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Precision Immunotherapy to Improve Sepsis Outcomes
The ImmunoSep Randomized Clinical Trial

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IMPORTANCE Sepsis is heterogeneous, and the optimal strategy for tailoring immunotherapy is uncertain.

OBJECTIVE To investigate whether precision immunotherapy guided by the presence of macrophage activation–like syndrome or sepsis-induced immunoparalysis improves organ dysfunction by day 9.

DESIGN, SETTING, AND PARTICIPANTS A randomized, double-blind, double-dummy, placebo-controlled clinical trial conducted in 6 countries. Patients with sepsis, defined by Sepsis-3, were included if they had community-acquired or hospital-acquired pneumonia or ventilator-associated pneumonia or bacteremia and sepsis and had displayed either macrophage activation–like syndrome (blood ferritin >4420 ng/mL) or sepsis-induced immunoparalysis (blood ferritin ≤4420 ng/mL and <5000 human leukocyte antigen DR receptors on CD45/CD14 monocytes). The first patient was enrolled August 5, 2021, and the last follow-up, April 29, 2024.

INTERVENTIONS Eligible patients were randomized to receive standard care and precision immunotherapy or standard care and placebo. Those in the precision immunotherapy group with macrophage activation–like syndrome received anakinra intravenously (IV) and placebo subcutaneously, and those with sepsis-induced immunoparalysis received subcutaneous recombinant human interferon gamma and IV placebo. Those in the placebo group received both IV and subcutaneous placebo. Treatment was administered for up to 15 days.

MAIN OUTCOMES AND MEASURES The primary end point was a decrease of at least 1.4 points in the mean Sequential Organ Failure Assessment (SOFA) score from baseline by day 9. The SOFA score evaluates 6 organ systems, ranging from 0, no dysfunction, to 4, failure, and the total score ranges from 0, normal, to 24, most severe form of multiorgan failure. Key secondary outcomes included 28-day mortality.

RESULTS Of 672 patients assessed for eligibility, 281 were randomized and 276 were included in the primary analysis population (mean [SD] age, 70 [13] years; 93 females [33.7%]; median baseline SOFA score, 9 [IQR, 7-11]). The SOFA decrease end point was attained by 46 of 131 patients (35.1%) in the precision immunotherapy group and by 26 of 145 patients (17.9%) in the placebo group (difference, 17.2% [95% CI, 6.8% to 27.2%]; $P = .002$). Mortality at 28 days was not statistically significantly different between groups. A total of 1069 serious treatment-emergent adverse events (88.8%) were reported; increased incidence of anemia was noted in the anakinra group; and hemorrhage in the recombinant human interferon gamma group.

CONCLUSIONS AND RELEVANCE Among patients with sepsis, precision immunotherapy targeting macrophage activation–like syndrome and sepsis-induced immunoparalysis improved organ dysfunction by day 9 compared with placebo.

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Supplemental content

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Sepsis is a life-threatening organ dysfunction due to the dysregulated host response to an infection.[1] Many randomized clinical trials (RCTs) studied immunotherapies but failed to demonstrate an improvement in outcome. This is likely related to the heterogeneity of immune dysregulation, which varies from hyperinflammation to immunosuppression. As such, a precision approach to immunotherapy in sepsis may be necessary,[2] relying on rapid, accurate classification of the immune dysregulation using biomarkers.[3]

Recent data suggest that patients with sepsis with shock can be classified by using blood ferritin concentrations and the expression of the human leukocyte antigen (HLA) DR on monocytes into 3 strata of immune activation. These include, (1) the macrophage activation-like syndrome, which is a hyperinflammatory condition driven by excess production of interleukin 1 (IL-1) by tissue macrophages; (2) sepsis-induced immunoparalysis, which is a hypoinflammatory condition driven by exhaustion and apoptosis of lymphocytes and often of myeloid cells; and (3) unclassified patients with neither of these 2 types of immune dysregulation.[4] Patients with macrophage activation-like syndrome who were randomized to receive a 7-day intravenous course of a recombinant human IL-1 receptor antagonist demonstrated a decrease in sequential Organ Dysfunction Score compared with placebo, although the effect was time-limited. Others suggest that the immunostimulating recombinant interferon gamma could reverse the effects of sepsis-induced immunoparalysis.[5]

This international multicenter phase 2b study aimed to assess if a precision immunotherapy strategy in sepsis tailored to the presence of macrophage activation-like syndrome or sepsis-induced immunoparalysis using either anakinra or recombinant human interferon gamma improved organ dysfunction compared with placebo.[6]

Key Points

Question Does immunotherapy tailored to the type of immune dysregulation improve outcomes among patients with sepsis?

Findings In this multicenter randomized clinical trial of 276 patients, precision immunotherapy, which included the administration of anakinra for patients with macrophage activation–like syndrome and recombinant human interferon gamma for patients with sepsis-induced immunoparalysis, decreased the Sequential Organ Failure Assessment score by at least 1.4 points by day 9 in 35.1% of patients in the immunotherapy group vs 17.9% in the placebo group.

Meaning A precision strategy of immunotherapy improved organ dysfunction at day 9 among patients with sepsis.

Methods

Trial Design

ImmunoSep was a prospective, multicenter, interventional, randomized, double-blind, double-dummy, placebo-controlled, clinical trial at 33 study sites in 6 countries (Greece, Germany, Italy, the Netherlands, Switzerland, and Romania; eTable 1 in Supplement). ImmunoSep is considered a phase 2b trial since the study drugs were tested in a precision approach for the first time. The study protocol and addenda were approved by the ethics committees and institutional review boards pursuant to country regulations (Supplement 1, eTable 2 in Supplement 2). The study was governed by the international standards for Good Clinical Practice, the Directive 2001/20/EC for Clinical trials and the General Data Protection Regulation 679/2016. The study was registered at EudraCT number: 2020-005768-74 and at Clinicaltrials.gov NCT04990232. This trial followed the Consolidated Standards of Reporting Trials (CONSORT) reporting guideline.[7]

Participants

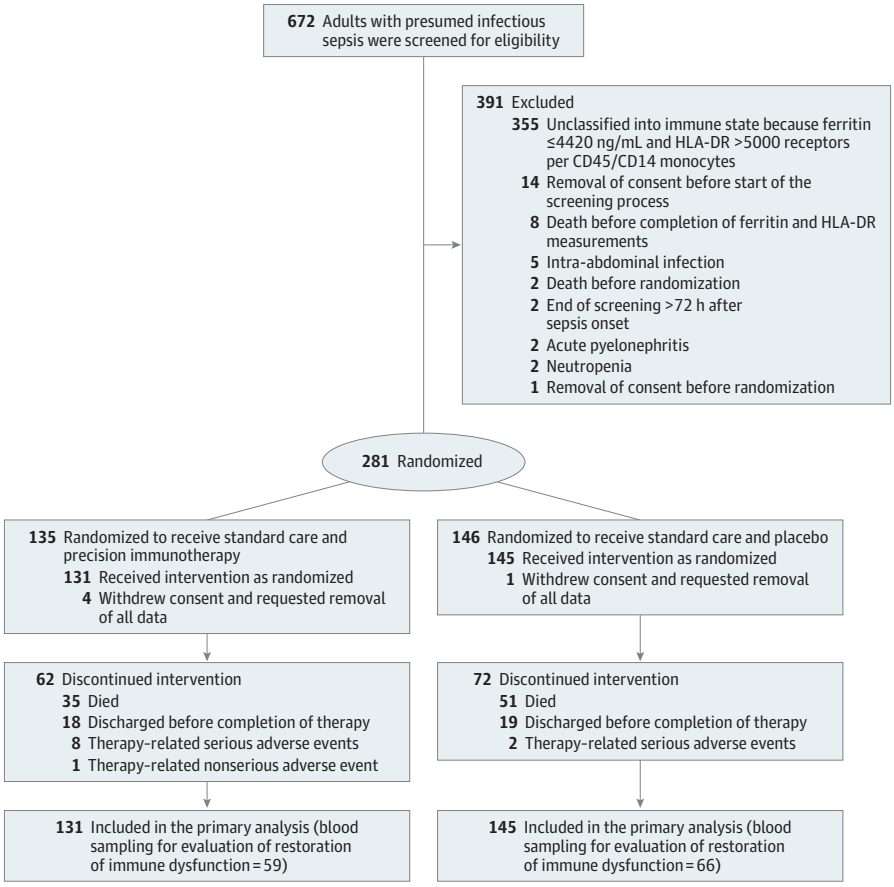
Prior to blood sampling and enrollment, written informed consent was provided by study participants or first-degree relatives if patients could not consent. Patients were adults with community-acquired pneumonia, hospital-acquired pneumonia, ventilator-associated pneumonia, or primary bacteremia, with sepsis as defined by the Sepsis-3 consensus definitions[1] and macrophage activation-like syndrome or sepsis-induced immunoparalysis. The maximum time window allowed between sepsis onset and start of blinded intervention was less than 72 hours. Patients were excluded if the primary sepsis source was (1) abdominal infections due to confounding from the time to source control, (2) urinary tract infections because they usually have better outcomes than sepsis from other causes,[8] or (3) SARS-CoV pneumonia in the absence of macrophage activation-like syndrome (details are available in eMethods and eTable 3 in Supplement 2). At enrollment, eligible patients had 6 mL of blood drawn into an ethylenediaminetetraacetic acid coated tube (Vacutainer, BD; Becton Dickinson). Biospecimens were shipped within 6 hours to the designated central laboratory in each participating country for measurements of ferritin and the number of HLA-DR receptors on CD45/CD14 monocytes (see detailed eMethods in Supplement 2). Patients with ferritin levels greater than 4420 ng/mL were classified as having macrophage activation-like syndrome[4]; and patients with ferritin levels of 4420 ng/mL or less and less than 5000 HLA-DR molecules on CD45/CD14-monocytes as having sepsis-induced immunoparalysis.[4] Patients with ferritin levels of 4420 or less ng/mL and 5000 or more HLA-DR receptors on CD45/CD14 monocytes were considered to be in an "unclassified immune state" and were not enrolled in the study (eTable 4 in Supplement 2).

Randomization and Allocation

Enrolled patients were randomized 1:1 into groups: (1) intervention strategy: standard care and precision immunotherapy, and (2) control strategy: standard care and placebo immunotherapy, using separate randomization per study site with the aid of a computer-generated sequencing (**Figure 1**). Patients received 1 intravenous (IV) injection every 8 hours and 1 subcutaneous injection every 48 hours for 15 days.

In the precision immunotherapy group, the IV injection was 200 mg of anakinra (Kineret, Swedish Orphan BioVitrum) dissolved in 0.9% of normal saline to a final volume of 20 mL for patients with macrophage activation-like

Figure 1. Flow of Patients Through the ImmunoSep Study



HLA-DR indicates human leukocyte antigen DR.

syndrome; and the subcutaneous injection was 100 µg of recombinant human interferon gamma (Imukin, Clinigen) to a final volume of 0.5 mL for patients with sepsis-induced immunoparalysis. Patients with macrophage activation-like syndrome also received subcutaneous dummy treatment; and patients with sepsis-induced immunoparalysis received IV dummy treatment. In the placebo group, the IV injection was 20 mL of 0.9% normal saline and the subcutaneous injection 0.5 mL of 0.9% normal saline. Creatinine clearance was calculated daily by the Cockcroft and Gault equation. Patients with clearance less than 30 mL/min received half the IV dose.

The study drug was prepared by unblinded study pharmacists and identically labeled. Except for the unblinded pharmacists, the investigators, attending physicians, nursing personnel, and participants remained blinded to the assigned intervention. The data and safety monitoring board performed regular safety evaluations.

Study Procedures

Baseline data included demographics, comorbidities, severity scores (Acute Physiology and Chronic Health Evaluation [APACHE] II, Charlson Comorbidity Index [CCI], and Sequential Organ Failure Assessment [SOFA] score), underlying infection, laboratory results (complete blood cell count, biochemistry, and coagulation), and microbiology (**Table 1**). The maximum SOFA scores and organ support treatments were captured each day of patients' intensive care unit (ICU) stay until discharge, including the receipt of mechanical ventilation, vasopressors, or continuous kidney replacement therapy. All serious and nonserious treatment-emergent adverse events were captured and reported using the MeDRA 27.0 classification system. All data were uploaded to the electronic case report form system created by the Hellenic Institute for the Study of Sepsis trial sponsor (HISS; https://sepsisonlinesepsis.gr/W_Home) and monitored by blinded and unblinded monitors. Biospecimens were also obtained on days 2, 4, 7, 15, 21, and 28 for measurements of ferritin and HLA-DR on CD45/CD14-monocytes.

End Points

The primary end point was the proportion of patients in each group who attained a 1.4-point or more decrease in the mean SOFA score by day 9. The mean SOFA change was calculated after subtracting the mean value of SOFA scores between days 2 and 9 from the baseline SOFA score on day 1. The measurement window of 9 days for the assessment of the end point was based on previous data from the Efficacy of Volume Substitution and Insulin Therapy in Severe Sepsis (VISEP)[9] and MAXSEP[10] RCTs, which showed that reduction of the mean

Table 1. Baseline Characteristics of Participants in the ImmunoSep Trial

	No. (%) of patients	
	Precision immunotherapy (n = 131)	Placebo (n = 145)
Male	89 (67.9)	94 (64.8)
Female	42 (32.1)	51 (35.2)
Age, mean (SD), y	69 (13)	70 (14)
Race and ethnicity[a]		
African	1 (0.8)	0
Middle Eastern	1 (0.8)	0
White	129 (98.5)	145 (100.0)
Medical history		
Diabetes	45 (34.4)	48 (33.1)
COVID-19[b]	34 (26.0)	35 (24.1)
Chronic obstructive pulmonary disease	26 (19.8)	39 (26.9)
Coronary heart disease	25 (19.1)	34 (23.4)
Atrial fibrillation	23 (17.6)	36 (24.8)
Heart failure	19 (14.5)	22 (15.2)
Cerebral stroke	18 (13.7)	18 (12.4)
Chronic kidney disease	13 (9.9)	16 (11.0)
Solid tumor malignancy without metastasis	12 (9.2)	9 (6.2)
Cerebral hemorrhage	9 (6.9)	9 (6.2)
Interventions		
Mechanical ventilation	116 (88.5)	129 (89.0)
Continuous venovenal hemofiltration	23 (17.6)	24 (16.6)
Underlying infection		
Ventilator-associated pneumonia	48 (36.6)	54 (37.2)
Hospital-acquired pneumonia	35 (26.7)	32 (22.1)
Community-acquired pneumonia	31 (23.7)	44 (30.3)
Primary bacteremia	16 (12.2)	12 (8.3)
Pneumonia by SARS-CoV-2	1 (0.8)	3 (2.1)
APACHE II score[c]		
Median (IQR)	20 (16-25)	19 (14-25)
≥25	38 (29.0)	40 (27.6)
<25	93 (71.0)	105 (72.4)
Charlson Comorbidity Index[d]		
Median (IQR)	4 (3-6)	5 (3-6)
≥5	54 (41.2)	76 (52.4)
<5	77 (58.8)	69 (47.6)
SOFA score[e]	10 (7-12)	9 (6-11)
Median (IQR)	10 (7-12)	9 (6-11)
≥10	67 (51.1)	68 (46.9)
<10	64 (48.9)	77 (53.1)
Po_2:FIo_2 ratio, median (IQR)	3 (2-3)	3 (2-3)
Platelets, median (IQR)	0 (0-1)	0 (0-1)
Glasgow coma scale, median (IQR)	1 (0-3)	1 (0-3)
Cardiovascular, median (IQR)	4 (3-4)	4 (3-4)
Bilirubin, median (IQR)	0 (0-1)	0 (0-0)
Creatinine or urine output, median (IQR)	0.5 (0-2)	0 (0-1)
Baseline laboratory		
Macrophage activation–like syndrome	25 (19.1)	23 (15.9)
Sepsis-induced immunoparalysis	106 (80.9)	122 (84.1)
Ferritin, median (IQR), ng/mL (reference: 30-350 ng/mL for men, 20-250 ng/mL for women)		
Macrophage activation–like syndrome	5438 (5000-7009)	6221 (5000-7500)
Sepsis-induced immunoparalysis	633 (353-1149)	703 (340-1488)

(continued)

Table 1. Baseline Characteristics of Participants in the ImmunoSep Trial (continued)

	No. (%) of patients	
	Precision immunotherapy (n = 131)	Placebo (n = 145)
mHLA-DR, median (IQR), antibodies per CD45/14 cell (reference: 15 000-40 000 Abs per CD-14 cell)		
Macrophage activation–like syndrome	3576 (2124-6205)	4990 (3068-7811)
Immunoparalysis	3043 (2297-4135)	3078 (1762-4004)
Total white blood cell count, mean (SD), per μL (reference: 4000-11 000 per μL)	17 003.8 (9075)	16 904.6 (9582.3)
Hemoglobin, mean (SD), g/dL (reference: 13.5-17.5 g/dL for men,12.0-15.5 g/dL for women)	10.39 (6.88)	9.83 (1.85)
Platelets, mean (SD), $\times 10^3$/μL (reference: 150 000-400 000 $\times 10^3$/μL)	201.4 (147.1)	209.5 (138.4)
International normalized ratio, median (IQR) (reference: 0.8-1.2)	1.2 (1.1-1.4)	1.2 (1.0-1.4)
Fibrinogen, mean (SD), mg/dL (reference: 200-400 mg/dL)	582.5 (231.5)	629.7 (924.7)
D-dimer, median (IQR), μg/dL (reference: <0.5 μg/dL)	14.3 (0.8-2301.0)	16.3 (0.7-2001.1)
Creatinine, median (IQR), mg/dL (reference: 0.7-1.2 mg/dL)	1.3 (0.8-2.0)	1.0 (0.7-1.8)
Aspartate aminotransferase, median (IQR), U/L (reference: 10-40 U/L)	41 (27-101)	44 (21-92)
Alanine aminotransaminase, median (IQR), U/L (reference: 7-56 U/L)	36 (20-77)	35 (17-75)
Total bilirubin, median (IQR), mg/dL (reference: 0.3-1.2 mg/dL)	0.7 (0.4-1.3)	0.6 (0.4-1.1)
Po_2:Fio_2 ratio, median (IQR), mm Hg (reference: >400 mm Hg)	161.6 (127.0-247.0)	171.9 (127.8-232.8)
Lactate, median (IQR), mg/dL (reference: 4.5-19.8 mg/dL)	15.3 (9.9-21.6)	15.3 (9.2-28.4)
C-reactive protein, median (IQR), mg/dL (reference: <5 mg/dL)	2.7 (1.4-19.0)	3.3 (1.5-13.9)
Procalcitonin, median (IQR), ng/mL (reference: <0.03 ng/mL)	1.3 (0.5-5.9)	1.3 (0.5-11.5)
Time between sepsis onset and initiation of the study drug, median (IQR), h	36.0 (24.0-48.0)	47.0 (24.0-48.0)

Abbreviations: APACHE, Acute Physiology and Chronic Health Evaluation; mHLA-DR, monocytic human leukocyte antigen DR; Pao_2:Fio_2, partial pressure of arterial oxygen to fraction of inspired oxygen; SOFA, Sequential Organ Failure Assessment.

SI conversion factors: To convert alanine aminotransferase and aspartate aminotransferase from U/L to μkat/L, multiply by 0.0167; bilirubin, from mg/dL to μmol/L, multiply by 17.104; creatinine from μg/dL to μmol/L, multiply by 88.4; lactate from mg/dL to mmol/L, multiply by 0.111.

[a] Self-reported from a list of options.

[b] Refers to history of resolved COVID-19 infection.

[c] The APACHE II is calculated using a weighted sum of 12 physiological variables (such as temperature, blood pressure, heart rate, respiratory rate, oxygenation, arterial pH, electrolytes and hematocrit levels, white blood cell count, and Glasgow Coma Scale), along with age and chronic health conditions. The score ranges from 0 to 71, with higher values indicating more severe illness and a higher risk of mortality.

[d] The Charlson's Comorbidity Index is determined by assigning weighted scores (1-6) to 19 predefined comorbid conditions based on their mortality risk. Scores range from 0 to 37, with higher scores representing greater comorbidity burden and increased risk of mortality.

[e] The SOFA score is calculated by assigning 0-4 points for the degree of dysfunction in the respiratory, cardiovascular, hepatic, coagulation, renal, neurological organ systems, based on specific clinical and laboratory criteria. Total score ranges from 0 to 24. Higher scores indicate more severe organ dysfunction and higher mortality risk.

SOFA score by 1.4 points was associated with reduced 28-day mortality.

There were 6 prespecified secondary end points. These included, (1) the attainment of a 1.4-point or more decrease of the mean SOFA score by day 9 in patients with either macrophage activation–like syndrome or sepsis-induced immunoparalysis, (2) 28-day mortality, (3) 90-day mortality, (4) attainment of at least a 1.4-point decrease of the mean SOFA score by day 15, (5) the reversal of sepsis-induced immune dysfunction (SIDF), and (6) the infection resolution by day 15. For patients with macrophage activation–like syndrome, the reversal of SIDF was a decrease of baseline ferritin by at least 15% ; for patients with sepsis-induced immunoparalysis, an increase of the absolute number of HLA-DR receptors on CD45/CD14 monocytes of more than 8000 per cell. On day 15, the state of infection was classified as resolved, intermediate, treatment failure, or superinfection by the site investigators using predefined criteria (eTable 3 in Supplement 2).

One sensitivity analysis of the primary end point was done excluding patients who were discharged earlier than day 9. Exploratory post hoc analyses included (1) the time to reversal of SIDF, (2) baseline APACHE II score, (3) baseline CCI, and (4) baseline SOFA score subgroups based on the likelihood of their predicting 28-day mortality. The cutoff points of these severity scores were defined by the Youden index of the respective receiver operator characteristics curves. Significant interactions were defined as P <.05.

Sample Size Calculation

The study was powered for the primary end point anticipated to be attained in 40% in the intervention group and in 20% in the control group. At the significance level of 5% and a power of 90%, the calculation yielded 117 patients per trial group. Considering a dropout rate of about 15%, 280 were needed.[6]

Statistical Analyses

The primary analysis included all patients randomized, who did not withdraw their consent or requested removal of all data. For patients who died before day 9, all values from the death day until day 15 were replaced by 24 (the maximum SOFA score). For patients discharged home or lost to follow-up before day 9, the last recorded SOFA score was carried forward. The SOFA score was parameterized as a continuous variable for all analyses.

Table 2. Primary and Main Secondary Outcomes of the ImmunoSep Trial

End points	No./total (%) of patients		Difference, % (95% CI)	OR unadjusted (95% CI)	*P* value
	Precision immunotherapy	Placebo			
Primary end point					
≥1.4-Point decrease of mean SOFA score d 2 to 9[a]	46/131 (35.1)	26/145 (17.9)	17.2 (6.8 to 27.2)	2.48 (1.42 to 4.32)	.002
Main secondary outcomes					
28-d Mortality	57/131 (43.5)	72/145 (49.7)	6.1 (−5.6 to 17.6)	0.78 (0.49 to 1.26)	.34
90-d Mortality	90/131 (68.7)	98/145 (67.6)	1.1 (−9.8 to 11.9)	1.05 (0.63 to 1.75)	.90
≥1.4-Point decrease of mean SOFA score d 2 to 15[a]	52/131 (39.7)	34/145 (23.4)	16.3 (5.3 to 26.8)	2.15 (1.28 to 3.61)	.004
Reversal of sepsis-induced immune dysfunction[b]	46/59 (78.0)	32/66 (48.5)	29.5 (12.6 to 44.0)	3.76 (1.72 to 8.22)	.001
Assessment of infection by d 15					
Resolution	58/131 (44.3)	46/145 (31.7)	NA	0.59 (0.38 to 0.91)[c]	.02
Intermediate	11/131 (8.4)	9/145 (6.2)			
Failure	32/131 (24.4)	44/145 (30.3)			
Superinfection	30/131 (22.9)	46/145 (31.7)			

Abbreviations: OR, odds ratio; NA, not applicable; SOFA, Sequential Organ Failure Assessment.

[a] The SOFA score is calculated by assigning 0 to 4 points for the degree of dysfunction of the respiratory, cardiovascular, hepatic, coagulation, kidney, and neurological organ systems, based on specific clinical and laboratory criteria. Total score ranges from 0 to 24. Higher scores indicate more severe organ dysfunction and higher mortality risk.

[b] Defined as at least a 15% decrease of ferritin for patients with macrophage activation–like syndrome remaining decreased over follow-up time blood draws; and increase of the absolute number of human leukocyte antigen DR receptors to more than 8000 per CD45/CD14 monocyte remaining higher than these values over follow-up time blood draws. Patients not having at least 2 serial blood draws to confirm the permanence of the changes were considered not to have attained reversal of sepsis-induced organ dysfunction.

[c] Using predefined criteria (eTable 3 in Supplement 2) any infection at day 15 was characterized as resolved, intermediate, treatment failure, or superinfection. The OR expresses the risk of worse outcome of the precision immunotherapy group vs the placebo group.

Comparisons for primary and all secondary end points were calculated by the Fisher exact test; the odds ratios (ORs) and 95% CIs by the Mantel-Haenszel test. A confirmatory model for the primary end point included a stepwise logistic regression for the proportion who achieved at least a 1.4-point decrease in SOFA score by day 9 as the dependent variable, with the blinded intervention, baseline CCI, SOFA score, and study site as the independent variables. Kaplan-Meier and Cox regression analyses reporting hazard ratios (HRs) with 95% CIs were used to illustrate survival. The time to reversal of SIDF was compared by Cox regression analysis. Comparisons of the state of infection by day 15—defined as resolved, intermediate, treatment failure, or superinfection—were conducted by ordinal regression analysis. $P < .05$ was considered statistically significant. Analysis was conducted using SPSS version 29.0.2.0 (IBM). All analyses followed those defined in the statistical analysis plan (Supplement 1).

Results

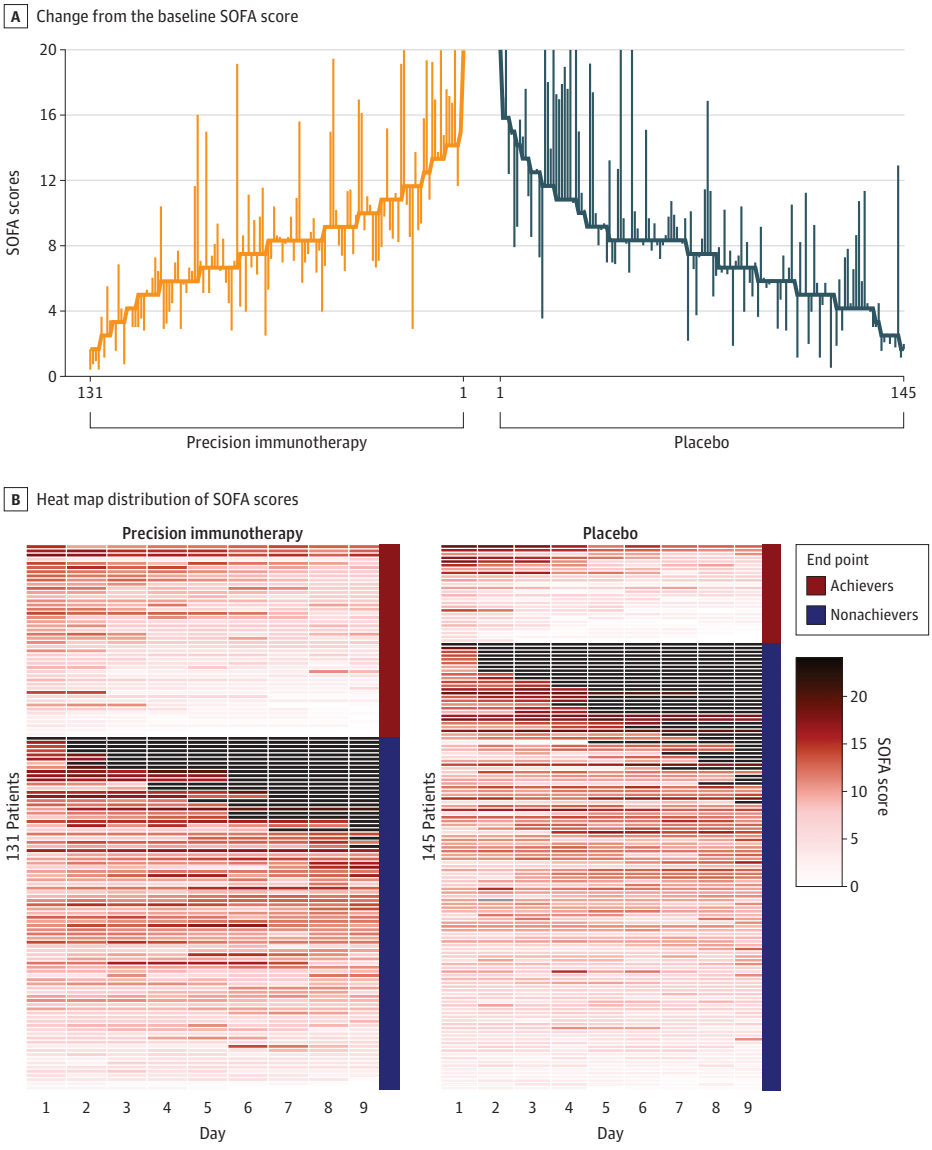
Patients

Among 672 patients screened for eligibility, 281 patients were randomized. The first patient was enrolled on August 5, 2021, and the follow-up of the last patient was completed on April 29, 2024. Five patients withdrew consent and requested removal of all their data, 4 in the precision immunotherapy group and 1 in the placebo group, leaving 276 patients (mean [SD] age,70 [13] years; 93 females [33.7%]) in the primary analysis population (Figure 1). Baseline characteristics were comparable between groups (Table 1; eTables 5 and 6 in Supplement 2). Forty-eight patients (17.4%) were classified with macrophage activation-like syndrome (25 allocated to anakinra treatment and 23 to placebo) and 228 patients (82.6%) with sepsis-induced immunoparalysis (106 allocated to recombinant human interferon gamma treatment and 122 allocated to placebo; eTable 7 in Supplement 2). In the precision immunotherapy group, 21 patients (16.0%) died before day 9 compared with 29 (20.0%) in the control group. Cumulatively, 8.3% of patients had SOFA scores carried forward because of ICU discharge earlier than day 9 (eTable 8 in Supplement 2).

Primary End Point

The primary end point (≥1.4-point decrease of mean SOFA score by day 9) was present in 46 of 131 patients (35.1%) in the precision immunotherapy group and 26 of 145 patients (17.9%) in the placebo group ($P = .002$; **Table 2** and **Figure 2**A). In a confirmatory model adjusted for baseline illness severity, the precision strategy was associated with greater odds of attaining the prespecified decrease in the SOFA score by day 9 (adjusted OR, 2.49; 95% CI, 1.42-4.36; eTable 9 in Supplement 2). To illustrate the change in SOFA score after randomization, heat maps reveal the total SOFA score was lower among the precision immunotherapy group than among the placebo group (Figure 2B and eFigure 1 in Supplement 2). A sensitivity analysis excluding patients who were discharged prior to day 9 was consistent with the primary analysis (eFigure 2 in Supplement 2).

Figure 2. Primary End Point



A, The parallel line plot represents change for each participant in the trial, from the baseline Sequential Organ Failure Assessment (SOFA) score measured before initiating the study drug to the mean SOFA score for days 2 through 9. Each single line represents this change for each participant and is ordered by baseline SOFA score.

B, The SOFA scores are presented for each treatment group over the 9 days of follow-up. Treatment started on day 1 (baseline). Each group is separated into achievers and nonachievers of the primary end point. Achievers were defined as patients reaching at least a 1.4-point decrease of the mean SOFA score between days 2 and 9 from the baseline SOFA score.

The SOFA score is calculated by assigning 0 to 4 points for the degree of dysfunction in respiratory, cardiovascular, hepatic, coagulation, kidney, and neurological organ systems, based on specific clinical and laboratory criteria. Total score ranges from 0 to 24. Higher scores indicate more severe organ dysfunction and higher mortality risk.

Secondary End Points

There were 6 prespecified secondary end points. First, the decrease of mean SOFA score of 1.4-points or more by day 9 was attained in both states of immune dysregulation (eTable 10 in Supplement 2). In patients with macrophage activation-like syndrome, the decrease of mean SOFA score by day 9 was attained by 12 of 25 patients (48.0%) in the precision immunotherapy group and 4 of 23 patients (17.4%) in the placebo group (P = .04). Similarly, among patients with sepsis-induced immunoparalysis, 34 of 106 patients (32.1%) in the precision immunotherapy group and 22 of 122 (18.0) in the placebo group yielded the prespecified reduction of mean SOFA score by day 9 (P = .02). Second, 28-day mortality occurred in 57 of 131 patients (43.5%) in the precision immunotherapy group and 72 of 145 patients in the placebo group (49.7%), a difference that did not reach statistical significance (P = .34, Table 2; eFigure 3 in Supplement 2). Third, no differences in 90-day mortality were found (Table 2; eFigure 4 in Supplement 2). Fourth, the attainment of at least a 1.4-point decrease of the mean SOFA score by day 15 was greater in the group of precision immunotherapy (39.7%; 51 of 131) than in the placebo group (23.4%; 34 of 145; P = .004). Fifth, in a subset of 125 patients, the reversal of SIDF by day 28 was found in 46 of 59 patients (78.0%) of the precision immunotherapy group and in 32 of 66 patients (48.5%) of the placebo group (P < .001, Table 2). Sixth, in ordinal regression models, the odds for a worse infection outcome by day 15 were significantly lower in the precision immunotherapy group (OR, 0.59; 95%CI, 0.38-0.91; P = .02) than in the placebo group (eFigure 5 in Supplement 2).

Post Hoc and Subgroup Analyses

The time to reversal of SIDF was significantly shorter in the precision immunotherapy group (eFigure 6 in Supplement 2). Interaction tests showed statistical significance of

Table 3. Most Common Serious Treatment-Emergent Adverse Events by System-Organ Class and Preferred Term, Classified by Relationship to Study Drug

Category	Probably or possibly related, No. (%)		Probably not related or unrelated, No. (%)	
	Precision immunotherapy (n = 131)	Placebo (n = 145)	Precision immunotherapy (n = 131)	Placebo (n = 145)
Any serious adverse event[a,b]	8 (6.1)	3 (2.1)	108 (82.4)	126 (86.9)
Blood and lymphatic system disorders[b]				
Anemia	0	0	47 (35.9)	38 (26.2)
Thrombocytopenia	5 (3.8)	1 (0.7)	9 (6.9)	8 (5.5)
Cardiac disorders[b]				
Atrial fibrillation	0	0	19 (14.5)	14 (9.7)
Bradycardia	0	0	6 (4.6)	6 (4.1)
Cardiac arrest	0	1 (0.7)	9 (6.9)	15 (10.3)
General disorders and administration site conditions[b]				
Multiple organ dysfunction syndrome[c]	2 (1.5)	0	51 (38.9)	58 (40.0)
Infections and infestations[b]				
Bacteraemia	0	0	36 (27.5)	27 (18.6)
Device-related infection	0	0	2 (1.5)	4 (2.8)
Fungaemia	0	0	17 (13.0)	12 (8.3)
Fungal infection	0	0	7 (5.3)	5 (3.4)
Pneumonia	0	0	35 (26.7)	32 (22.1)
Sepsis[d]	0	0	9 (6.9)	12 (8.3)
Septic shock[d]	0	0	29 (22.1)	17 (11.7)
Urinary tract infection	0	0	4 (3.1)	7 (4.8)
Kidney and urinary disorders[b]				
Acute kidney injury	0	0	21 (16.0)	19 (13.1)
Respiratory, thoracic, and mediastinal disorders[b]				
Bronchial obstruction	0	0	3 (2.3)	3 (2.1)
Hypoxia	0	0	4 (3.1)	7 (4.8)
Pleural effusion	0	0	5 (3.8)	3 (2.1)
Pneumothorax	0	0	10 (7.6)	7 (4.8)
Respiratory failure	0	0	2 (1.5)	7 (4.8)
Tracheal stenosis	0	0	7 (5.3)	8 (5.5)
Vascular disorders[b]				
Hemorrhage	0	0	6 (4.6)	0

[a] The serious treatment-emergent adverse events were classified by relationship to the study drug using Medra 27.0 for events captured during the 90 days of follow-up for the enrolled 276 patients. In the analysis, these adverse events were graded as *probably related*, which signifies strong time relationship to the drug or relapse if reinduced, and another etiology is improbable or clearly less probable; *possibly related*, strong time relationship to the drug and an alternative etiology is as probable or less probable; *probably not related*, slight or no time relationship to the drug and/or a more probable alternative etiology; and *unrelated*, causality by an underlying or concomitant disease or another pharmaceutical product, with no time relationship and a much more probable alternative etiology. Site investigator graded treatment-emergent adverse events.

[b] These data represent the number of patients with at least 1 event, whereas all other data in the table correspond to the number of events.

[c] Represents the progression to Multiple organ dysfunction syndrome of the initial sepsis or septic shock for which the patient was enrolled in the study.

[d] Represents a new episode of sepsis or septic shock after the resolution of the initial sepsis or septic shock for which the patient was enrolled in the study.

interaction of the precision immunotherapy group with a CCI of 5 or higher and a SOFA score 10 or higher for the achievement of primary end point (eFigures 7 in Supplement 2); and of the precision immunotherapy group with a CCI of 5 or higher and a SOFA score 10 or higher for the decrease of 28-day mortality (eFigure 8 in Supplement 2). No significant interactions were found between any subgroup and precision immunotherapy for an effect on 90-day mortality (eFigure 9 in Supplement 2).

Adverse Events

A total of 1069 serious treatment-emergent adverse events were reported in 245 patients (88.8%); 13 were serious adverse reactions probably (n = 3) or possibly (n = 10) related to the study drug; 2 serious adverse reactions were reported in the anakinra group, 7 in the recombinant human interferon gamma group, and 4 in the placebo group. Six serious adverse reactions were considered suspected unexpected serious adverse reactions for 5 patients; 3 patients (2.5%) received placebo and 2 patients (1.9%) recombinant human interferon gamma (eTable 12 in Supplement 2). Two significant differences were found in the incidence of serious treatment-emergent adverse events: increase of anemia in the anakinra group; and hemorrhage in the recombinant human interferon gamma group. Notably, 4 of the hemorrhagic cases in the recombinant human interferon gamma group occurred in patients with thrombocytopenia; however, no differences in the incidence of thrombocytopenia were found between the 2 groups (**Table 3**; eTable 13 in Supplement 2).

Comparisons of the nonserious treatment-emergent adverse events indicated decreased incidence of bradycardia in the recombinant human interferon gamma group; decreased signs

of ileus in the anakinra group; and more creatinine increase, fibrinogen decrease, and γ-glutamyl transferase increase in the recombinant human interferon gamma group (eTable 14 in Supplement 2). The number of patients needed to treat and to harm were calculated (eTable 15 in Supplement 2).

Discussion

In this multicenter RCT, a precision immunotherapy strategy targeting macrophage activation-like syndrome and sepsis-induced immunoparalysis improved organ dysfunction by day 9 compared with placebo. Although no significant effect was found for mortality, significant differences were found for the other secondary end points including overall improvement of organ dysfunction by day 15, reversal of SIDF, and resolution of the underlying infection. No safety concerns were raised.

These findings are consistent with previous work targeting immune dysregulation in sepsis. First, precision immunotherapy for severe infections has been increasingly considered since the COVID-19 pandemic: a strategy of anakinra treatment guided by soluble urokinase plasminogen activator receptor concentrations as a biomarker of lung hyperinflammation has been registered by the European Medicines Agency and for Emergency Use Authorization by the US Food and Drug Administration for treatment of patients with COVID-19 with pneumonia.[11] Second, in the 1990s, continuous IV anakinra infusion was studied in 2 large-scale phase 3 RCTs that failed to demonstrate survival benefit in sepsis.[12,13] Interestingly, however, a post hoc reanalysis of the first trial based on hepatobiliary dysfunction and disseminated intravascular coagulation as criteria for macrophage activation-like syndrome showed that patients treated with anakinra had a significantly lower 28-day mortality than patients treated with placebo (35% vs 65%).[14]

Similarly, recombinant human interferon gamma has been proposed as a treatment for sepsis due to its immunostimulatory mechanisms. Recombinant human interferon gamma restored the low HLA-DR levels on blood monocytes of healthy volunteers who had been previously exposed to experimental endotoxemia.[15] In a single-arm open-label trial, recombinant human interferon gamma administered subcutaneously to 9 patients with septic shock and low monocytic HLA-DR levels rapidly increased HLA-DR levels and the capacity of circulating monocytes to produce tumor necrosis factor α.[5] Favorable clinical responses with reciprocal increases of monocytic HLA-DR expression are also reported in a small-series study of patients with invasive *Candida* or *Aspergillus* infections.[16] Notably, our current findings differ from a recent multicenter study of the prevention of health care–associated pneumonia with recombinant human interferon gamma vs placebo in critically ill patients.[17] This prevention study was prematurely stopped due to an increased incidence of pneumonia with recombinant human interferon gamma treatment (34.5% vs 15.1%, respectively), although 28-day mortality was lower among patients receiving recombinant human interferon gamma than among those receiving placebo (12.7% vs 17%, respectively). However, enrollment was not limited to patients with sepsis-induced immunoparalysis.

The current work demonstrates an improvement in organ function measured by the SOFA score. This end point may be considered a surrogate marker of improved outcome and has been used by others to demonstrate the efficacy of drugs such as nangibotide[18] and adrecizumab.[19]

The majority of screened patients were excluded from the current trial because their immune state was unclassified. This suggests that ferritin and HLR-DR levels, alone, do not capture the full extent of immune dysregulation. Others report that latent classes may be present or that a profile of dysregulation could be derived using machine learning and multiomic approaches.[20-22] A comparison of how these immunotypes, individually or combined, can be used for enrichment in clinical trials of immunotherapy agents is an urgent priority.

Limitations

This trial has several limitations. First, the primary end point of a change in SOFA score is a surrogate outcome, so future adequately powered trials should test these strategies on patient-centered outcomes. Second, the measurement of ferritin and HLA-DR measures may not be feasible across hospitals, and the complexity and assay time could limit scaling and implementation. It is notable that average time from sepsis onset to when the study drug was first administered was 36 to 48 hours. Third, the stability of macrophage activation-like syndrome and sepsis-induced immunoparalysis subtypes over time deserves further study. Fourth, the study findings are generalizable only to patients with sepsis with pneumonia or bacteremia, and other etiologies of sepsis were excluded.

Conclusions

Among patients with sepsis, a precision immunotherapy strategy targeting macrophage activation-like syndrome and sepsis-induced immunoparalysis improved organ dysfunction by day 9 compared with placebo.

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