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SHORT REPORT

Role of glucocorticoids on inflammatory response in nonimmunosuppressed patients with pneumonia: a pilot study

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Role of glucocorticoids on inflammatory response in nonimmunosuppressed patients with pneumonia: a pilot study. C. Montón, S. Ewig, A. Torres, M. El-Ebiary, X. Filella, A. Rañó, A. Xaubet. ©ERS Journals Ltd 1999.

ABSTRACT: The aim of the study was to assess the potential role of glucocorticoids (GC) in modulating systemic and pulmonary inflammatory responses in mechanically ventilated patients with severe pneumonia.

Twenty mechanically ventilated patients with pneumonia treated at a respiratory intensive care unit (RICU) of a 1,000-bed teaching hospital were prospectively studied. All patients had received prior antimicrobial treatment. Eleven patients received GC (mean±SD dose of *i.v.* methylprednisolone 677±508 mg for 9±7 days), mainly for bronchial dilatation. Serum and bronchoalveolar lavage fluid (BALF) tumour necrosis factor (TNF)-α, interleukin (IL)-1β, IL-6 and C-reactive protein levels were measured in all patients.

The inflammatory response was attenuated in patients receiving GC, both systemically (IL-6 1,089±342 *versus* 630±385 pg·mL^{-1}, p=0.03; C-reactive protein 34±5 *versus* 19±5 mg·L^{-1}, p=0.04) and locally in BALF (TNF-α 118±50 *versus* 24±5 pg·mL^{-1}, p=0.05; neutrophil count: 2.4±1.1 × 10^9 cells·L^{-1} (93±3%) *versus* 1.9±1.8 × 10^9 cells·L^{-1} (57±16%), p=0.03). Four of the 11 (36%) patients receiving GC died compared to six (67%) who were not receiving GC (p=0.37).

The present pilot study suggests that glucocorticoids decrease systemic and lung inflammatory responses in mechanically ventilated patients with severe pneumonia receiving antimicrobial treatment.

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In pulmonary infections, the release of cytokines and other inflammatory mediators from alveolar macrophages serves as a useful mechanism in the elimination of invading pathogens [1]. However, excessive release can potentially be harmful to the host and particularly to the lung. The modulation of the inflammatory response, which aims to create a balance between the beneficial and harmful effects, has received considerable interest [2]. The role of glucocorticoids (GC) in the treatment of bacterial pneumonia in humans is unknown.

The present study was therefore carried out to elucidate the potential role of GC in modulating the systemic and pulmonary inflammatory responses in mechanically ventilated patients with severe pneumonia.

Patients and methods

Twenty consecutive mechanically ventilated patients with pneumonia were studied. Patients with nosocomial pneumonia were included upon diagnosis of pneumonia, and those with community-acquired pneumonia (CAP) upon admission to the intensive care unit (ICU). Exclusion criteria were: immunosuppression other than that due to GC treatment, coagulation disorders and refractory respiratory failure. Eleven of the 20 patients received a mean±SD dose of *i.v.* methylprednisolone 677±508 mg for 9±7 days prior to the investigation, mainly for bronchial dilatation. Timing of blood sampling and bronchoscopy was within 6 h after the last dose of GC (range 2–6 h). The study was approved by the local Ethical Committee and informed consent was obtained from family members.

Blood samples were collected from all the patients for determination of cytokine levels. Immediately thereafter, all patients underwent protected specimen brush (PSB) followed by bronchoalveolar lavage (BAL). The BAL samples were taken from the area most prominently affected on chest radiographs or (in the case of bilateral infiltrates) in the right lower lobe. Five aliquots of sterile saline were instilled and aspirated. The first aliquot (20 mL) was discarded. The remaining four aliquots (30 mL each) were pooled, with half being sent to the microbiology laboratory and the other half to the biochemistry laboratory. The mean BAL fluid obtained was 33±3 mL. Microorganisms were considered causative according to criteria described previously [3].

All patients received volume controlled mechanical ventilation. The tidal volume was in the range of 6–8 mL·kg^{-1}, and a positive end-expiratory pressure (PEEP) of 5 cmH_2O was applied. The ventilator settings were adapted appropriately during the procedure to ensure proper ventilation and oxygenation. The changes in mechanical ventilator settings in all patients were similar.

Total and differential cell count of the BAL fluid was performed as described elsewhere [3]. Serum and BAL fluid tumour necrosis factor (TNF)-α, interleukin (IL)-1β, IL-6, and C-reactive protein (CRP) levels were measured by a solid phase enzyme-linked immunosorbent assay (ELISA) method based on the quantitative immunometric sandwich enzyme immunoassay technique on a microtitre plate (EASIA; Medgenix Diagnostics SA, Fleurus, Belgium) as described previously [3]. Results are expressed as mean±SEM in $pg \cdot mL^{-1}$ of serum or BAL fluid. The sensitivity of the technique allows the detection of levels as low as 2 $pg \cdot mL^{-1}$ for IL-1β and IL-6, and 3 $pg \cdot mL^{-1}$ for TNF-α. Plasma CRP levels were measured by means of immunonephrometry.

The nonparametric Mann–Whitney U-test was used to compare means. The Chi-squared test (Fisher's exact test when needed) was used to compare proportions. The significance levels were set at p=0.05.

Results

Eight patients had CAP and 12 had hospital-acquired pneumonia (HAP). All patients had received prior antimicrobial treatment for a mean±SD of 27±26 h before the study. Macrolides were administered in eight patients (seven with CAP, five receiving GC). Four of eight patients with CAP and seven of 12 patients with HAP received GC treatment. Comorbid illnesses in patients not receiving GC included: chronic obstructive pulmonary disease (COPD) (2); cardiac diseases (3); postsurgical (3); and miscellaneous (1). In patients receiving GC, comorbid illnesses included: COPD (6); cardiac diseases (1); stroke (2); and trauma (2).

Age, simplified acute physiology score (SAPS II), multiple organ failure (MOF) score, acute lung injury score, arterial oxygen tension (P_{a,O_2})/inspiratory oxygen fraction (F_{I,O_2}) ratio, duration of mechanical ventilation, length of ICU stay, and leukocyte count, did not differ between patients receiving or not receiving GC.

Causative micro-organisms were determined in seven patients (two patients not receiving GC and five receiving GC). The eight pathogens were isolated included: *Streptococcus pneumoniae* (1), *Staphylococcus aureus* (2), *Enterobacter* spp. (2), *Pseudomonas aeruginosa* (2), and *Acinetobacter* spp. (1). Antimicrobial treatment was modified in three patients with CAP and seven patients with HAP.

There was a consistent trend for an attenuated inflammatory response (TNF-α levels, IL-1β levels and IL-6 levels in both serum and BAL, as well as CRP levels in serum) in patients receiving GC (table 1). Whereas serum leukocyte count was higher in patients receiving GC, the opposite was true for BAL fluid neutrophil count.

Cytokine expression was not significantly different in patients with CAP as compared to HAP. Likewise, there were no differences in cytokine expression when comparing cases of CAP and HAP receiving or not receiving GC.

In a subanalysis excluding patients with COPD (two patients not receiving GC, six receiving GC), the trend for an attenuated inflammatory response in patients receiving GC remained unchanged.

Survivors and nonsurvivors were not significantly different as regards serum and BAL fluid TNF-α, IL-1β, IL-6 and CRP levels, whether receiving GC or not. However, in the group of patients receiving GC, there was a trend for higher serum and BAL fluid IL-6 levels in nonsurvivors. Also, there was a trend for TNF-α levels to be higher in nonsurvivors in both groups, and to be lower in survivors receiving GC (table 2).

Ten (50%) patients died (four of 11 (36%) receiving GC treatment, and six of nine (67%) not receiving GC (p=0.37)). Three of eight (38%) patients with CAP and seven of 12 (58%) patients with HAP died (p=0.38).

Table 1. – Cytokine expression in both study groups

	Not receiving GC (n=9)	Receiving GC (n=11)	p-value
Serum			
TNF-α $pg \cdot mL^{-1}$	43±7	28±4	0.15
IL-1β $pg \cdot mL^{-1}$	4±2	1±0.4	0.50
IL-6 $pg \cdot mL^{-1}$	1089±342	630±385	0.03
CRP $mg \cdot dL^{-1}$	34±5	19±5	0.03
Blood leukocyte count $\times 10^9$ $cells \cdot L^{-1}$	13±2.4	15.6±2.1	0.60
BAL			
TNF-α $pg \cdot mL^{-1}$	118±50	24±5	0.05
IL-1β $pg \cdot mL^{-1}$	91±35	57±17	0.31
IL-6 $pg \cdot mL^{-1}$	1569±965	889±432	0.49
Neutrophil count %	93±3	57±16	
($\times 10^9$ $cells \cdot L^{-1}$)	(2.4±1.1)	(1.9±1.8)	0.03

Data are presented as mean±SEM. GC: glucocorticoids; TNF-α: tumour necrosis factor-α; IL: interleukin; CRP: C-reactive protein; BAL: bronchoalveolar lavage.

Discussion

These findings suggest that the inflammatory response (serum IL-6, BAL neutrophil counts and CRP) may be attenuated in patients with severe pneumonia who receive *i.v.* GC.

Several *in vitro* studies have demonstrated that GC decrease cytokine expression in human cells and inhibit migration of phagocytic cells [4, 5]. Concentrations of TNF-α, IL-1β and IL-6 were chosen to be measured, since these cytokines are known to be produced by airway epithelial cells and activated pulmonary macrophages in response to a variety of infectious agents and other triggers of airway inflammation. The findings of the present study suggest that GC also diminishes the release of cytokines (mainly IL-6 in serum and BAL) *in vivo*. Consistent with these findings, were the results that CRP (an acute phase protein related to IL-6), and neutrophil counts in BAL were decreased in patients receiving GC. Possible explanations for the latter include GC effects on neutrophil migration and/or accelerated neutrophil apoptosis in a cytokine-depleted milieu.

The following potential confounders should be considered when interpreting the results of this study. Firstly, the different doses of GC used may have affected the results. However, these differences are more likely to underestimate the effect of GC on the inflammatory response. Secondly, it should be noted that all patients were receiving broad spectrum antibiotics, thus these results could only be extrapolated to pulmonary infections treated

Table 2. – Cytokine expression in both survivors and nonsurvivors with and without glucocorticoids (GC)

	Survivors	Nonsurvivors	p-value
Without GC			
n	3	6	
Serum TNF-α $pg \cdot mL^{-1}$	33±6	61±15	0.16
Serum IL-1β $pg \cdot mL^{-1}$	7±3.6	2.8±2.1	0.54
Serum IL-6 $pg \cdot mL^{-1}$	1046±777	1111±398	0.90
BAL TNF-α $pg \cdot mL^{-1}$	238±101	45±17	0.14
BAL IL-1β $pg \cdot mL^{-1}$	130±94	66±19	0.10
BAL IL-6 $pg \cdot mL^{-1}$	3223±2520	576±216	0.34
BAL neutrophil count $\times 10^9$ $cells \cdot L^{-1}$ (%)	2.1±1.2 (81±6)	1.9±1.8 (74±20)	0.84
Serum C-reactive protein $mg \cdot dL^{-1}$	27±4	40±6	0.64
With GC			
n	7	4	
Serum TNF-α $pg \cdot mL^{-1}$	23±4	37±8	0.11
Serum IL-1β $pg \cdot mL^{-1}$	1.0±0.49	1.5±0.9	0.79
Serum IL-6 $pg \cdot mL^{-1}$	214±156	1356±999	0.23
BAL TNF-α $pg \cdot mL^{-1}$	26±8	21±5	0.79
BAL IL-1β $pg \cdot mL^{-1}$	62±23	48±23	0.64
BAL IL-6 $pg \cdot mL^{-1}$	360±155	1814±1086	0.31
BAL neutrophil count $\times 10^9$ $cells \cdot L^{-1}$ (%)	2.0±0.8 (77±3)	2.1±1.2 (81±16)	0.64
Serum C-reactive protein $mg \cdot dL^{-1}$	20±7	18±6	1.00

Data are presented as means±SEM. TNF-α: tumour necrosis factor-α; IL: interleukin.

with antibiotics. The effect of the antibiotics on the inflammatory response *in vivo* is not well-known. Thirdly, evidence from animal and human studies has shown that combined effects of biochemical and biophysical injury induced by mechanical ventilation could initiate or propagate systemic inflammatory responses [6]. However, these aspects have not been settled in humans. Finally, since six of 11 patients receiving GC had COPD, a population expected to have an increased baseline lung and systemic inflammatory response [7], a separate analysis excluding these patients was performed. However, the trend for an attenuated inflammatory response in patients receiving GC remained unchanged.

The impact of GC on outcome in pneumonia is unknown. In this study, however, the mortality rate in patients receiving GC was 36% (4/11) compared to 67% (6/9) for patients not receiving GC. Survivors receiving GC had lower serum TNF-α levels compared to nonsurvivors with and without GC treatment. Accordingly, others [8] have found persistently elevated TNF-α levels in nonsurvivors with acute respiratory distress syndrome.

In summary, the present study suggests that glucocorticoids decrease systemic and lung inflammatory responses in patients with severe pneumonia. The clinical efficacy of glucocorticoid treatment in patients with pneumonia should be assessed in prospective, controlled, randomized trials.

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