

Efficacy of anakinra in reducing progression to organ dysfunction in patients with pneumonia (INSPIRE): a randomised, double-blind, placebo-controlled, phase IIa trial



Georgios Tavoulareas,^a Olga Kontakou-Zoniou,^b Nikolaos Antonakos,^a Elisavet Tasouli,^c George Adamis,^d Nikolaos Kakavoulis,^c Evangelos Michelakis,^e Ilias Skopelitis,^e Konstantina Dakou,^b Christos Psarrakis,^a Panagiotis Koufargyris,^a Myrto Astriti,^d Styliani Sympardi,^c and Evangelos J. Giamarellos-Bourboulis^{a,b,*}



^aFourth Department of Internal Medicine, National and Kapodistrian University of Athens, Medical School, Athens, Greece

^bHellenic Institute for the Study of Sepsis, Athens, Greece

^cFirst Department of Internal Medicine, Thrasio General Hospital of Eleusis, Athens, Greece

^dFirst Department of Internal Medicine, G. Gennimatas General Hospital of Athens, Athens, Greece

^eThird Department of Internal Medicine, Aghios Panteleimon General Hospital, Nikaia, Greece

Summary

Background Early recognition of risk of death in pneumonia and start of precision immunotherapy to improve outcomes is an unmet need. We hypothesized that a precision strategy approach combining early recognition of interleukin (IL)-1 activation coupled with Anakinra treatment may improve pneumonia outcome.

Methods INSPIRE is a prospective, double-blind randomized placebo-controlled trial which recruited hospitalized adults with community-acquired or hospital-acquired pneumonia, with qSOFA (quick sequential organ failure assessment) equal to 1 and plasma presepsin (soluble CD14) more than 350 pg/ml. Patients were 1:1 randomised to standard-of-care medication plus either subcutaneous placebo or subcutaneous Anakinra 100 mg once daily for 10 days. The primary endpoint was progression into organ dysfunction defined as meeting at least one of the following two conditions; (i) at least 2-point increase of the baseline SOFA score by day 7 and/or (ii) death by day 90. This was analyzed in the intention-to-treat (ITT) population. This trial is registered with the EU Clinical Trials Register (2022-002390-28) and [ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT05785442) (NCT05785442).

Findings Patients were enrolled between March 2023 and June 2024; 30 patients in the placebo arm and 30 patients in the Anakinra arm were the ITT population. The primary endpoint was met in 50.0% (15 patients) of placebo-treated and in 20.0% (6 patients) of Anakinra-treated patients (difference 30.0% [5.9 to 49%]; p: 0.011). 90-day mortality was 43.3% (13 patients) and 20.0% (6 patients) (difference 23.3% [0 to 43.7%]; p: 0.029). The overall incidence of serious treatment-emergent adverse events (TEAEs) in the placebo group was 50% and in the Anakinra group 33.3%. None of the serious TEAEs was judged to be related to treatment assignment. Production of TNF α and IFN γ by blood mononuclear cells was decreased.

Interpretation Presepsin-guided Anakinra treatment prevents progression of pneumonia to organ dysfunction and death. The mechanism of benefit is associated with attenuation of cytokine production.

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Introduction

Severe community-acquired or hospital-acquired pneumonia is a leading cause of mortality worldwide. The annual incidence of community-acquired

pneumonia (CAP) requiring hospitalization increases dramatically with age and healthcare costs escalate substantially when hospital admission is necessary.^{1,2} The mortality due to hospital-acquired pneumonia

*Corresponding author. Fourth Department of Internal Medicine, National and Kapodistrian University of Athens, Medical School, 4th Department of Internal Medicine, ATTIKON University Hospital, 1 Rimini Street, 124 62, Athens, Greece.

E-mail address: egiamarel@med.uoa.gr (E.J. Giamarellos-Bourboulis).

Research in context

Evidence before this study

A PubMed search between 1 January 2015 and 1 January 2023 using the keywords community-acquired pneumonia/hospital-acquired pneumonia AND mortality AND adults and limited to clinical trials retrieved that mortality of pneumonia (CAP) widely ranges between 4% and 28%. Early immunotherapy requires the use of biomarkers which can provide accurate information on both the risk for an unfavorable outcome and the immune cascade which drives disease progression. This precision strategy of early recognition and management is an unmet need.

Added value of this study

The INSPIRE phase IIa randomized controlled trial (RCT) provides a novel precision strategy of early risk recognition and immunotherapy for CAP and HAP. Blood presepsin is the soluble CD14 molecule, shed from the cell membranes after stimulation of innate immune cells by pathogen-associated

molecular patterns. Levels above 350 pg/ml in patients without organ dysfunction signify risk for unfavorable outcome mediated by interleukin (IL)-1 activation. This guides treatment with the IL-1 receptor antagonist Anakinra leading to substantial clinical improvement. Benefit is translated to decreased odds of progression into organ dysfunction and death as well as earlier hospital discharge. The production of pro-inflammatory cytokines by peripheral blood mononuclear cells, namely TNF α , IFN γ and IL-1, is decreased.

Implications of all the available evidence

INSPIRE provides the first evidence from a prospective RCT to support early immunotherapy in CAP and HAP guided by biomarkers. The rationale of this precision strategy relies on early recognition of the activation of IL-1 pathway which mediates progression into sepsis and organ dysfunction.

(HAP) reaches 15–30%.³ Progression into sepsis and organ dysfunction is the common pathway for CAP and HAP to threaten life.⁴ One promising strategy to prevent pneumonia progression is to early recognize the patient at risk and administer immunotherapy to block the pathway which drives sepsis.

Cluster of Differentiation 14 (CD14) is a 55 kDa glycoprotein primarily expressed on the surface of macrophages and monocytes. It binds to a broad range of pathogen-associated molecular patterns (PAMPs) and facilitates downstream signal transduction through toll-like receptors (TLRs). Upon activation, CD14 undergoes internalization and enzymatic cleavage, releasing its soluble CD14 subtype (sCD14-ST), also known as presepsin.⁵ A recent study of our group found that presepsin blood levels more than 350 pg/ml are diagnostic of sepsis and predict unfavorable outcomes in patients with bacterial and viral CAP.⁶ Some patients with infections and qSOFA (quick sequential organ failure assessment) score equal to 1 bring the risk of progression into organ dysfunction; biomarkers may assist to early depict these patients.⁷ These observations prompted the initiation of the INSPIRE (Immunotherapy Navigated by Serum Presepsin for Infections of the REspiratory tract) randomized controlled trial (RCT). In the INSPIRE trial, patients with CAP or HAP without clinical signs of full-blown sepsis are screened by presepsin. Blood levels more than 350 pg/ml indicate the patient at risk under activation of TLRs and guide early treatment with the interleukin (IL)-1 receptor antagonist Anakinra to prevent progression into organ dysfunction. This predictive enrichment strategy is anticipated to discriminate patients with early IL-1 activation and high risk of unfavorable outcome

irrespective the type of pneumonia and the underlying pathogen.

Methods

Ethics approval

INSPIRE is a randomized, double-blind, placebo-controlled phase IIa trial conducted in four Internal Medicine departments of public hospitals in Greece between March 2023 and June 2024. The selection of participating study sites was done since they provide beds and expertise for intensive care unit (ICU) level care including non-interventional and mechanical ventilation and administration of vasopressors and related drugs when needed. ICU level care is available in Greece outside the formally designated ICUs, when needed, in designated Departments of Internal Medicine because of shortage of ICU beds. In the case of availability of ICU beds, patients are immediately transferred from the ICU level care beds to the formal ICU beds. The protocol was licensed by the National Ethics Committee of Greece (approval 109/22 of 10.10.2022) and the National Organization for Medicines of Greece (approval IS108-22 of 14.09.2022) after registration in the EudraCT database (2022-002390-28). The study was registered in [ClinicalTrials.gov](https://clinicaltrials.gov) (NCT05785442; published 2 March 2023; protocol found at <http://sepsis.gr>) before the inclusion of the first patient. Written informed consent was provided by the patients or their legal representative.

Study design and participants

Participants were adults (≥ 18 years) of either sex with CAP or HAP; qSOFA (quick Sequential Organ Failure

Assessment) score equal to 1; and presepsin levels >350 pg/ml. For women of reproductive age, the use of dual contraceptive therapy was mandatory during the study period. CAP was defined as a new consolidation on chest imaging (plain X-ray or computed tomography) in a patient with symptoms compatible with pneumonia (e.g. fever, dyspnea, cough, and sputum production) and no history of contact for two or more days with hospital environment or with health-care facility the last 90 days. HAP was defined as a new consolidation on chest imaging in a patient with symptoms compatible with pneumonia (e.g. fever, dyspnea, cough, and sputum production) presenting 48 h or more after hospital admission, which was not under incubation at the time of admission. Main exclusion criteria were infection by SARS-CoV-2, stage IV malignancy, partial pressure of arterial oxygen (PaO_2)/fraction of inspired oxygen (FiO_2) <150 mmHg necessitating non-invasive ventilation or mechanical ventilation, Intensive Care Unit (ICU) hospitalization, oral or intravenous (IV) intake of corticosteroids at a daily dose ≥ 0.4 mg/kg prednisone equivalent for more than the past 15 days; qSOFA score equal to 0, 2, or 3; any anti-cytokine treatment the last one month; and pregnancy or lactation.

Randomization and blinding

Patients meeting all inclusion criteria and none of the exclusion criteria were randomly assigned (1:1) to the standard-of-care (SoC) and anakinra arm or SoC and placebo arm via a computer-generated system. Anakinra was available as pre-filled syringes containing 100 mg to a final volume of 0.67 ml. An unblinded pharmacist at each study site prepared the placebo injections with normal saline (N/S 0.9% w/v) at the same volume and syringe to exactly resemble the Anakinra injections. Study drugs were stored at the study site in a refrigerator at 2–8 °C with temperature recording. The unblinded pharmacist covered the syringe with one corresponding label and handed it over to one blinded study investigator for subcutaneous injection. After the administration of the injection, the empty syringe was stored for accountability. The unblinded pharmacist did not disclose the treatment assignment and was not involved in any other study procedure. Patients, attending physicians, and study staff, including the assessors of the patients, remained blinded to treatment assignment.

Procedures

Anakinra (100 mg per injection) was administered subcutaneously once daily for ten consecutive days. The minimum required duration of treatment was four days. The SoC treatment was set according to local guidelines, and it was a β -lactam/ β -lactamase inhibitor or a third-generation cephalosporin or a fluoroquinolone in combination with a macrolide.

Linezolid, glycopeptides and corticosteroids were administered as SoC treatment at the discretion of the attending physician. Screening began after obtaining informed consent. A thorough review of each patient's past medical history was performed to rule out the presence of exclusion criteria. Patients with symptoms compatible with pneumonia underwent chest imaging with plain X-ray and/or CT scan. Patients without exclusion criteria and meeting clinical inclusion criteria were subject to blood draw of 4 ml via venipuncture of one antecubital vein under aseptic conditions. Plasma presepsin was measured at the study central lab (Laboratory of Immunology of Infections, 4th Department of Internal Medicine, ATTIKON University General Hospital) using the PATHFAST assay (PHC, Japan) by one independent technician blind to clinical information; patients with levels >350 pg/ml were enrolled. The assay is widely available as a point-of-care bedside test and the total turnaround time for the analysis is 15 min. Patients with presepsin ≤ 350 pg/ml were followed up for 90 days for changes of SOFA (sequential organ failure assessment) score and survival.

Study visits were scheduled from day 1 to day 10 and on days 14, 28, and 90. Day 1 was defined as the day of the study drug initiation. Comorbidities and the Acute Physiology and Chronic Health Evaluation (APACHE) II score were captured on day 1. During all study visits, SOFA scores, survival, concomitant medication, routine laboratory, microbiology and non-serious and serious treatment-emergent adverse events (TEAE) were recorded in an electronic case report form. Blood samples were collected daily the first 10 days for measurements of presepsin, procalcitonin (PCT), Interleukin Adhesion Molecule (ICAM)-1, Vascular Adhesion Molecule (VCAM)-1 and P-selectin and for isolation and cytokine stimulation of peripheral blood mononuclear cells (PBMCs) (see [Supplementary Methods](#)).

Outcomes

The primary endpoint of the study was progression into organ dysfunction. This was a composite endpoint defined as either two or more points increase of SOFA score by day 7 from baseline day 1 or death by day 90. The secondary endpoints were: the changes in SOFA score throughout the follow-up period; the incidence of new organ-specific dysfunction; the time to hospital discharge; 28-day mortality; 90-day mortality; the time to attenuation of sepsis-induced inflammation as described by the PCT rule; the changes in presepsin levels from baseline to day 10; and the changes of cytokine production capacity by PBMCs. Separate secondary endpoints were the progression to organ dysfunction by day 10 and 90-day mortality between patients who failed screening due to presepsin levels ≤ 350 pg/ml and patients enrolled and allocated in the SoC plus placebo arm. A reduction in PCT of greater than 80% or a concentration below 0.5 ng/ml was

considered indicative of attenuation of sepsis-induced inflammation.⁸

Two post-hoc analyses were also done which were not provisioned in the statistical analysis plan. In the first analysis, we calculated the SCORE2 of eight variables suggested by the US Food and Drug Administration (Supplementary Table S1)^{9,10} to predict unfavorable outcome between patients who failed screening due to presepsin levels ≤ 350 pg/ml and patients enrolled and allocated in the SoC plus placebo arm. In the second analysis, we measured serum calprotectin (S100A8/A9) (see Supplementary Methods), which is a danger-associated molecular pattern (DAMP) acting as TLR4 agonist,¹¹ as predictor of unfavorable outcome and of response to Anakinra treatment.

Statistical analysis

The study was powered under the assumption that the primary endpoint would be met by 65% of the patients in the SoC and placebo arm and 30% of the patients in the SoC and Anakinra arm using the data for pneumonia worsening coming from the SAVE and SAVE-MORE trials.^{12,13} To demonstrate this difference with 80% power at a level of statistical significance of 5%, 30 patients were enrolled in each arm. Analysis was done according to the intention-to-treat (ITT) principle. Because of the small number of patients to be allocated for each study site, a blocked randomization scheme was adopted with only four patients per block (Supplementary Table S2). Quantitative variables were expressed by means and standard deviation (SD) if they followed normal distribution and by medians and quartiles if they followed non-normal distribution. Quantitative characteristics were compared using Student's t-test for normally distributed data and the Mann-Whitney U test for non-normally distributed data. Dichotomous variables were expressed as percentages with 95% confidence intervals (CIs) and compared using Fisher's exact test. Odds ratios (ORs) and 95% CIs were calculated by the Mantel-Haenszel test. The confidence intervals for the between groups differences were calculated by the Wilson procedure without correction for continuity. The study primary endpoint was analyzed by multiple logistic regression analysis with APACHE II score of day 1, SOFA score of day 1 and the Charlson's comorbidity index (CCI) as covariates. It was decided in the statistical analysis plan to add treatment with IV corticosteroids as a covariate after the recent guidelines for the treatment of CAP/HAP.¹⁴ Hazard ratio (HR) and 95% CIs were calculated. Cox regression analyses were done for 28-day and 90-day mortalities using the same covariates. Time to hospital discharge was compared using Cox regression analysis where patients dying in hospital before day 90 were considered non-discharged. Receiver operator characteristics (ROC) curve analysis was done to define the cut-off of baseline change of presepsin which favors

the primary endpoint. The time to attainment of the presepsin change was compared between the two arms of treatment by Cox regression analysis. Cytokine changes in PBMCs supernatants on follow-up days more than 30% from baseline were considered significant, as described elsewhere,¹⁵ and compared. P-values < 0.05 were considered statistically significant. Statistical analysis was conducted using IBM SPSS Statistics 26.0.

Role of the funding source

The sponsor of the study, the Hellenic Institute for the Study of Sepsis (HISS), was responsible for the study design, conduct, data analysis, interpretation, and the decision to submit for publication. PHC and Sobi did not have any role in the study design, data collection, analysis, interpretation, writing of the manuscript or decision to publish.

Results

The first patient was enrolled on 6 March 2023, and the follow-up of the last patient was completed on 23 June 2024. The statistical analysis plan was finalized on 28 December 2023; and the final lock of the database was done on 30 September 2024. 371 patients were assessed for eligibility (Fig. 1) and 60 patients were randomized; 30 into the SoC and placebo arm; and 30 into the SoC and Anakinra arm. No data was missing and there was strict adherence to the study protocol by the investigators. All enrolled patients were of Caucasian origin. No differences were found between groups at baseline before the start of the study drug for severity scores, biomarkers, microbiology and the use of antibiotics, intravenous corticosteroids and supplementary oxygen (Table 1). All patients were screened less than 24 h from the diagnosis of CAP or HAP. No patient had aspiration pneumonia. No patient was lost to follow-up. There was no need for a Data Safety Monitoring Board since Anakinra has a well-known safety profile for respiratory tract infections.^{12,13}

The composite primary endpoint of progression into organ dysfunction, defined as either 2 or more points increase in SOFA score by day 7 or death by day 90, was met by 50% of patients in the Placebo group and by 20% in the Anakinra arm (30.0% difference; 95% CIs 3.5 to 51.7%) (Table 2). This was confirmed by logistic regression analysis showing that the APACHE II score and Anakinra treatment were the only variables associated with the primary endpoint; Anakinra treatment was protective from progression into organ dysfunction (adjusted OR 0.18 [95% CIs 0.05 to 0.67]; $p: 0.011$) (Supplementary Table S3). The total SOFA score was lower in the Anakinra group on days 6 and 7 (Supplementary Table S4). A sensitivity analysis confirmed the protective effect of Anakinra from progression into organ dysfunction in patients with CAP

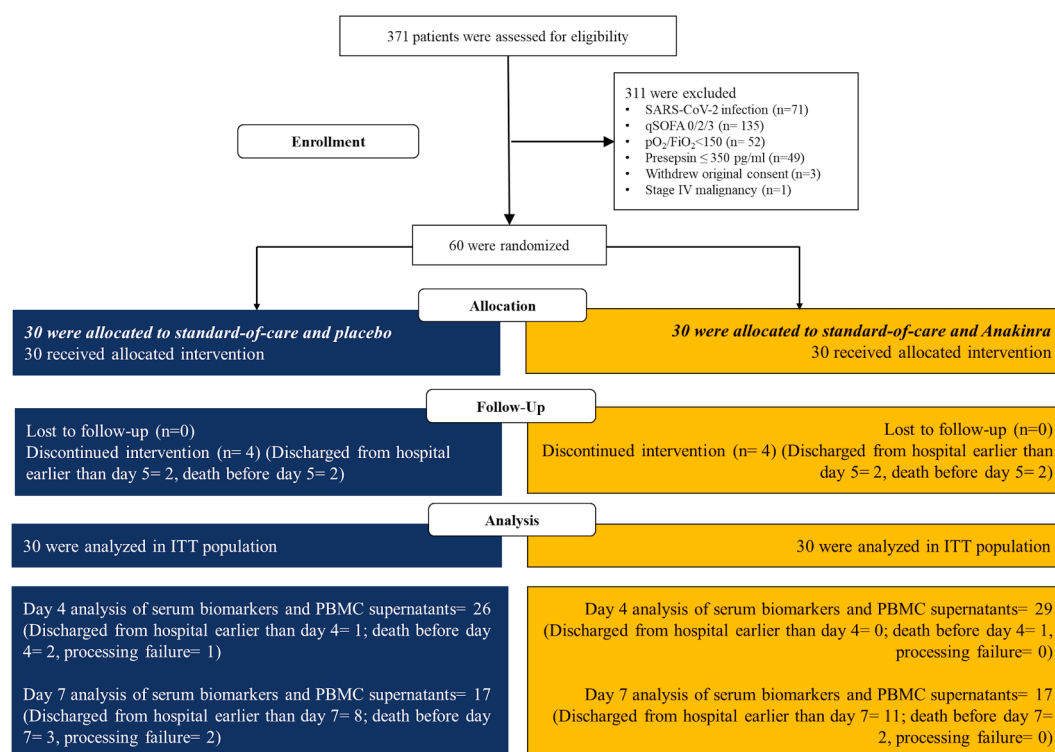


Fig. 1: Study flow chart. Abbreviations FiO₂, fraction of inspired oxygen; ITT, intention-to-treat; n, number of patients; PBMCs, peripheral blood mononuclear cells; pO₂, partial oxygen pressure; qSOFA, quick sequential organ failure assessment score.

(Supplementary Table S5). The classification of study participants into each of the elements of the composite endpoint showed that most of patients who experienced ≥2-point increase of SOFA score died by day 90 (Supplementary Table S6).

Allocation to Anakinra treatment managed to attain most of the secondary study endpoints (Table 2). Eleven out of 30 patients treated with SoC and Placebo experienced significant decreases of SOFA score over follow-up (36.7%) compared to 20 out of 30 patients treated with SoC and Anakinra 20 (66.7%) (30.0% difference; 95% CIs 2.5 to 52.3%). The time to hospital discharge alive was shorter in the SoC and Anakinra group (Supplementary Figure S1). Multiple Cox regression analysis including APACHE II score, CCI, SOFA score and co-administration of intravenous corticosteroids showed survival benefit by day 28 with Anakinra treatment (adjusted HR 0.29; 95% CIs 0.08 to 0.99; p: 0.049) (Supplementary Figure S2). Using a similar multiple Cox regression model significant 90-day survival benefit was found with Anakinra treatment by day 90 (adjusted HR 0.32 [0.12 to 0.89; p: 0.029]) (Fig. 2 and Supplementary Table S7).

In total 19 patients, 13 allocated to the SoC and placebo and six allocated to the SoC and Anakinra group died by Day 90. Ten and four of these deaths occurred by Day 28. Analysis limited to patients who

failed screening due to presepsin levels ≤350 pg/ml and patients with presepsin >350 pg/ml randomized in the SoC and placebo group, showed that the sensitivity, specificity, positive predictive value and negative predictive value of presepsin >350 pg/ml to predict 28-day mortality was 66.7%, 68.8%, 33.3%, and 89.8% respectively. In total 37 patients progressed into need of ICU level care; 20 patients from the SoC and placebo group (66.7%) and 17 patients from the SoC and Anakinra group (56.7%) (difference 10.0%; 95% CIs -13.9 to 32.5%). From the 37 patients progressing into ICU level care, a) 33 patients progressed into need for high-flow oxygenation; 11 (33.3%) died by day 28; b) six patients progressed further into need for mechanical ventilation; four patients died (66.7%) by day 28; and c) 19 patients progressed into need of vasopressors; 11 patients died (57.9%) by day 28 (Supplementary Figure S3). Overall, 28-day mortality of patients needing ICU level care was 32.4% (12 patients); and 90-day mortality was 40.5% (15 patients). The causes of death of the 15 patients were respiratory failure (3 patients); new sepsis (7 patients); pulmonary embolism (1 patient); status epilepticus (1 patient); sudden cardiac arrest (1 patient); candidemia (1 patient); and COVID-19 pneumonia (1 patient). No decision for support withdrawal was taken for any patient. Another four patients died by day 90 following hospital discharge:

	SoC + Placebo (N = 30)	SoC + Anakinra (N = 30)
Age (years), mean (SD)	70.9 (16.2)	74.0 (13.5)
Male/Female, n (%)	20 (66.7)/10 (33.3)	16 (53.3)/14 (46.7)
Body mass index (kg/m ²), mean (SD)	26.9 (5.2)	28.7 (6.4)
APACHE II score, mean (SD)	10.7 (3.7)	11.1 (4.7)
CCI, mean (SD)	4.57 (2.80)	4.83 (2.28)
CURB65 score, mean (SD)	1.57 (0.85)	1.63 (0.72)
SOFA score, mean (SD)	4.30 (4.42)	3.59 (1.82)
PSI, mean (SD)	99.2 (27.7)	107.5 (28.7)
Community-acquired pneumonia, n (%)	28 (93.3)	28 (93.3)
Hospital-acquired pneumonia, n (%)	2 (6.7)	2 (6.7)
Presepsin (pg/ml) median (Q1–Q3)	570.5 (411.8–681.0)	565.0 (428.4–934.0)
Procalcitonin (ng/ml), median (Q1–Q3)	0.59 (0.18–2.66)	0.44 (0.19–1.16)
C-reactive protein (mg/l), median (Q1–Q3)	148.0 (97.6–194.3)	158.0 (107.0–278.9)
Ferritin (ng/ml), median (Q1–Q3)	305.0 (168.4–550.4)	397.6 (155.7–660.0)
White Blood Cell count (/mm ³), mean (SD)	11,167.2 (4155.2)	13,310.0 (8400.1)
Neutrophil count (/mm ³), mean (SD)	9123.4 (3803.9)	11,497.3 (8197.6)
Lymphocyte count (/mm ³), mean (SD)	1120.7 (615.1)	920.7 (559.2)
Platelet count (x10 ³ /mm ³), mean (SD)	243.4 (127.2)	235.6 (121.5)
Creatinine (mg/dl), mean (SD)	1.28 (0.62)	1.56 (1.61)
ALT (U/L), median (Q1–Q3)	18.0 (11.0–40.5)	24.0 (16.8–47.0)
AST (U/L), median (Q1–Q3)	27.0 (18.5–51.0)	30.0 (21.0–55.3)
Total bilirubin (mg/dl), mean (SD)	0.69 (0.49)	0.83 (0.59)
Lactate (mmol/l), median (Q1–Q3)	1.20 (1.05–3.54)	1.24 (0.97–1.67)
pO ₂ /FiO ₂ , mean (SD)	253.1 (83.1)	273.1 (110.1)
International normalized ratio, mean (SD)	1.19 (0.33)	1.17 (0.16)
Comorbidities, n (%)		
Type 2 diabetes mellitus	13 (43.3)	9 (30.0)
Chronic heart failure	5 (16.7)	5 (16.7)
Chronic obstructive pulmonary disease	4 (13.3)	10 (33.3)
Chronic renal disease	6 (20.0)	5 (16.7)
Coronary heart disease	5 (16.7)	6 (20.0)
Atrial fibrillation	8 (26.7)	5 (16.7)
Ischemic stroke	3 (10.0)	3 (10.0)
Smoking	12 (40.0)	8 (26.7)
Non-metastatic solid tumor malignancy	3 (10.0)	5 (16.7)
Isolated pathogens, ^a n (%)		
<i>Staphylococcus aureus</i> ^b	6 (20.0)	7 (23.3)
<i>Streptococcus pneumoniae</i>	0 (0)	3 (10.0)
<i>Klebsiella pneumoniae</i>	5 (16.7)	0 (0)
<i>Pseudomonas aeruginosa</i>	3 (10.0)	1 (3.3)
<i>Haemophilus influenzae</i>	1 (3.3)	2 (6.7)
Viruses	2 (6.7)	4 (13.3)
Standard-of-care treatment		
Antibiotics, n (%)		
β-lactams/β-lactamase inhibitors	5 (16.7)	7 (23.3)
3rd generation cephalosporins	10 (33.3)	5 (16.7)
Piperacillin/Tazobactam	17 (56.7)	14 (46.7)
Macrolides	11 (36.7)	9 (30.0)
Fluoroquinolones	2 (6.7)	3 (10.0)
Linezolid	10 (33.3)	7 (23.3)
Glycopeptides	7 (23.3)	5 (16.7)

(Table 1 continues on next page)

one patient by sepsis; one patient by surgical site infection; one patient by acute renal injury; and another patient by sudden cardiac arrest.

The time to achievement of favorable PCT kinetics did not differ between the two groups (data not shown). Following ROC analysis, any more than or equal to 50% decrease of presepsin from baseline was linked with achievement of the primary endpoint. The time to attain this decrease was shorter in the SoC and Anakinra group ([Supplementary Figure S4](#)).

In order to validate the predictive role of presepsin towards progression into organ dysfunction, two more secondary endpoints were studied comparing patients who failed screening due to presepsin levels ≤350 pg/ml with patients randomized in the SoC and placebo group: the attainment of the composite endpoint of progression into organ dysfunction by day 10 (defined as any increase of SOFA score by at least two points and/or death) and 90-day mortality. The progression into organ dysfunction by day 10 was noted in one out of 49 patients with presepsin ≤350 pg/ml (2.0%) compared to 8 out of 30 patients treated with SoC and placebo (26.7%; difference 24.6%; 95% CIs 9.4 to 42.5%; p: 0.001). Mortality during the 90 days of follow-up was higher with presepsin more than 350 pg/ml compared to patients with presepsin ≤350 pg/ml ([Supplementary Figure S5](#)). Presepsin and calprotectin could indicate patients who progressed into organ dysfunction early, contrary to PCT ([Supplementary Figure S6](#)). No differences in serum levels of VCAM-1, ICAM-1 and P-selectin were found ([Supplementary Table S8](#)).

The SCORE2 suggested by the US FDA to indicate patients with COVID-19 eligible for Anakinra treatment,^{9,10} managed to predict patients with presepsin >350 pg/ml with sensitivity 98.3% and positive predictive value 76.6% ([Supplementary Tables S9 and S10](#)). Patients with SCORE2 ≥3 had a worse outcome ([Supplementary Figure S7](#)).

Following ROC curve analysis, a calprotectin cut-off of 6.8 ng/ml was found to predict unfavorable outcome (OR 4.09; 95% CIs 1.37 to 12.25; p: 0.012). Patients with calprotectin ≥6.8 ng/ml had worse outcome ([Supplementary Figure S8](#)). The time to >50% decrease of calprotectin was significantly shorter among patients receiving treatment with SoC and Anakinra than in the SoC and Placebo group ([Supplementary Figure S9](#)).

Major changes in cytokine production by the PBMCs after stimulation were found between the two arms of treatment. Patients allocated to treatment with SoC and Anakinra experienced greater odds for decrease in the PBMC production capacity for TNFα and for IFNγ ([Table 3](#) and [Supplementary Table S11](#)). Treatment with SoC and Anakinra was accompanied by greater likelihood for decrease of IL-1ra by the PBMCs without any significant changes of IL-36γ ([Supplementary Table S11](#)). The PBMCs production capacity for IL-10

and IL-17 remained unaltered (Table 3 and Supplementary Table S11).

No SUSARs were captured and the overall incidence of serious TEAEs was 50.0% and 33.3% in the SoC and Placebo arm and in the SoC and Anakinra arm; this was 90.0% and 86.7% for the non-serious TEAEs. No differences were found between the two groups (Supplementary Tables S12 and S13). The most common serious TEAEs were infections and infestations (23.3% and 26.7% respectively) and cardiac disorders (10.0% and 3.3% respectively). The most common non-serious TEAEs were anemia (20.0% and 33.3% respectively) and diarrhea (20.0% and 16.7% respectively).

Discussion

INSPIRE is the first RCT that demonstrated the clinical benefit of presepsin, a biomarker of early risk prediction and identification of pathogenesis driven by IL-1, to guide immunotherapy with Anakinra in CAP/HAP. Presepsin-guided Anakinra treatment prevented progression into organ dysfunction and decreased 90-day mortality. Anakinra-treated patients experienced earlier hospital discharge. The mechanism of Anakinra action was associated with modulation of the cytokine production capacity from PBMCs.

The mortality of patients with pneumonia allocated to the SoC and Placebo arm reaching 33.3% by day 28 and 43.3% by day 90 seems exceedingly high. To further explain this phenomenon, Supplementary Table S14 summarizes the prognostic performance of several presepsin cut-offs for mortality between days 28 and 30.^{6,16–21} Most of these studies suggest predictive cut-offs higher than 350 pg/ml. This difference may be due to the overall small number of patients enrolled in each study, to the different implicated pathogens or to

	SoC + Placebo (N = 30)	SoC + Anakinra (N = 30)
(Continued from previous page)		
Number of patients treated with appropriate antibiotics ^c /number of patients with at least one isolated microorganism ^d (%)	13/13 (100)	10/11 (90.9)
IV corticosteroids, ^e n (%)		
Hydrocortisone 50 mg q6h	3 (10.0)	1 (3.3)
Methylprednisolone 40 mg q8h	13 (43.3)	14 (46.7)
Oxygen supplementation by mask, n (%)	26 (89.7)	26 (89.7)

Abbreviations ALT, alanine aminotransferase; AST, aspartate aminotransferase; APACHE, acute physiology and chronic health evaluation; CCI, Charlson's comorbidity index; CURB65, score by confusion, urea ≥ 40 mg/dl, respiratory rate ≥ 30 breaths/minute, systolic blood pressure < 90 mmHg and age ≥ 65 years; FiO₂, fraction of inspired oxygen; IV, intravenous; n, number; PCR, polymerase chain reaction; pO₂, partial oxygen pressure; PSI, pneumonia severity index; Q, quartile; q6h, every 6 h; q8h, every 8 h; SD, standard deviation; SOFA, sequential organ failure assessment. ^aBy sputum culture or BioFire FilmArray PCR; nil patient had positive blood culture. ^bAll patients treated with linezolid. ^cDefined as receiving from study start at least one antibiotic active against the isolated species according to the antimicrobial susceptibility testing. ^dSome patients had more than one microorganism isolated from sputum. ^eCorticosteroid treatment started together with the other drugs of the SoC.

Table 1: Baseline characteristics of the enrolled patient population.

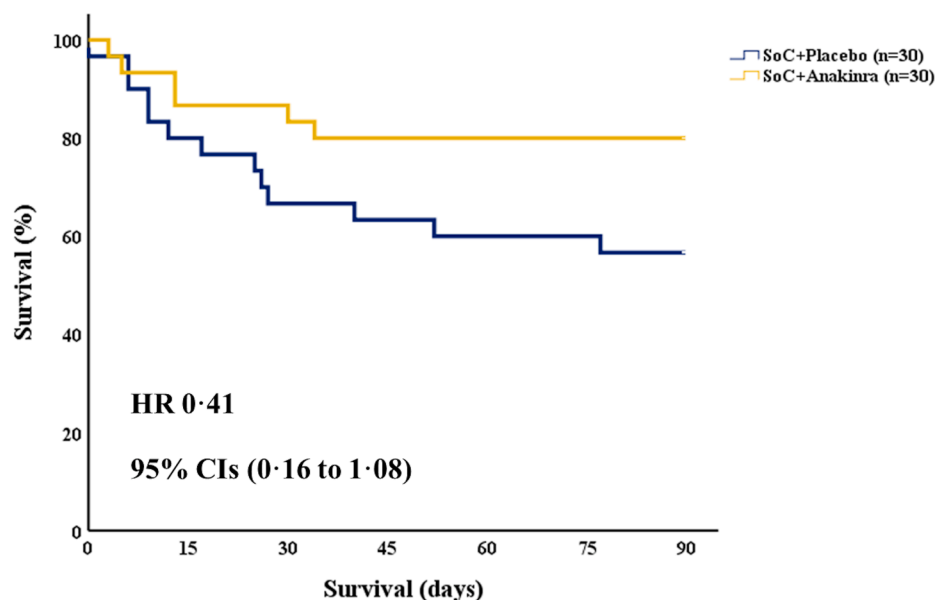
the different study ethnicities. A recent study of 119 patients with sepsis from China indicates that the relative increase of presepsin is a better predictor of mortality than any absolute value.^{22,23} Results also suggest that in patients with pneumonia and one sign of qSOFA presepsin more than 350 pg/ml is a tool of prognostic enrichment for risk for death where alertness for early ICU admission is warranted. These patients are also at risk for death even after day 28.

Ancillary treatments targeting the immune component in severe pneumonia and sepsis have been extensively studied.²⁴ In most of these studies, patients with severe pneumonia participated since they had

	SoC and placebo	SoC and Anakinra	% difference (95% CIs)	Effect size (95% CIs)	p-value
Primary endpoint					
Progression into organ dysfunction, n (%)	15 (50)	6 (20)	30 (5.9 to 49.8)	0.18 (0.05–0.67) ^a	0.011
Secondary endpoints					
Any ≥ 2 -point decrease of SOFA score from baseline until day 28, n (%; 95% CIs)	11 (36.7)	20 (66.7)	30 (4.8 to 50.4)	3.46 (1.10 to 9.89)	0.038
Incidence of ARDS by day 28, n (%; 95% CIs)	5 (16.7)	2 (6.7)	10 (–7.4 to 27.6)	0.36 (0.06 to 2.00)	0.424
Time until hospital discharge (days), median (Q1–Q3)	22 (7–28)	10 (6–16)	^b	^b	0.046 ^d
Mortality by day 28, n (%; 95% CIs)	10 (33.3)	4 (13.3)	20 (–1.6 to 39.6) ^c	0.29 (0.08 to 0.99) ^d	0.049
Mortality by day 90, n (%; 95% CIs)	13 (43.3)	6 (20.0)	23.3 (0–43.7) ^c	0.32 (0.12 to 0.89) ^d	0.029
Favorable PCT kinetics, ^e n (%; 95% CIs)	25 (83.3)	26 (86.7)	3.3 (–14.2 to 20.9)	1.16 (0.67 to 2.02) ^b	0.589
Favorable presepsin kinetics, ^f n (%; 95% CIs)	14 (46.7)	22 (73.3)	26.7 (1.9 to 47.3)	2.05 (1.04 to 4.03) ^b	0.045

Abbreviations ARDS, acute respiratory distress syndrome; CI, confidence interval; HR, hazard ratio; PCT, procalcitonin; n, number of patients; Q, quartile; ROC, receiver operator characteristics; SoC, standard-of-care; SOFA, sequential organ failure assessment. ^aAdjusted OR and p-value after multiple logistic regression analysis. ^bCannot be calculated. ^cCalculated by the Wilson procedure without correction for continuity. ^dAdjusted HR and p-value after multiple Cox regression analysis. ^eDefined as at least 80% decrease of baseline PCT (before start of the study drug) or PCT below 0.5 ng/ml by day 7. ^fDefined as at least 50% decrease of baseline presepsin (before start of the study drug) by day 10. The 50% cut-off was defined as the Youden index after ROC curve analysis of the change of presepsin which favors the primary endpoint.

Table 2: Study primary and secondary endpoints.



Patients at risk (n)

SoC + Placebo	30	24	20	19	18	17	17
SoC + Anakinra	30	26	25	24	24	24	24

Fig. 2: Impact of presepsin-guided Anakinra treatment on 90-day mortality. Patients are randomized to treatment with SoC and Placebo or SoC and Anakinra. **Abbreviations** CI, confidence interval; HR, hazard ratio; n, number of patients; SoC, standard-of-care.

full-blown sepsis with organ dysfunctions. Early studies from the 1990s failed to demonstrate the benefit of IL-1 blockade in sepsis.^{25,26} However, a reanalysis of the data nearly two decades later identified a subgroup with features of macrophage activation that experienced an approximate 30% reduction in mortality with anakinra treatment.²⁷ This subgroup with macrophage activation is only 6% of patients with sepsis.²⁸ A novel strategy using immunotherapy for pneumonia was suggested during the COVID-19 pandemic. Early recognition of IL-1 activation with the biomarker suPAR (soluble urokinase plasminogen activator receptor), well before

signs of organ dysfunction appear, guides Anakinra treatment of SARS-CoV-2 pneumonia. Treated patients have 0.36 odds ratio for worse outcome as expressed by the World Health Organization Clinical Progression Scale (WHO-CPS) compared to the placebo group.¹²

The prevention of progression into organ dysfunction in the INSPIRE trial is apparently due to the anti-inflammatory properties of Anakinra i.e. of inhibition of both IL-1 β and IL-1 α . The inhibition of IL-1 attenuated the production capacity of the PBMCs for the pro-inflammatory cytokines TNF α and IFN γ . Likewise IL-1ra production decreased indicating decrease of IL-1 β

	SoC and placebo	SoC and Anakinra	% difference (95% CIs)	p-value
$\geq 30\%$ decrease of the production of TNF α^a after stimulation with LPS, n/N (%)	8/26 (30.8)	19/29 (65.5)	34.8 (8.3 to 55.1)	0.015
$\geq 30\%$ decrease of the production of IFN γ^a after stimulation with HKCA, n/N (%)	4/24 (16.7)	12/26 (46.2)	29.5 (3.6 to 50.4)	0.035
$\geq 30\%$ decrease of the production of IL-1ra without decrease of IL-23 and IL-36 γ^a after stimulation with LPS, n/N (%)	1/22 (4.5)	9/25 (36.0)	31.5 (8.1 to 51.3)	0.012
$\geq 30\%$ increase of the production of IL-10 a after stimulation with HKCA, n/N (%)	9/22 (40.9)	15/29 (55.6)	14.7 (-12.7 to 39.1)	0.39
$\geq 30\%$ decrease of the production of IL-17A a after stimulation with HKCA, n/N (%)	7/22 (31.8)	9/27 (33.3)	1.5 (-24.0 to 28.3)	1.00

Abbreviations CI, confidence interval; HKCA; heat-killed *Candida albicans*; IFN, interferon; IL, interleukin; LPS, lipopolysaccharide; n, number of patients; N, total number of tested subjects; PBMCs, peripheral blood mononuclear cells; SoC, standard-of-care; TNF α , tumor necrosis factor-alpha. ^aIn supernatants of PBMCs compared to baseline before start of the study drug.

Table 3: Impact of presepsin-guided Anakinra treatment on cytokine production capacity from PBMCs.

production. No effect on the pro-inflammatory IL-36 γ of the IL-1 family was found. Anakinra treatment rapidly decreased blood presepsin. IL-1 β acts through an auto-inflammatory loop on the cell membranes of tissue macrophages²⁹ and the rapid decrease of the soluble CD14/presepsin molecule indicates the cessation of this auto-inflammatory activation. Post-hoc analysis of calprotectin levels confirmed the role of this DAMP protein in IL-1 mediated inflammation. An early reduction in calprotectin concentrations was observed in the Anakinra-treated group compared to Placebo group as early as Day 2 of treatment. These findings highlight the potential of calprotectin as an early and sensitive biomarker for monitoring response to Anakinra treatment. The method of measurement is particle-enhanced turbidimetric immunoassay with 20 min turnaround time; the assay is CE-IVD marked.

The study has several limitations. First, the sample size was relatively small, and larger studies are needed to validate the findings. Second, our study focused on respiratory tract infections, and generalizability to other sources of infection should be explored separately. Third, despite the study's initial goal to include patients with HAP, their actual number was low, limiting the applicability of the results to patients with CAP. Fourth, we acknowledge that presepsin testing may not be readily available in many acute care facilities. Our post-hoc analyses support that SCORE2 and blood calprotectin may be used as alternatives. Finally, presepsin-guided treatment with Anakinra requires health care settings which provide ICU level care, since several of the patients progress into organ dysfunction.

There are several considerations for future research stemming from this study. The role of presepsin in management remains unclear. A previous study demonstrated that the use of presepsin reduced the duration of antimicrobial treatment in septic patients without increasing the risk of adverse outcomes.²⁹ Exploring the correlation of presepsin with other components involved in sepsis pathophysiology could yield valuable insights. For instance, Boermeester et al. showed that patients with severe sepsis suffered from perturbations of the hemostatic mechanism, evidenced by improvement in coagulation parameters following IL-1 inhibition.³⁰ Since derangements of the coagulation cascade and endothelial dysfunction are processes incited by IL-1,³¹ presepsin might serve as a surrogate marker for multiple physiological responses driven by pronounced IL-1 release.

The multiple Cox regression model suggests that intake of corticosteroids was associated with unfavorable 90-day outcomes. The use of corticosteroids for severe CAP has recently become a matter of debate. In a randomized study on 795 patients hospitalized in 31 French sites, it was found that intravenous

hydrocortisone at a total daily dose of 200 mg significantly decreased 28-day mortality (6.2% versus 11.9% in the placebo arm).³² These results failed to be reproduced by the corticosteroid domain of the REMAP-CAP platform trial on 535 patients with severe CAP treated with hydrocortisone and 122 comparators. Analysis using Bayesian model showed that the probability of more than 20% reduction of the odds for 90-day mortality with treatment was 7.1% and for harm 84.3%; this led to premature end of the study for futility.³³ These contradictory findings make necessary the conduct of additional studies.

The INSPIRE trial paves the way of selective enrichment for precision management of CAP and HAP. This withholds a two step-strategy. Presepsin is the biomarker which selects patients at early activation of the IL-1 cascade. Increased presepsin guides Anakinra treatment with the goal to prevent progression into organ dysfunction and decrease mortality. The SCORE2 suggested by the US FDA to select patients with COVID-19 pneumonia who experience Anakinra treatment benefit and/or measurement of circulating calprotectin can be used as alternatives to presepsin for patient selection and treatment monitoring.

Contributors

GT wrote the study protocol, wrote the original draft, revised the manuscript for intellectual content and approved the final version for submission.

EJG-B conceptualized the study, was responsible for the acquisition of funding and study resources, supervised the study, analyzed the data, wrote the original draft, revised the manuscript for intellectual content and approved the final version for submission.

OK-Z was the study clinical research associate, contributed to data acquisition, investigation and project administration, revised the manuscript for intellectual content and approved the final version for submission.

NA, ET, GA, NK, IS, IS, CP, Ga, and SS contributed to data acquisition, investigation and project administration, revised the manuscript for intellectual content and approved the final version for submission. KD developed the study database, curated the data, analyzed the data, revised the manuscript for intellectual content and approved the final version for submission.

PK performed laboratory analyses, revised the manuscript for intellectual content and approved the final version for submission.

All authors have full access to the data of the study. EJG-B and KD accessed and verified all data. All authors had final responsibility for the decision to submit the manuscript.

Data sharing statement

Data are available with publication by the corresponding author by a signed data access agreement.

Declaration of interests

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The other authors do not declare any conflict of interest.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at <https://doi.org/10.1016/j.lanepe.2025.101573>.

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