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Editorial

Arguments in Favor of Corticosteroids in Pneumonia

Corticoides en la neumonía: argumentos a favor

Oriol Sibila

Servei de Pneumologia, Hospital de la Santa Creu i Sant Pau, Barcelona, Spain

The relationship between pneumonia and corticosteroids is one of the most important questions that has still yet to be resolved in the field of respiratory infections. More than fifty years have passed since the publication of the first study on the effect of corticosteroids in pneumococcal pneumonia,¹ and it still is not clear towards which side the scale tips: the benefits or potential risks.

A recent study by Snijders et al,² the first randomized, double-blind, placebo-controlled clinical assay in 213 patients with community-acquired pneumonia (CAP) requiring hospitalization, found no clinical benefits on administering prednisolone, adjuvant to antibiotic treatment, but did find an increase in the lack of response to treatment later, suggesting that its routine use in CAP provides no benefits and may even be detrimental. Despite these findings, many questions still need to be answered, and we have sufficient evidence to believe that the use of corticosteroids in selected cases can be beneficial.

First of all, we cannot forget that the mortality due to pneumonia, particularly in the case of severe pneumonia, has not varied in recent years despite the advances made in antibiotic therapy.³ This important fact suggests that there are factors other than the germ that mark the prognosis of the disease, such as the inflammatory response of the host. It is well known that the arrival of the germ in the alveolar space causes a complex inflammatory response in which several defense mechanisms and inflammatory mediators intervene.⁴ This reaction is directed at limiting the progression of the infection and at destroying the microorganism and is absolutely essential for the adequate fight of the host against the germ, but its action is beneficial as long as it is limited to the control of the local infection. When this reaction is disproportionate, there is a systemic translation that unfavorably influences the evolution of the infection. Recent studies have related the excess of this inflammatory response, measured by acute phase reactants like C-reactive protein (CRP) and proinflammatory cytokines like interleukin (IL)-6 or tumor necrosis factor alpha (TNF-alpha), as markers of the lack of response to treatment⁵ and mortality^{6,7} due to CAP.

Corticosteroids, thanks to their anti-inflammatory action mechanism at the genomic level,^{8,9} have shown to be potential modulators of this inflammatory response. A first study by Montón et al, in patients with severe pneumonia who required mechanical ventilation,¹⁰ detected a decrease in inflammatory cytokines in serum as well as in bronchoalveolar lavage (BAL) in those patients that had received coadjuvant corticosteroid treatment (in most cases as bronchodilator treatment associated with antibiotic treatment), suggesting an immunosuppressant effect. The relationship between the intensity of the inflammatory response, the dose of corticoids and the prognosis of pneumonia was later studied by Agustí et al.¹¹ In this study, the authors evaluated the levels of inflammatory cytokines in patients with severe pneumonia that had received corticoid treatment for long periods of time (> 30 days) and they compared these with a group of patients with severe pneumonia without corticosteroid treatment and another group of patients with severe pneumonia and corticosteroid treatment for a short period of time (9 ± 7 days, in most cases as bronchodilator treatment). They observed that the inflammatory response, both local as well as systemic, was quite higher in the patients without corticosteroid treatment, quite lower in the patients with prolonged corticosteroid treatment and with intermediate levels in the patients that had received a short corticosteroid treatment. In addition, the mortality in the group of patients with prolonged corticoid treatment was similar to the mortality of those who did not receive steroid treatment. On the contrary, and interestingly, those patients that had received treatment with steroids for a short period of time and who showed an attenuated inflammatory response had a tendency towards lower mortality. These results suggested that the profound attenuation of the inflammatory response by a prolonged corticosteroid treatment can be as detrimental as the exaggerated inflammatory response itself, but a "moderated" attenuation with "short" corticosteroid treatment can be beneficial for the prognosis of the disease.

In the experimental field, in a study carried out in an animal model of severe pneumonia in pigs¹² in which the effect of corticosteroids was studied by comparing three groups of animals with pneumonia induced by *Pseudomonas aeruginosa* (without treatment, with antibiotic treatment and with antibiotic treatment + corticosteroids), it was seen that the pigs treated with antibiotics +

E-mail address: osibila@santpau.cat

corticosteroids experienced a decrease in the local inflammatory response and a lower bacterial count in the lung samples analyzed. This important finding was previously demonstrated in *in vitro* studies with U937 monocytic human cells. In this article, Meduri et al.¹³ found that, after infecting the cells with different bacteria and administering different doses of methylprednisolone, the cells lines with corticosteroids presented a decrease in intracellular survival and a decrease in the reproduction of the microorganisms. And in another experimental study based on a model of sepsis induced by pneumonia caused by *Escherichia coli* in mice,¹⁴ the authors observed that the mice that received hydrocortisone together with ceftriaxone had a greater survival than the animals that only received antibiotic treatment. These facts support the beneficial effect of corticoids in the animal models of severe pneumonia.

In order for this modulation of the inflammatory response to have clinical translation and improve the prognosis of the disease, randomized and controlled clinical assays are needed, based on the hypothesis that the patients that can experience a benefit are those that suffer severe pneumonia with increased inflammatory response, a hypothesis that is not considered by the recent study by Snijders et al.² In other words, the place where corticosteroids play a fundamental role in pneumonia is where the antibiotics do not reach and in those cases in which mortality remains high despite adequate antibiotic therapy, but not routinely in all pneumonia cases. In the only randomized, double-blind, placebo-controlled assay carried out to date in patients affected with severe pneumonia,¹⁵ the authors demonstrated a reduction in the mortality in the group treated with hydrocortisone (at a low dosage for 7 days), as well as better modulation of the systemic inflammatory response (determined by serum C-reactive protein) and a significant improvement in the main clinical variables studied, such as chest radiography, MODS severity scale, PaO₂/FiO₂ ratio and ICU and hospital stay. Given the spectacularity of the results, this study was suspended after an intermediate analysis, including a total of only 46 patients, a fact which itself is its main limitation in order to generalize the results. Continuing on with severe pneumonia, we only found one other study that evaluated the effect of corticosteroids: a retrospective study of 308 patients with severe CAP, detecting a reduction in 30-day mortality in those patients that had received corticosteroid treatment for different indications when compared with patients that had not received it.¹⁶ And, indirectly, a recent meta-analysis of 12 randomized double-blind, placebo-controlled clinical assays in patients affected by sepsis (most of the time secondary to severe pneumonia) has given evidence of lower mortality in those patients treated with corticosteroids in low doses (300 mg hydrocortisone or equivalent) during short periods of time (7-10 days).¹⁷

Finally, two studies with parallel observations should be highlighted as they also advise upon the possible beneficial effect of corticosteroids in pneumonia. The first is the study by MJ Fine et al.,¹⁸ which analyzed the factors that are associated with mortality in more than 15,000 cases of pneumonia with the aim of creating a predictive scale, and where surprisingly chronic obstructive pulmonary disease (COPD) did not add any points to the PSI scale (*Prognostic Score Index*), which is currently widely used. The interpretation that has been made of this finding is that corticosteroids, commonly used in COPD exacerbations, may be responsible for this pathology's not worsening CAP prognosis. And in the second, along this same line, reference is made to the

Spanish multicenter Neumofail study,¹⁹ which searched for factors related to the lack of response to treatment in CAP. In said study, COPD was detected, together with the anti-flu vaccine and antibiotic treatment, as the only protecting factors. Once again, it was hypothesized that the routine use of corticosteroids in COPD justifies this finding.²⁰

Thus, although the scientific evidence is still limited and extensive randomized, controlled clinical assays are needed to reach solid conclusions, the findings set forward can orientate us towards a possible beneficial effect corticosteroid treatment in pneumonia always under the premise of three conditions: 1) patients with severe pneumonia; 2) high inflammatory response; and 3) corticosteroid treatment at low doses for short periods of time.

References

1. Wagner HN, Bennet IL, Lasagna L, Cluff LE, Rosenthal MB, Mirick GS. The effect of hydrocortisone upon the course of pneumococcal pneumonia treated with penicillin. *Bull Johns Hopkins Hosp.* 1956;98:197-215.
2. Snijders D, Daniels JMA, De Graaff C, Van der Werf T, Boersma W. Efficacy of corticosteroids in community-acquired pneumonia. A Randomized double-blinded clinical trial. *Am J Respir Crit Care Med.* 2010;181:975-82.
3. Diaz LA, Mortensen EM, Anzueto A, Restrepo MI. Novel targets in the management of pneumonia. *Ther Adv Respir Dis.* 2008;2:387-400.
4. Mizgerd JP. Acute lower respiratory tract infection. *N Engl J Med.* 2008;14:716-27.
5. Menéndez R, Cavalcanti M, Reyes S, Mensa J, Martínez R, Marcos MA, et al. Markers of treatment failure in hospitalised community-acquired pneumonia. *Thorax.* 2008;63:447-52.
6. Menéndez R, Martínez R, Reyes S, Mensa J, Filella X, Marcos MA, et al. Biomarkers improve mortality prediction by prognostic scales in community-acquired pneumonia. *Thorax.* 2009;64:587-91.
7. Martínez R, Menéndez R, Reyes S, Polverino E, Cilloniz C, Martínez A, et al. Factors associated with inflammatory cytokine patterns in community-acquired pneumonia. *Eur Respir J.* 2010;37:393-9.
8. Cosio BG, Torrego A, Adcock IM. Molecular mechanisms of glucocorticoids. *Arch Bronconeumol.* 2005;41:34-41.
9. Rhen T, Cidlowski JA. Antiinflammatory action of glucocorticoids – new mechanisms for old drugs. *N Engl J Med.* 2005;20:1711-23.
10. Montón C, Ewig S, Torres A, El-Ebiary M, Filella X, Rañó A, et al. Role of glucocorticoids on inflammatory response in nonimmunosuppressed patients with pneumonia: a pilot study. *Eur Respir J.* 1999;14:218-20.
11. Agustí C, Rañó A, Filella X, González J, Moreno A, Xaubet A, et al. Pulmonary infiltrates in patients receiving long-term glucocorticoid treatment. Etiology, prognostic factors and associated inflammatory response. *Chest.* 2003;123:488-98.
12. Sibila O, Luna CM, Agustí C, Baquero S, Gando S, Patrón JR, et al. Effects of glucocorticoids in ventilated piglets with severe pneumonia. *Eur Respi J.* 2008;32:1037-46.
13. Meduri GU, Kanangat S, Bronze M, Patterson DR, Meduri CU, Pak C, et al. Effects of methylprednisolone on intracellular bacterial growth. *Clin Diagn Lab Immunol.* 2001;8:1156-63.
14. Li Y, Cui X, Li X, Solomon SB, Danner RL, Banks SM, et al. Risk of death not alter the efficacy of hydrocortisone therapy in a mouse *E. Coli* pneumonia model. Risk and corticosteroids in sepsis. *Intensive Care Med.* 2008;34:568-77.
15. Confalonieri R, Rubino G, Potena A, Piatella M, Parigi P, Puccio G, et al. Hydrocortisone infusion for severe community-acquired pneumonia: a preliminary randomised study. *Am J Respir Crit Care Med.* 2005;171:242-8.
16. García-Vidal C, Calbo E, Pascual V, Ferrer C, Quintana S, Garau J. Effects of systemic steroids in patients with severe community-acquired pneumonia. *Eur Respir J.* 2007;30:951-6.
17. Annane D, Bellissant E, Bollaert PE, Briegel J, Confalonieri M, De Gaudio R, et al. Corticosteroids in the treatment of severe sepsis and septic shock in adults. A systematic review. *JAMA.* 2009;301:2362-75.
18. Fine MJ, Auble TE, Yealey DM, Hanusu BH, Weissfeld LA, Singer DE, et al. A prediction rule to identify low-risk patients with community-acquired pneumonia. *N Eng J Med.* 1997;336:243-50.
19. Menéndez R, Torres A, Rodríguez de Castro F, Zalacain R, Aspa J, Martín Villasclaras JJ, et al. Risk factors of treatment failure in community acquired pneumonia: implications for disease outcome. *Thorax.* 2004;59:960-5.
20. Torres A, Menéndez R. Mortality in COPD patients with community-acquired pneumonia. Who is the third partner? *Eur Respir J.* 2006;28:262-3.