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Effect of corticosteroids on myocardial injury among patients hospitalized for community-acquired pneumonia: rationale and study design. The colosseum trial

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Abstract

Community-acquired pneumonia (CAP) is often complicated by elevation of cardiac troponin, a marker of myocardial injury that can be isolated or associated with myocardial infarction (MI). A retrospective study showed that corticosteroid treatment lowers the incidence of MI during the hospital stay. No data exist so far on the effect of corticosteroids on myocardial injury in CAP patients. The primary objective of the study is to evaluate if methylprednisolone is able to reduce myocardial injury, as assessed by serum high-sensitivity cardiac T Troponin (hs-cTnT), in a cohort of patients hospitalized for CAP. Secondary aims are to evaluate the potential effect of methylprednisolone on cardiovascular events during hospitalization, at 30 days from hospital admission and during 2 years' follow-up. The trial will also examine whether the potential protective effects of methylprednisolone might be due to platelet activation down-regulation. Double-blind randomized placebo-controlled trial. One hundred twenty-two eligible patients will be randomized to a week treatment with iv methylprednisolone (20 mg b.i.d) or placebo from hospital admission. Serum hs-cTnT will be measured at admission and every day until up 3 days from admission. ECG will be monitored every day until discharge. After discharge, all patients will be followed-up 2 years. This is the first clinical trial aimed at examining whether methylprednisolone treatment may reduce myocardial injury. The results of this trial may constitute the basis for conducting a larger multicenter trial aimed to evaluate the effect of corticosteroid on cardiovascular events in this setting.

Keywords Pneumonia · Corticosteroid · Troponin · Myocardial infarction

Pneumonia and cardiovascular complications

Community-acquired pneumonia (CAP) is the most common infection leading to hospitalization in intensive care units and the most common cause of death associated with infective diseases in developed countries [1]. At the global level, lower respiratory tract infections, including pneumonia, are the fourth most common cause of death [2]. Age and co-morbidities greatly increase the risk of death: in Europe,

approximately 90% of deaths due to pneumonia occur in people aged > 65 years [1].

Pneumonia is usually considered to be an acute process confined to the lungs unless the disease is complicated by severe sepsis. However, pneumonia affects essential parts of the cardiovascular system, which are probably responsible for the substantial burden of acute cardiac complications that has been documented thoroughly in large cohorts [3].

Epidemiological studies have shown that respiratory tract infections are associated with an increased risk for the development of acute cardiovascular events [3]. This link is further supported by studies indicating that influenza vaccination is associated with reduced risk of hospitalization for pneumonia, heart disease, cerebrovascular disease, and the risk of death from all causes during influenza seasons in the elderly [4].

A recent study aimed at assessing the typology of cardiovascular events occurring during CAP documented that about 30% of patients may suffer from cardiovascular events

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including heart failure, atrial fibrillation (AF) and myocardial infarction (MI) [5]. In particular, we have recently demonstrated that in the early phase of pneumonia (within 48–72 h of presentation), patients may suffer from heart failure (24%), atrial fibrillation (9%) and myocardial infarction (8%), respectively [6]. Of note, enhanced platelet activation was significantly associated with MI, suggesting a role for platelets in triggering coronary thrombosis [7].

Evaluation of cardiac complications in patients with CAP is of particular clinical relevance as patients experiencing cardiovascular complication are at increased short- and long-term mortality [5, 8, 9].

In addition to this, a large number of CAP patients may have enhanced isolated levels of high-sensitivity cardiac T Troponins (hs-cTnT), a marker of myocardial injury [7, 10], indicating that CAP is often complicated by myocardial damage, a phenomenon which may be predictive of poor outcome as documented by an enhanced mortality risk associated with elevated Troponin levels [3, 11, 12].

In a retrospective analysis of 753 patients hospitalized for CAP, iv corticosteroid treatment was associated with a lower incidence of in-hospital MI [13]. No data, however, were reported regarding the effect of corticosteroid treatment on T troponin. Glucocorticoids inhibit the expression and action of many cytokines involved in the inflammatory response [14] and exert an antiplatelet effect [15, 16], which may contribute to reducing myocardial injury. This potential effect on platelet function could have a role in the early phase of CAP, in which enhanced platelet activation has been associated with an increased risk of MI [9, 17].

Thus, we speculated that systemic corticosteroids could have an important protective role in reducing myocardial damage and eventually mortality, in patients hospitalized for CAP.

Pneumonia and glucocorticoids

Glucocorticoids such as hydrocortisone, methylprednisolone, prednisolone, and dexamethasone have been tested for pneumonia and related conditions like sepsis, septic shock, and acute respiratory distress syndrome [18]. The overarching rationale is that glucocorticoids could mitigate exaggerated and potentially deleterious aspects of the host's inflammatory response. Corticosteroids have typically been prescribed to target the acute phase of these conditions. However, the results of these studies have been mixed. For example, a meta-analysis of more than 30 trials in septic shock suggested that glucocorticoids reduce the duration of septic shock and may reduce mortality [19]. However, a meta-analysis of trials in pneumonia [20], the most common cause of sepsis, reported significant heterogeneity in terms of both patient characteristics and type of glucocorticoids used and found an uncertain effect on

mortality but consistent reduction in duration of mechanical ventilation, length of hospitalization, and time to clinical stability. Consequently, the efficacy of glucocorticoids remains unclear, treatment guidelines can be controversial [21–25], and clinicians continue to struggle with decisions regarding optimal approaches. Recently, a precision medicine approach showed that the acute use of methylprednisolone decreased treatment failure among patients with CAP and an exaggerated immune response as evidenced by high circulating C-reactive protein levels [26].

Primary endpoint

The primary goal of the study is to determine whether early methylprednisolone treatment will reduce myocardial injury.

We will evaluate the effectiveness of i.v. methylprednisolone 20 mg (b.i.d.) vs. placebo for 7 days started within 24 h of hospital admission in preventing an increase of high-sensitivity cardiac T Troponin (hs-cTnT) in patients hospitalized for CAP.

Secondary endpoints

Secondary aims will be to test the effect of methylprednisolone and on cardiovascular events during hospitalization, at 30 days from hospital admission and during 2 years' follow-up. Furthermore, biochemical variables related to platelet activation will be measured.

In particular, we will evaluate:

1. Any cardiovascular event (i.e. MI, new or worsening heart failure, new-onset AF, stroke) during hospitalization.
2. Total mortality at short-term (30 days) or long-term follow-up (2 years).
3. Major Adverse Cardiac and Cerebrovascular Events [MACCE] (i.e. a combined end-point of cardiovascular mortality, MI, and stroke at short-term (30 days) or long-term follow-up (2 years).
4. Biomarkers of platelet activation (serum TxB_2, sP-selectin; sCD40L, platelet recruitment), inflammation (serum hs-CRP) and oxidative stress (serum sNOX2-dp, urinary and serum isoprostanes) during hospitalization.

Study design

This is a phase 3, no-profit, multicenter, double-blind, placebo-controlled, randomized, intervention trial of 1-week treatment with methylprednisolone vs placebo in patients hospitalized for CAP.

Patients

The study will be conducted on patients with CAP admitted in three university hospitals in Italy.

Patients will be recruited if they fulfill the inclusion/exclusion criteria (Table 1), after giving written informed consent. All patients will be recruited within 24 h from hospital admission. All patients will be recruited consecutively within 12 months from the start of the study.

Antibiotic therapy will be initiated in accordance with the hospital guidelines.

Data will be collected on demographic characteristics, co-morbidities, and empirical antibiotic therapy. At baseline, patients will be evaluated by routine blood laboratory tests including high sensitivity C reactive protein (hs-CRP), 12-lead ECG, M-mode- and 2-dimensional echocardiography with echo color-Doppler and arterial blood gas test.

Patients will be seen daily during their hospital stay by 1 or more of the investigators, who will record clinical data in a computer-assisted protocol.

The study will be conducted in accordance with the principles embodied in the Declaration of Helsinki.

The study protocol has been registered at the ClinicalTrials.gov (NCT03745664).

Treatment

Recruited patients will be randomized to two treatment groups (methylprednisolone or placebo) (Fig. 1).

Methylprednisolone or placebo will be given in a double-blind fashion at the dose of 40 mg/day (20 mg × 2/day).

The treatment with methylprednisolone or placebo will last 7 days (or the time of hospitalization if the patient is discharged in a period less or more than 7 days).

Patients will be randomized to receive either an intravenous bolus of methylprednisolone (20 mg every 12 h) or placebo for 7 days within 24 h of hospital admission. Randomization will be based on a 1-to-1 allocation of prenumbered boxes containing dosing units with an identical appearance for methylprednisolone and placebo. Patients, investigators, and data assessors will be blinded to treatment allocation.

Stopping rules

Any condition requiring acute treatment with glucocorticoids during hospitalization will result in an immediate exit from the trial: the doctors will be suddenly informed about the real treatment to give the patient the most appropriate care.

Similarly, any adverse condition that could be ascribable to the treatment (methylprednisolone or placebo) will result in an immediate exit from the trial.

In any moment, patients could decide to stop the treatment and exit from the trial.

Timeline of events and assessments

In-hospital assessment

At baseline, before treatment administration, after 12, 24, 36, 48, 60, 72 h and at hospital discharge, blood samples (5 ml) will be collected for hs-cTnT.

At baseline, 72 h and at the end of the treatment, serum samples (5 ml), plasma (10 ml) and the urine will be collected for the assay of markers of platelet activation, inflammation and oxidative stress.

At baseline and at the end of treatment, patients will undergo echocardiography. At baseline and (at least) every 24 h, patients will undergo ECGs.

Table 1 Inclusion and exclusion criteria of the trial

| Inclusion criteria |
| --- |
| Patients aged 18 years or older |
| Diagnosis of CAP: (a) have a clinical presentation of an acute illness with one or more of the following signs or symptoms suggesting CAP: presence of rales, rhonchi, bronchial breath sounds, dullness, increased fremitus and egophony, fever (> 38.0 C), tachycardia, chills, dyspnea, coughing (with or without productive cough), chest pain; (b) have the presence of new consolidation(s) suggesting pneumonia on chest X-ray or TC scan; (c) pneumonia will considered as CAP if is diagnosed upon hospitalization and the patient has not been discharged from an acute care facility within 14 days preceding the clinical presentation |
| Exclusion criteria |
| Use of corticosteroids in the previous 30 days |
| Health care-associated pneumonia (HCAP) [38] |
| Reported severe immunosuppression (human immunodeficiency virus infection, immunosuppressive conditions or medications) |
| Preexisting medical condition with a life expectancy of less than 3 months |
| Uncontrolled diabetes mellitus |
| Gastritis with or without major gastrointestinal bleeding within 3 months |
| Necessity of mechanical ventilation |
| Dementia/cognitive impairment |
| Any condition requiring acute treatment with glucocorticoids |
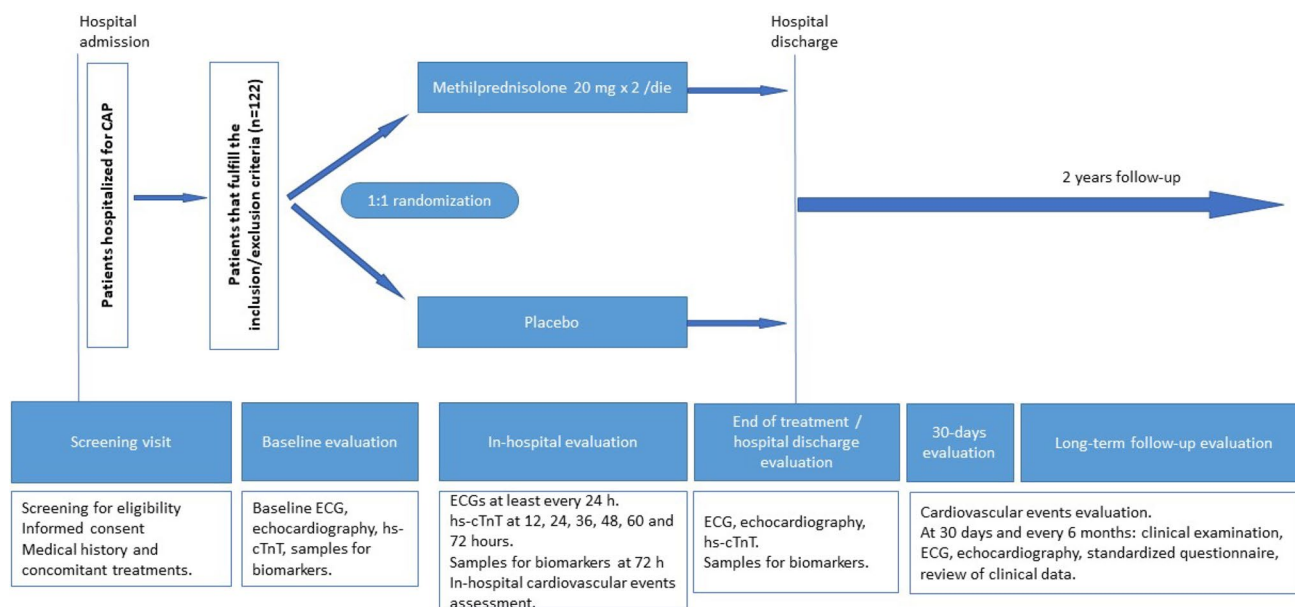
Fig. 1 Trial design

Follow-up assessments

All patients will be followed-up for the entire duration of the study and outcome events will be recorded. Patients will be checked after 30 days from hospitalization and every 6 months for vital status evaluation: ECG, M and B-mode echocardiogram, standardized questionnaire and clinical examination will be carried out and compliance with the prescribed drugs will be checked. Follow-up data will be also obtained by review of hospital databases, medical records, death certificates or telephone interviews.

Outcome evaluation

Primary outcome

The primary goal of the study is to determine whether providing early treatment with methylprednisolone will reduce myocardial injury.

Thus, the primary endpoint of the study will be a significant reduction of the maximum hs-cTnT increase within 72 h from admission. As we previously showed, we expect a raise of hs-cTnT over the 99° percentile within the first 72 h in about 55% of patients [7], that can be isolated or associated to MI. Troponins, measured with high sensitive assays, are a highly sensitive and specific marker of myocardial injury. Even when not associated to MI, they have an important prognostic role in elderly patients in terms of coronary heart disease and mortality [11].

To evaluate hs-cTnT, blood samples will be collected at baseline and after 12, 24, 36, 48, 60 and 72 h from hospital admission and at hospital discharge.

Hs-cTnT levels will be measured by the Elecsys 2010 (Roche Diagnostics, Indianapolis, IN) in a dedicated core laboratory. According to the manufacturer, the 99th-percentile cutoff point of the hs-cTnT is 0.014 µg/l, and a coefficient of variation of < 10% is achieved at 0.013 µg/l [27].

Secondary outcomes

Laboratory analyses

As secondary endpoints, biomarkers of platelet activation (serum TxB_2, sP-selectin; sCD40L), inflammation (hs-CRP) and oxidative stress (sNOX2-dp [28], urinary and serum isoprostanes) during hospitalization will be evaluated.

Blood and urine samples will be collected at baseline, at 72 h and at hospital discharge. Serum, plasma and urines will be frozen at − 80 °C until assayed and measured a core laboratory.

Serum TxB_2 will be measured by a commercially available immunoassay (Amersham Pharmacia Biotech, Little Chalfont, United Kingdom). Intra- and inter-assay coefficients of variation were 4.0% and 3.6%, respectively [29].

Plasma sCD40L and sP-selectin levels will be measured with commercial immunoassays (Tema Ricerca, Italy). Intra-assay and interassay coefficients of variation are 5 and 7% for sCD40L, 4.3 and 6.1% for sP-selectin.

Blood levels of soluble NOX2-derived peptide (sNOX2-dp), a marker of NADPH oxidase activation, will be detected

by ELISA as previously described [28, 30]. The peptide is recognized by the specific monoclonal antibody against the amino acidic sequence (224–268) of the extra-membrane portion of Nox2 (the catalytic core of NADPH oxidase), which is released in the medium upon platelet activation. Values are expressed as pg/ml; intra-assay and inter-assay coefficients of variation are 5.2% and 6.0%, respectively.

Serum F2-isoprostane (8-iso-PGF$_{2\alpha}$-III) will be measured by the enzyme immunoassay method (DRG International) as previously described [31, 32]. The values are expressed as pmol/l. Intra-assay and inter-assay coefficients of variation are 5.8% and 5.0%, respectively.

Urinary F2-isoprostanes will be measured in triplicate for each sample by a validate EIA assay method [30]. 8-iso-PGF$_{2\alpha}$ concentration will be corrected for recovery and creatinine excretion and expressed as pg/mg of urinary creatinine. Intra-assay and inter-assay coefficients of variation are 2.1% and 4.5%, respectively.

Cardiovascular events

As above reported, other secondary endpoints will be the reduction of any cardiovascular event during hospitalization.

This composite outcome will consist of any of the following events: i.e. MI, new or worsening heart failure (HF), new-onset AF, stroke, cardiovascular death.

MI will be defined in concordance with the Fourth Universal Definition of Myocardial Infarction [33].

A new episode of AF was considered a newly recognized episode of AF during the hospitalization in individuals that were in sinus rhythm before hospital admission as documented by medical records, ECGs, rhythm strips, Holter-monitors [34].

New or worsening HF will be considered in patients with worsening signs, symptoms and supportive findings on echocardiography and/or chest radiograph consistent with this diagnosis (i.e.: new or worsening paroxysmal nocturnal dyspnea; neck vein distention on clinical exam; pulmonary rales; radiographic cardiomegaly; radiographic evidence of pulmonary edema; left ventricular ejection fraction < 40%; S3 gallop; hepatojugular reflux; bilateral ankle edema; initiation or increase in dosage of loop diuretics, ACE-inhibitor/ARB therapy, vasodilators or evidence-based beta-blocker therapy for heart failure; weight loss > 4.5 kg in 5 days in response to treatment).

The occurrence of stroke will be determined on the basis of clinical manifestations and will be confirmed by computed tomography (CT) or magnetic resonance imaging [35].

Cardiovascular death will include fatal MI; fatal stroke; sudden death; death due to cardiogenic shock in patients with NYHA-IV HF; death related to cardiovascular investigation/procedure/operation; death due to other specified cardiovascular causes.

Diagnoses will be done by a medical doctor, who is unaware of the treatment.

Finally, mortality and major adverse cardiac and cerebrovascular events (MACCE) will be assessed in a short- (30 days) and long-term follow-up.

MACCE will consist of a combined end-point of cardiovascular death, MI, and stroke.

Follow-up visits and follow-up data will be obtained by doctors, who will be unaware of the kind of intra-hospital treatment (methylprednisolone or placebo).

Data collection

Data will be collected using an electronic case report form specifically generated for the study. A unique identifier will be assigned by the investigator to each trial subject to protect the subject's identity and will be used in lieu of the subject's name when the investigator reports adverse events and/or other trial-related data.

For each patient recruited clinical and pharmacological records will be collected with particular interest to cardiovascular risk factors profile and pharmacological therapy before, during and after hospitalization will be collected. Moreover, the Pneumonia Severity Index [36] and the CURB-65 [37] will be verified at baseline, each item of these two indexes will be also collected. Any drug-allergy will be recorded.

The data will be computerized, and all data will be available to all researcher personals in agreement with the criteria and procedures established by current legislation. Using a validation plan integrated into the data entry software, data were checked for missing or wrong encodings. All samples will be coded to ensure the anonymity of the patient and entered in conjunction with clinical data in a computerized database protected by double access code/password.

Data will be transferred to the web-central database. Using a validation plan integrated into the data entry software, data will be checked for missing or contradictory entries and values out of the normal range. A final database will be created and validated by the study coordinator. Patient's identification name will be registered by recruiting personnel, but it will not be transferred to the central database. A serial of consecutive numbers will identify patients.

According to the Good Clinical Practice, all operational activities will be undertaken within the quality assurance system to verify that the requirements for quality of the trial-related activities will be respected.

Randomization

A stratified randomization technique will be employed, balancing covariates like age, PSI classes, sex, and coronary heart disease. An independent investigator will make

allocation using computer-generated random numbers. After staff will obtain the patient's consent, they will telephone a contact who is independent of the recruitment process for allocation consignment.

Blinding

Doctors and any primary care provider/s involved in the participant's non-trial management will be blinded to the group allocations. Individual participants will be not told their group allocation until the end of their involvement in the trial and after the completion of the trial.

Statistical analysis

Categorical variables will be reported as counts (percentage) and continuous variables were expressed as mean ± standard deviation (SD) or median and interquartile range (IQR). Differences between percentages will be assessed by Chi-square test or Fisher exact test. Student unpaired t test and ANOVA analysis will be used for normally distributed continuous variables. Appropriate nonparametric tests (Mann–Whitney, Kruskal–Wallis tests and Spearman rank correlation test) will be employed for all the other variables.

Wald confidence intervals will be obtained and test for odds-ratios and adjusted odds ratios will be computed based on the estimated standard errors.

The bivariate and multivariate effects of prognostic factors and treatments on the incidence of intra-hospital AF will be assessed by regression models.

Kaplan–Meier curves will be built for the occurrence of clinical endpoints. Log-rank test will be performed to analyze differences in survival distributors between subgroups. Univariate and multivariate Cox models will be used to assess clinically relevant variables and effects on the primary endpoint. A forward stepwise model selection procedure based on the AIC will be used to select the best multivariate regression model. A two-sided p value < 0.05 will be considered as statistically significant. All analyses will be performed using SPSS v. 25 (IBM, Armonk, NY, USA) and R v. 3.0.2 (R development core team, Vienna, Austria).

Sample size determination

We computed the sample size required with respect to a two-tailed two-sample Student's t test, considering as (i) a rise in troponin levels in 50% of patients, (ii) a decrease of hs-cTnT from 0.115 µg/l in the placebo group to 0.065 µg/l in the methylprednisolone group, (iii) standard deviation of the differences SD of 0.067 µg/l, (iii) type I error probability $\alpha = 0.05$ and power $1 - \beta = 0.80$. This resulted in 58 patients per group, for a total of $n = 116$ patients enrolled. To take into account a possible drop-out of 5%, we plan to enroll a total of $n = 122$ patients.

The expected levels of hs-cTnT have been conservatively obtained from analyzing data from previous studies [6]. The expected differences between treatments have been conservatively obtained by analyzing data of a cohort of 110 CAP patients at Policlinico-Umberto I, among which 50% were treated with corticosteroid. In this cohort, within 72 h from admission, patients treated with corticosteroid showed lower values of hs-cTnT than patients no treated (0.065 ± 0.054 vs. 0.115 ± 0.067; $p = 0.001$).

Discussion

This trial will be the first multicenter, double-blind, placebo-controlled trial to examine whether treatment with i.v. methylprednisolone (20 mg b.i.d.) may reduce hs-cTnT increase during CAP and eventually cardiovascular events during a short- and long-term follow-up. The trial will also examine whether the potential protective effects of methylprednisolone might be due to a reduction of platelet activation.

The novelty of this proposal is in its primary end-point, i.e. myocardial injury, as expressed as increased levels of hs-cTnT during the hospitalization phase. The rationale is that an increase of hs-cTnT during the acute phase of pneumonia is associated with early cardiovascular complications and has been consistently associated with worse short-term and long-term outcomes [9, 12].

Another important novelty concerns the use of a specific glucocorticoid, i.e. methylprednisolone.

The choice of methylprednisolone over other types of glucocorticoids stem from different considerations. Methylprednisolone is widely used in patients with pneumonia [14] and, in most of the controlled trials (RCT) involving CAP patients, was used intravenously at a dose ranging from 20 mg every day to 20 mg every 6 h [14].

Methylprednisolone is a prednisolone derivative with similar anti-inflammatory action. In an ex vivo study, prednisolone, but not dexamethasone, showed to inhibit platelet aggregation, platelet–monocyte interactions, and thrombus formation under flow [16]. These effects have been corroborated by an ex vivo study demonstrating that corticosteroid treatment was associated with reduced urinary excretion of Thromboxane (Tx) B2. The underlying mechanism seems to be dependent upon corticosteroid's ability to impair arachidonic release from platelet membrane via PLA2 down-regulation and ensuing reduced TxB2 biosynthesis [15]. The antiplatelet effect of methylprednisolone is not shared by other glucocorticoids and could be highly relevant in a clinical setting in which inflammation and enhanced platelet

activation could play a synergic role in enhance cardiovascular risk.

The possible clinical impact of such a treatment could be meaningful as pneumonia is one of the most important cause of death in elderly patients and the costs of the proposed treatment are very low because it consists in an inexpensive and known drug that will be given for no more than 7 days. Possible side effects can be considered negligible as previously shown by different RCTs in this setting [14]. Indeed, corticosteroids side effects are usually related to the dose and duration of therapy. Many of the adverse effects only occur over prolonged administration and most short-term adverse events are reversible when the drug is discontinued [20].

Conclusion

CAP, especially in elderly patients with comorbidities, is associated with an enhanced risk of cardiovascular disease, the leading cause of death worldwide. Our hypothesis is that treatment with systemic methylprednisolone could reduce myocardial injury during the acute phase of pneumonia and eventually cardiovascular events and mortality during a short- and long-term follow-up.

A treatment capable of reducing myocardial injury during CAP will open new perspectives in the therapeutic approach of pneumonia. If the hypothesis of this trial will be confirmed by data, the results will support the call for larger trial with cardiovascular events as the primary endpoint to evaluate the potential effectiveness of corticosteroids to counteract the enhanced cardiovascular risk associated to CAP.

Compliance with ethical standards

Conflict of interest The authors have no conflict of interest to declare related to this study.

Statement of human and animal rights All procedures followed will be in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000.

Informed consent All participants will provide informed consent prior to their participation.

References

1. Torres A, Peetermans WE, Viegi G, Blasi F (2013) Risk factors for community-acquired pneumonia in adults in Europe: a literature review. Thorax 68:1057–1065

2. Lozano R, Naghavi M, Foreman K et al (2012) Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet 380:2095–2128

3. Corrales-Medina VF, Musher DM, Shachkina S, Chirinos JA (2013) Acute pneumonia and the cardiovascular system. Lancet 381:496–505

4. Nichol KL, Nordin J, Mullooly J, Lask R, Fillbrandt K, Iwane M (2003) Influenza vaccination and reduction in hospitalizations for cardiac disease and stroke among the elderly. N Engl J Med 348:1322–1332

5. Corrales-Medina VF, Musher DM, Wells GA, Chirinos JA, Chen L, Fine MJ (2012) Cardiac complications in patients with community-acquired pneumonia: incidence, timing, risk factors, and association with short-term mortality. Circulation 125:773–781

6. Violi F, Cangemi R, Falcone M et al (2017) Cardiovascular complications and short-term mortality risk in community-acquired pneumonia. Clin Infect Dis 64:1486–1493

7. Cangemi R, Casciaro M, Rossi E et al (2014) Platelet activation is associated with myocardial infarction in patients with pneumonia. J Am Coll Cardiol 64:1917–1925

8. Corrales-Medina VF, Alvarez KN, Weissfeld LA et al (2015) Association between hospitalization for pneumonia and subsequent risk of cardiovascular disease. JAMA 313:264–274

9. Cangemi R, Calvieri C, Falcone M et al (2015) Relation of cardiac complications in the early phase of community-acquired pneumonia to long-term mortality and cardiovascular events. Am J Cardiol 116:647–651

10. Cangemi R, Calvieri C, Bucci T et al (2014) Is NOX2 upregulation implicated in myocardial injury in patients with pneumonia? Antioxid Redox Signal 20:2949–2954

11. Saunders JT, Nambi V, de Lemos JA et al (2011) Cardiac troponin T measured by a highly sensitive assay predicts coronary heart disease, heart failure, and mortality in the Atherosclerosis Risk in Communities Study. Circulation 123:1367–1376

12. Vestjens SM, Spoorenberg SM, Rijkers GT et al (2017) High-sensitivity cardiac troponin T predicts mortality after hospitalization for community-acquired pneumonia. Respirology. 22(5):1000–1006

13. Cangemi R, Falcone M, Taliani G et al (2018) Corticosteroid use and incident myocardial infarction in adults hospitalized for community-acquired pneumonia. Ann Am Thorac Soc. 16(1):91–98

14. Wan YD, Sun TW, Liu ZQ, Zhang SG, Wang LX, Kan QC (2016) Efficacy and safety of corticosteroids for community-acquired pneumonia: a systematic review and meta-analysis. Chest 149:209–219

15. Cangemi R, Carnevale R, Nocella C et al (2018) Glucocorticoids impair platelet thromboxane biosynthesis in community-acquired pneumonia. Pharmacol Res 131:66–74

16. Liverani E, Banerjee S, Roberts W, Naseem KM, Perretti M (2012) Prednisolone exerts exquisite inhibitory properties on platelet functions. Biochem Pharmacol 83:1364–1373

17. Santos-Gallego CG, Badimon JJ (2014) The sum of two evils: pneumonia and myocardial infarction: is platelet activation the missing link? J Am Coll Cardiol 64:1926–1928

18. Yende S, Thompson BT (2016) Evaluating glucocorticoids for Sepsis. Jama. 316(17):1769–1771

19. Annane D, Bellissant E, Bollaert PE, Briegel J, Keh D, Kupfer Y (2015) Corticosteroids for treating sepsis. Cochrane Database Syst Rev. 12:CD002243

20. Chen Y, Li K, Pu H, Wu T (2011) Corticosteroids for pneumonia. Cochrane Database Syst Rev. 12:CD007720

21. Mandell LA, Wunderink RG, Anzueto A et al (2007) Infectious Diseases Society of America/American Thoracic Society consensus guidelines on the management of community-acquired pneumonia in adults. Clin Infect Dis 44(Suppl 2):S27–S72

22. Lim WS, Baudouin SV, George RC et al (2009) BTS guidelines for the management of community acquired pneumonia in adults: update 2009. Thorax 64(Suppl 3):iii1–iii55

23. Eccles S, Pincus C, Higgins B, Woodhead M, Guideline Development G (2014) Diagnosis and management of community and hospital acquired pneumonia in adults: summary of NICE guidance. BMJ 349:g6722

24. Athlin S, Lidman C, Lundqvist A, Naucler P, Nilsson AC, Spindler C, Stralin K, Hedlund J (2018) Management of community-acquired pneumonia in immunocompetent adults: updated Swedish guidelines 2017. Infect Dis (Lond) 50:247–272

25. Woodhead M, Blasi F, Ewig S et al (2011) Guidelines for the management of adult lower respiratory tract infections–full version. Clin Microbiol Infect 17(Suppl 6):E1–E59

26. Torres A, Sibila O, Ferrer M et al (2015) Effect of corticosteroids on treatment failure among hospitalized patients with severe community-acquired pneumonia and high inflammatory response: a randomized clinical trial. JAMA 313:677–686

27. Reichlin T, Hochholzer W, Bassetti S et al (2009) Early diagnosis of myocardial infarction with sensitive cardiac troponin assays. N Engl J Med 361:858–867

28. Pignatelli P, Carnevale R, Cangemi R, Loffredo L, Sanguigni V, Stefanutti C, Basili S, Violi F (2010) Atorvastatin inhibits gp91phox circulating levels in patients with hypercholesterolemia. Arterioscler Thromb Vasc Biol 30:360–367

29. Pignatelli P, Carnevale R, Pastori D et al (2012) Immediate anti-oxidant and antiplatelet effect of atorvastatin via inhibition of Nox2. Circulation 126:92–103

30. Loffredo L, Carnevale R, Cangemi R et al (2013) NOX2 up-regulation is associated with artery dysfunction in patients with peripheral artery disease. Int J Cardiol 165:184–192

31. Cangemi R, Pignatelli P, Carnevale R et al (2012) Platelet iso-prostane overproduction in diabetic patients treated with aspirin. Diabetes 61:1626–1632

32. Pastori D, Carnevale R, Bartimoccia S et al (2015) Does mediterranean diet reduce cardiovascular events and oxidative stress in atrial fibrillation? Antioxid Redox Signal 23:682–687

33. Thygesen K, Alpert JS, Jaffe AS, Chaitman BR, Bax JJ, Morrow DA, White HD, Executive Group on behalf of the Joint European Society of Cardiology/American College of Cardiology/American Heart Association/World Heart Federation Task Force for the Universal Definition of Myocardial I (2018) Fourth Universal Definition of Myocardial Infarction (2018). J Am Coll Cardiol 72:2231–2264

34. Violi F, Carnevale R, Calvieri C et al (2015) Nox2 up-regulation is associated with an enhanced risk of atrial fibrillation in patients with pneumonia. Thorax 70:961–966

35. Kernan WN, Ovbiagele B, Black HR et al (2014) Guidelines for the prevention of stroke in patients with stroke and transient ischemic attack: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke 45:2160–2236

36. Fine MJ, Auble TE, Yealy DM et al (1997) A prediction rule to identify low-risk patients with community-acquired pneumonia. N Engl J Med 336:243–250

37. Myint PK, Kamath AV, Vowler SL, Maisey DN, Harrison BD (2005) The CURB (confusion, urea, respiratory rate and blood pressure) criteria in community-acquired pneumonia (CAP) in hospitalised elderly patients aged 65 years and over: a prospective observational cohort study. Age Ageing 34:75–77

38. Falcone M, Venditti M, Shindo Y, Kollef MH (2011) Healthcare-associated pneumonia: diagnostic criteria and distinction from community-acquired pneumonia. Int J Infect Dis 15:e545–e550