Supplementary Online Content


**Trial protocol**

This supplementary material has been provided by the authors to give readers additional information about their work.
Corticosteroids in Severe Community-Acquired Pneumonia with High Inflammatory Response: a Randomized Trial

Protocol

Study design and patients

Patients will be prospectively enrolled at three teaching hospitals in Spain (Hospital Clinic, Barcelona, Hospital Universitario La Fe, Valencia, and Hospital Universitari Son Dureta, Palma de Mallorca). The local Ethics Committees approved the study protocol and written informed consent will be obtained from all participants or their authorized representatives.

Patients will be eligible if they meet the following criteria: 1) Age ≥ 18 years, 2) clinical symptoms suggesting CAP (cough, fever, pleuritic chest pain or dyspnoea), 3) new chest radiographic infiltrate, 4) severe CAP criteria, defined by ATS criteria modified by Ewig and co-workers or Pneumonia Severity Index (PSI) class V, and 5) C-reactive protein (CRP) at admission > 15 mg/dL. We choose 15 mg/dl based on the observation of a higher percentage of treatment failures in this group in our database of CAP collected in the three previous years (personal database observation).

Patients will be excluded from the study if one of the following criteria apply: 1) prior treatment with systemic corticosteroids (chronic treatment or any administration on admission), 2) nosocomial pneumonia, 3) reported severe immunosuppression (HIV infection and immunosuppressive conditions or medications), 4) pre-existing medical condition with a life expectancy < 3 months, 5) uncontrolled diabetes mellitus, 6) major gastrointestinal bleed within 3 months of the current hospitalization, or 7) a condition requiring acute treatment > 1mg/kg/day of methylprednisolone (MPDN) or its equivalent (i.e. severe bronchospasm).
Procedures

Patients will be randomized in a double-blinded design to receive either intravenous 0.5 mg/kg/12h of MPDN or placebo for a total of 5 days started within 36 hours of hospital admission. Randomization will be based on one-to-one allocation of pre-numbered boxes containing dosing units with identical appearance for MPDN and placebo for intravenous administration. Patients, investigators and data assessors will be blinded to treatment allocation.

All patients will be treated with antibiotics according to current international guidelines. Switch from intravenous to oral therapy and duration of the antibiotic treatment will be entirely left to the discretion of the medical team, as will be the decisions to transfer patients to ICU or hospital discharge.

Definitions

The primary efficacy outcome is the rate of treatment failure stratified as early or late. Early treatment failure is defined as clinical deterioration within 72h of treatment, as indicated by the need for invasive mechanical ventilation and/or shock not present at baseline, or death. Late treatment failure is defined as radiographic progression (increase >50% of pulmonary infiltrates compared to baseline), persistence of severe respiratory failure (PaO₂/FiO₂ <200, with respiratory rate >30 min⁻¹ in non-intubated patients), development of shock or need for invasive mechanical ventilation not present at baseline, or death between 72-120h after treatment initiation. These criteria have been used previously with modifications. Secondary efficacy outcomes include time to clinical stability, assessed by using the criteria defined by Halm and colleagues, length of ICU and hospital stay, and in-hospital mortality.
The following data will be collected on admission: age, gender, smoking history, clinical symptoms, physical examination and co-morbidities. The initial risk class will be calculated using the PSI and severity criteria will be assessed according to the ATS criteria modified by Ewig et al. Patients will be evaluated daily for treatment failure and time to clinical stability until day 5. Adverse events and mortality will be recorded during hospital stay.

Microbial examination will be performed at the time of clinical presentation collecting sputum, urine, two samples of blood, and nasopharyngeal swab samples. Thoracocentesis, endotracheal aspirates and broncoalveolar lavage (BAL) fluid will be obtained when possible. All the samples will be tested for Gram and Ziehl-Nielsen stains and cultured for bacterial, fungal and mycobacterial pathogens. The aetiology will be considered definite if one of the following criteria was met: 1) positive blood culture (in the absence of an apparent extrapulmonary focus), 2) positive bacterial culture of pleural fluid or transthoracic needle aspiration samples, 3) elevated serum levels of IgM against *Chlamydophila pneumoniae* (>1:64), *Coxiella burnetii* (>1:80) and *Mycoplasma pneumoniae* (any positive titre), 4) positive urinary antigen for *Legionella pneumophila* (Binax Now Legionella pneumophila urinary antigen test; Trinity Biotech, Bray, Ireland), 5) positive urinary antigen for *Streptococcus pneumoniae* (Binax Now Streptococcus pneumoniae urinary antigen test; Emergo Europe, The Netherlands), 6) bacterial growth in cultures of TBAS (≥10^5 cfu/ml), protected specimen brushing (PSB) (≥10^3 cfu/ml) or BAL fluid (≥10^4 cfu/ml), 7) seroconversion (i.e. a fourfold increase in IgG titres) for *Chlamydophila pneumoniae* and *Legionella pneumophila* >1:128, *Coxiella burnetii* >1:80 and respiratory viruses (influenza viruses A and B, parainfluenza viruses 1 and 3, respiratory syncytial virus, adenovirus), and 8) detection of antigens by immunofluorescence assay plus virus
isolation or detection by reverse transcriptase (RT)-PCR testing for respiratory
viruses (influenza viruses A and B, parainfluenza viruses 1 and 3, respiratory
cyncitial virus, adenovirus).

Standard laboratory assessment performed at presentation will include renal
and liver functions, electrolytes, blood glucose, CRP, and haematology. Arterial
blood gases will be performed at admission and thereafter as clinically indicated.

Cytokines, procalcitonin and CRP determinations will be obtained on the first
day and after 72h and 7 days of treatment, centrifuged and frozen at -80°C until
analysis. Determination of IL-6, IL-8 and IL-10 levels will be performed using a
commercial enzyme immunoassay technique (Biosource, Nivelles, Belgium). An
immunoluminometric technique was used to measure procalcitonin (Liaison Brahms
PCT; DiaSorin, Saluggia, Italy) with a detection limit of 0.3 ng/ml. CRP will be
measured with an immunoturbidimetric method using a commercially available test
(Bayer Diagnostics, Leverkusen, Germany) with an Advia 2400.

Adverse events during hospital stay will be carefully monitored and classified
as being possibly related to corticosteroids (hyperglycemia, super-infection,
gastrointestinal bleeding, and delirium) or not.

**Statistical analysis**

The study is based on the assumption that the placebo group would have a
35% treatment failure rate. According to a two-sided 5% type I error and 80% power
to detect a 20% reduction in treatment failure by MPDN, as compared with placebo,
the sample size is 60 patients in each group. An interim analysis will be performed at
50% of patient accrual.

Efficacy data will be analyzed for both the intention-to-treat (ITT) and the per-
protocol (PP) populations. The ITT population will include all randomized patients
who receive at least one dose of study drug. The PP population will include all
randomized patients who: a) meet all inclusion/exclusion criteria, b) attain a sufficient
compliance to the treatment received, i.e. at least 6 doses of study drug, and c) do
not present serious deviations from the protocol.

We will show number of patients (%) for categorical variables and median (1st
quartile-3rd quartile) for continuous variables with non-normal distribution or
mean±SD for those with normal distribution. Categorical variables will be compared
with the chi-square test or Fisher’s exact test. Continuous variables will be compared
using the Student’s t-test or the nonparametric Mann-Whitney U-test. As supportive
analyses, we will perform logistic regression models to examine differences in
primary outcome and in-hospital mortality between the two groups. We will also
assess differences in secondary outcomes between both treatment groups with Cox
proportional hazard regression models. The primary and secondary outcomes will
analyzed both with no adjustment for baseline variables and with adjustment for
potential confounders. Missing data will not be imputed. All tests are two-tailed and
significance is set at 5%. All analyses will be performed with SPSS 15 or later.