters evaluated as contact avoidance (all subjects who continued contact had no recurrence of acute febrile symptoms and noted improvement in their clinical condition), we believe it is reasonable to treat this disease with lower doses rather than higher. This may be especially relevant since farmers often require corticosteroids for up to six months every winter that their disease flairs up. Another way to decrease further the potential effects of long term corticosteroid therapy may be to give the drug on alternate days (11) or eventually use targeted delivery methods (12).

We do not know whether the long term outcome would differ between the two groups. Based on previous studies it is very unlikely that either form of initial treatment would significantly modify outcome; corticosteroids do not improve long term outcome (4,5). A long term outcome study is impossible for our group of subjects. Most of those who chose to cease contact have done so on a permanent basis and their outcome may be different because of that decision, not because of the initial treatment. Farmers who stayed on the farm are for the most part still in contact and may have had or may eventually have recurrences, either acute or subacute in nature.

Subjects were not randomized into either treatment arm for reasons already discussed. The groups, although unequal in number and in the proportion of farmer's lung, were similar in terms of all clinical parameters compared. Therefore, we believe that selection bias was not responsible for the relatively small differences in the outcome of each group.

An interesting observation in this study is the persistence of a high intensity lymphocytic alveolitis after one month, despite the marked clinical, functional and radiological improvement. Since the percentages of lymphocytes were similar in both studies, we do not believe that the higher BAL fluid return was responsible for this finding. This finding corroborates our previous studies showing that BAL lymphocytosis persists in farmers with a history of farmer's lung, especially those who stay on the farm and in asymptomatic seropositive farmers (13). Perhaps variables other than the number of lymphocytes in the BAL can differentiate the two (14-16).

One significant difference between the two groups both at diagnosis and especially in response to the treatment arm was the level of neutrophils in the BAL fluid. The initial higher number of these cells could be explained by the fact that all cases of humidifier lung and bird fancier's lung were in this group. Perhaps they were more acutely in contact with the

Figure 5 Correlation between chest radiograph (XR) score and carbon dioxide lung diffusion capacity (DLCO) at diagnosis for all subjects of both groups ($P=0.0014$)

offending environment. The acuteness of hypersensitivity pneumonitis is associated with BAL neutrophilia (17). The persistence of relatively high numbers of neutrophils after one month of steroid treatment was surprising, however, especially since all of these subjects were clinically improved and since these cells returned to normal values in the off contact group. Two hypotheses to explain this finding are that continued exposure contributed towards maintaining the neutrophilia or that corticosteroids were responsible for this finding. Corticosteroids are known to increase blood leukocytosis by demarginating these cells. A similar mechanism may take place in the lungs.

CONCLUSIONS

Although BAL findings remain abnormal, both contact avoidance and low dose corticosteroids are effective in controlling symptoms and improving lung function in acute hypersensitivity pneumonitis. Contact avoidance remains the obvious treatment when feasible. Based on the marked improvement in our patients in either arm of this study, it is unlikely that higher doses of corticosteroids or the addition of corticosteroids in subjects who cease contact would significantly add to the initial treatment of the disease.

REFERENCES

1. Cormier Y, Schuyler M. Hypersensitivity pneumonitis. In: Bone RC, ed. Textbook of Pulmonary Medicine, Vol 2 Part M: Interstitial Lung Disease. St Louis: Mosby Year Book, 1992:1-9.
2. Fink JN. Clinical features of hypersensitivity pneumonitis. *Chest* 1986;89:193S-5S.
3. Richerson HB, Bernstein IL, Fink JN, et al. Guidelines for the clinical evaluation of hypersensitivity pneumonitis. *J Allergy Clin Immunol* 1989;84:839-44.
4. Kokkarinen JI, Tukiainen HO, Terho EO. Effect of corticosteroid treatment on the recovery of pulmonary function in farmer's lung. *Am Rev Respir Dis* 1992;145:3-5.
5. Mönkäre S, Haahtela T. Farmer's lung - a 5-year follow-up of eighty-six patients. *Clin Allergy* 1987;17:143-51.
6. Chemlik F, Dolico G, Reed CE, Dickie H. Farmer's lung. *J Allergy Clin Immunol* 1975;54:180-8.
7. Cotes JE, Hall M. The transfer factor for the lung, normal

- values in adults. In: Arcangeli P, ed. *Normal Values For Respiratory Functions in Man*. Torino: Pan Minerva Medica 1970;327-43.
8. Grimby G, Söderholm B. Spirometric studies in normal subjects. III. Static lung volumes and maximum voluntary ventilation in adults with a note on physical fitness. *Acta Med Scand* 1963;173:199-206.
 9. Cormier Y, Bélanger J, Tardif A, Leblanc P, Laviolette M. Relationship between radiographic changes, pulmonary function, and bronchoalveolar lavage fluid lymphocytes in farmer's lung disease. *Thorax* 1986;41:28-33.
 10. Fink JN. Hypersensitivity pneumonitis. *J Allergy Clin Immunol* 1984;74:1-9.
 11. MacGregor RR, Sheagren JN, Lipsett MD, Wolff SM. Alternate day prednisone therapy. Evaluation of delayed hypersensitivity response, control of disease and steroid side effects. *N Engl J Med* 1969;280:1427-31.
 12. Tremblay GM, Térien M-H, Assayag E, Cormier Y. Liposomal dexamethasone effectiveness in the treatment of hypersensitivity pneumonitis in mice. *Eur J Clin Invest* 1993;23:656-61.
 13. Leblanc P, Bélanger J, Laviolette M, Cormier Y. Farmer's lung disease: relationship between continued exposure, alveolitis, and clinical status. *Arch Intern Med* 1986;146:153-7.
 14. Jouanel P, Motta C, Brun J, et al. Phospholipids and microviscosity in broncho-alveolar lavage fluid from control subjects and from patients with extrinsic allergic alveolitis. *Clin Chimica Acta* 1981;115:211-21.
 15. Larsson K, Eklund A, Malmberg P, Björmer L, Lundgren R, Belin L. Hyaluronic acid (hyaluronan) in BAL fluid distinguishes farmers with allergic alveolitis from those with asymptomatic alveolitis. *Chest* 1992;101:109-14.
 16. Trentin L, Marcer G, Chilosi M, et al. Longitudinal study of alveolitis in hypersensitivity pneumonitis patients: an immunologic evaluation. *J Allergy Clin Immunol* 1988;82:577-85.
 17. Fournier E, Tonnel AB, Gosset Ph, et al. Early neutrophil alveolitis after antigen inhalation in hypersensitivity pneumonitis. *Chest* 1985;88:563-6.