Adjunctive corticosteroid therapy decreases lung permeability in patients with AIDS-related *Pneumocystis carinii* pneumonia

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OBJECTIVE: To assess the effect of adjunctive corticosteroid therapy on lung permeability as measured by Tc-DTPA lung clearance scan in patients with AIDS-related *Pneumocystis carinii* pneumonia (PCP).

METHODS: Sixteen patients with microbiologically proven AIDS-related PCP were prospectively studied using sequential Tc-DTPA lung clearance scan. All patients received standard antimicrobial treatment. Six patients received adjunctive oral corticosteroids in addition to the usual antimicrobial therapy. Tc-DTPA lung clearance scan was performed at baseline and during the second week of therapy. All scans were read by a blinded single observer using a standardized protocol.

RESULTS: Baseline Tc-DTPA lung clearance half time ($T_{\frac{1}{2}}$) was 12±2 and 9±1 mins in the noncorticosteroid and corticosteroid treated groups, respectively. During the second week of therapy, Tc-DTPA $T_{\frac{1}{2}}$ lung clearance was 17±8 and 24±9 mins for the noncorticosteroid and corticosteroid treated groups, respectively. The change in Tc-DTPA lung clearance between baseline and week 2 was significantly greater ($P<0.02$) in the corticosteroid treated patients.

CONCLUSION: Data suggest that the use of adjunctive corticosteroid therapy decreases lung permeability, as measured by Tc-DTPA lung clearance scan, in patients with AIDS-related PCP. *(Pour résumé, voir page 56)*

Key Words: *AIDS, Corticosteroids,* Pneumocystis carinii *pneumonia, Tc-DTPA lung clearance scan*

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Une thérapie adjuvante aux corticostéroïdes diminue la perméabilité pulmonaire chez les patients atteints d'une pneumonie à *Pneumocystis carinii* liée au SIDA

OBJECTIF : Évaluer l'effet d'une thérapie adjuvante aux corticostéroïdes sur la perméabilité pulmonaire mesurée par scintigraphie de la clairance respiratoire du DTPA marqué au Technetium (Tc-DTPA) chez des patients atteints d'une pneumonie à *Pneumocystis carinii* (PPC) liée au SIDA.

MÉTHODES : Seize patients atteints de PPC liée au SIDA démontrée par un examen microbiologique ont fait l'objet d'une étude prospective à l'aide d'une scintigraphie séquentielle de la clairance respiratoire du Tc-DTPA. Tous les patients ont reçu un traitement antimicrobien usuel. Six patients ont reçu un traitement adjuvant aux corticostéroïdes par voie orale en plus du traitement antimicrobien usuel. Une scintigraphie initiale de base de la clairance respiratoire du Tc-DTPA a été pratiquée puis une autre au cours de la deuxième semaine de traitement. Toutes les scintigraphies ont été interprétées en aveugle par un seul observateur suivant un protocole standardisé.

RÉSULTATS : La demi-vie ($T_{\frac{1}{2}}$) de la clairance respiratoire du Tc-DTPA de base était respectivement de 12±2 et de 9±1 minutes chez les patients non traités aux corticostéroïdes et chez ceux traités aux corticostéroïdes. Au cours de la deuxième semaine de traitement, la $T_{\frac{1}{2}}$ de la clairance respiratoire du Tc-DTPA était respectivement de 17±8 et de 24±9 minutes chez les patients non traités aux corticostéroïdes et chez ceux traités aux corticostéroïdes. Le changement dans la clairance respiratoire du Tc-DTPA entre la première scintigraphie et celle pratiquée au cours de la deuxième semaine était nettement plus important ($P<0,02$) chez les patients traités aux corticostéroïdes.

CONCLUSIONS : Ces résultats laissent supposer qu'un traitement adjuvant aux corticostéroïdes diminue la perméabilité pulmonaire mesurée par scintigraphie de la clairance respiratoire du Tc-DTPA chez les patients atteints de PPC liée au SIDA.

THE ROLE OF ADJUNCTIVE CORTICOSTEROIDS IN THE CONtext of AIDS-related *Pneumocystis carinii* pneumonia (PCP) has been the focus of a number of clinical trials over the past several years (1-5). A number of reports have documented a decrease in mortality among patients with severe AIDS-related PCP when adjunctive corticosteroids are used (1-3). Furthermore, significant benefits in oxygenation and exercise tolerance have been demonstrated with the use of adjunctive corticosteroids in patients with mild and moderate AIDS-related PCP (4,5). This has led to the recommendation that adjunctive corticosteroids be routinely used in patients with moderate to severe AIDS-related PCP (6).

Despite the unequivocal clinical benefit of adjunctive corticosteroid use in this context, the ultimate mechanism responsible for this effect is not known (1-6). It has been widely speculated, however, that corticosteroids decrease the alveolar inflammation associated with active PCP, and this would in turn reduce lung permeability leading to improved gas exchange, exercise tolerance and ultimately survival (5,7). Although attractive, this remains an untested hypothesis.

Technetium diethylene triamine pentaacetate (Tc-DTPA) clearance scan has been used to estimate lung permeability in a variety of settings (8-10). Recently, Tc-DTPA lung clearance has been found to be significantly increased in patients with AIDS-related PCP as a nonspecific marker of alveolar inflammation and associated increased permeability (11-14). In fact, Tc-DTPA lung clearance scan has been used in some centres, including ours, as an alternative to the gallium lung scan in the diagnostic work-up of human immunodeficiency virus (HIV) infected individuals presenting with respiratory symptoms (15).

We therefore conducted the present study to assess the effects of adjunctive corticosteroids on lung permeability as measured by Tc-DTPA lung clearance scan.

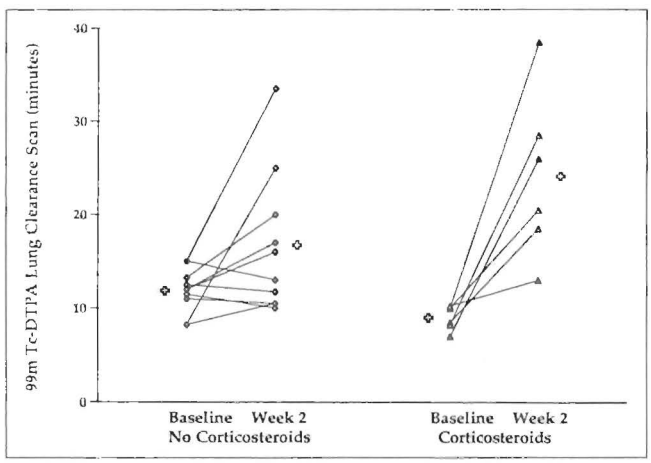

Figure 1) *Results of Tc-DTPA lung clearance scan, showing improvement in lung permeability between lung scans. + Group mean*

PATIENTS AND METHODS

Consecutive, unselected patients referred for Tc-DTPA lung clearance scan as part of the evaluation of HIV-associated respiratory symptoms were prospectively studied. Only ambulatory patients with microbiologically proven AIDS-related PCP were included in the study. All patients were treated with antimicrobials (including trimethoprim-sulfamethoxazole, intravenous pentamidine or dapsone plus trimethoprim) for a minimum of 14 days. Corticosteroid treatment was used in a nonrandomized fashion as prescribed by the treating physician. Corticosteroid treated patients received oral prednisone at a dose of 60 mg for seven days followed by a tapering regimen over the subsequent week, as previously described (4,5).

All 16 patients included in the study had a baseline Tc-DTPA lung clearance scan performed within 48 h of starting

antimicrobials, as previously described (16-18). In brief, an aerosol containing 925 MBq of 99mTc-DTPA in isotonic saline was generated by a radio aerosol kit (Medipart, Inc RNC, Illinois). Median mass diameter of the aerosol particles was 1.8±1.65 µm. While wearing a nose clip, study subjects inhaled the aerosol for a period of 2 mins at normal tidal volume in an upright position through a mouth piece. Lung radioactivity was monitored by an Anger A camera during the inhalation period and for the next 7 mins. Counts were acquired with 30 s frames with the areas of interest located over the right and left lung as identified using standard software (16). Counts were plotted against time and the least squares best fit slope of the data was calculated from the time at which peak radioactivity was observed (16). Follow-up Tc-DTPA lung scan was performed using the same equipment and protocol during the second week of therapy. All scans were analyzed and interpreted at once by a single experienced observer who was blinded to the patient's treatment. Lung clearance half time ($T_{\frac{1}{2}}$), expressed in minutes, was compared between groups using the Wilcoxon rank sum test.

RESULTS

A total of 16 patients were studied; six received adjunctive corticosteroid therapy and 10 did not. All patients were ambulatory and had mild to moderate AIDS-related PCP. All patients responded favourably to treatment. Nearly all patients had an improvement in lung permeability between lung scans, as demonstrated by a prolongation in Tc-DTPA lung clearance (Figure 1).

Mean Tc-DTPA $T_{\frac{1}{2}}$ lung clearance at baseline was 12±2 and 9±1 mins in the noncorticosteroid and corticosteroid treated groups, respectively. At week 2 the mean Tc-DTPA $T_{\frac{1}{2}}$ lung clearance scan was 17±8 and 24±9 mins in the noncorticosteroid and corticosteroid treated groups, respectively. The change in Tc-DTPA $T_{\frac{1}{2}}$ lung clearance scan was 5±7 mins versus 15±9 mins in the noncorticosteroid and corticosteroid treated groups, respectively ($P<0.02$).

DISCUSSION

These results show that Tc-DTPA lung clearance is increased around the time of PCP diagnosis and improves slowly over the first two weeks of antimicrobial treatment in patients with AIDS-related PCP. More important, our data demonstrate that adjunctive corticosteroids significantly decrease Tc-DTPA lung clearance. This lends support to the hypothesis that the beneficial effect of corticosteroids may be related to their ability to accelerate the resolution of the underlying permeability defect associated with AIDS-related PCP.

Our data support previous reports demonstrating an accelerated clearance of Tc-DTPA in patients with AIDS-related PCP (11-14). We extend this observation by demonstrating that Tc-DTPA lung clearance remains increased during the second week of therapy, but this was significantly improved by the use of adjunctive corticosteroid therapy.

Tc-DTPA has been shown to be a sensitive method to assess lung permeability in a variety of settings, including acute exposure to cigarette smoke, respiratory distress syndrome or any process associated with alveolar inflammation such as intrinsic allergic alveolitis (8-10). In all instances the increased Tc-DTPA clearance has been attributed to an increase in lung permeability. Similarly, improvement of the underlying process has been associated with a consistent decrease in Tc-DTPA lung clearance also attributed to an improvement in lung permeability.

A major limitation of our study is that patients were not randomly allocated to receive or not receive corticosteroid therapy. Given current recommendations for the use of corticosteroids and the prevalent biases among treating physicians, it is reasonable to expect that adjunctive corticosteroids were preferentially prescribed for patients with relatively more severe disease. This is supported by the fact that Tc-DTPA lung clearance tended to be faster at baseline among those patients who were treated with adjunctive corticosteroids, indicating that corticosteroid treated patients tended to have a greater permeability defect at baseline and therefore more severe PCP than those treated without corticosteroids. A second limitation related to the nonrandomized nature of the study was the lack of standardization of antimicrobial use. However, we are not aware of any data supporting the notion that different antimicrobial regimens have a differential effect on lung permeability as measured by Tc-DTPA lung clearance.

We conclude that the beneficial effect of adjunctive corticosteroids is at least partially attributable to their ability to reverse the permeability defect characteristic of AIDS-related PCP.

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