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Effect of Intravenous Interferon β-1a on Death and Days Free From Mechanical Ventilation Among Patients With Moderate to Severe Acute Respiratory Distress Syndrome
A Randomized Clinical Trial

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IMPORTANCE Acute respiratory distress syndrome (ARDS) is associated with high mortality. Interferon (IFN) β-1a may prevent the underlying event of vascular leakage.

OBJECTIVE To determine the efficacy and adverse events of IFN-β-1a in patients with moderate to severe ARDS.

DESIGN, SETTING, AND PARTICIPANTS Multicenter, randomized, double-blind, parallel-group trial conducted at 74 intensive care units in 8 European countries (December 2015-December 2017) that included 301 adults with moderate to severe ARDS according to the Berlin definition. The radiological and partial pressure of oxygen, arterial (Pao_2)/fraction of inspired oxygen (Fio_2) criteria for ARDS had to be met within a 24-hour period, and the administration of the first dose of the study drug had to occur within 48 hours of the diagnosis of ARDS. The last patient visit was on March 6, 2018.

INTERVENTIONS Patients were randomized to receive an intravenous injection of 10 µg of IFN-β-1a (144 patients) or placebo (152 patients) once daily for 6 days.

MAIN OUTCOMES AND MEASURES The primary outcome was a score combining death and number of ventilator-free days at day 28 (score ranged from −1 for death to 27 if the patient was off ventilator on the first day). There were 16 secondary outcomes, including 28-day mortality, which were tested hierarchically to control type I error.

RESULTS Among 301 patients who were randomized (mean age, 58 years; 103 women [34.2%]), 296 (98.3%) completed the trial and were included in the primary analysis. At 28 days, the median composite score of death and number of ventilator-free days at day 28 was 10 days (interquartile range, −1 to 20) in the IFN-β-1a group and 8.5 days (interquartile range, 0 to 20) in the placebo group ($P = .82$). There was no significant difference in 28-day mortality between the IFN-β-1a vs placebo groups (26.4% vs 23.0%; difference, 3.4% [95% CI, −8.1% to 14.8%]; $P = .53$). Seventy-four patients (25.0%) experienced adverse events considered to be related to treatment during the study (41 patients [28.5%] in the IFN-β-1a group and 33 [21.7%] in the placebo group).

CONCLUSIONS AND RELEVANCE Among adults with moderate or severe ARDS, intravenous IFN-β-1a administered for 6 days, compared with placebo, resulted in no significant difference in a composite score that included death and number of ventilator-free days over 28 days. These results do not support the use of IFN-β-1a in the management of ARDS.

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Visual Abstract

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Supplemental content

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Acute respiratory distress syndrome (ARDS) is a life-threatening form of respiratory failure characterized by hypoxemia, pulmonary edema not explained by cardiac failure or fluid overload, and diffuse bilateral radiographic opacities occurring in the presence of a predisposing factor.[1,2] No approved drug therapy for ARDS exists. Thus, treatment for ARDS is based on management of the underlying disease and supportive care. Despite substantial progress in ventilatory strategies, the hospital mortality rate of ARDS remains approximately 40%.[3] The key pathophysiological event underlying ARDS is an uncontrolled inflammatory response resulting in injury to the epithelium and endothelium of the alveolar-capillary barrier with increased pulmonary vascular leakage.[1,2]

Adenosine has anti-inflammatory properties and is one of the physiological regulators, reducing endothelial cell permeability.[4] Cluster of differentiation 73 (CD73) is the enzyme expressed on endothelial and epithelial cells that regulates adenosine production by converting extracellular adenosine monophosphate to active adenosine.[5] Interferon (IFN) β-1a has been shown to upregulate CD73, prevent vascular leakage,[6] and inhibit leukocyte recruitment.[7] A pilot open-label nonrandomized phase 1/2 study showed that administration of recombinant human IFN-β-1a was associated with significantly lower 28-day mortality compared with nontreatment in patients with ARDS.[8]

This trial was conducted to test the hypothesis that treatment with intravenous recombinant human IFN-β-1a would improve outcomes in patients with ARDS.

Key Points

Question Does treatment with systemic interferon β-1a provide clinical benefit in adults with moderate or severe acute respiratory distress syndrome?

Findings In this randomized clinical trial that included 301 patients, intravenous interferon β-1a administered for 6 days, compared with placebo, resulted in no significant difference in a composite score that included death and number of ventilator-free days over 28 days (median, 10.0 vs 8.5 days).

Meaning These results do not support the use of interferon β-1a in the management of moderate or severe acute respiratory distress syndrome.

Methods

The trial was approved by the national regulatory authorities and central/local ethics boards, and written informed consent was obtained in accordance with local processes. The study design, protocol, and statistical analysis plan (SAP) have been previously published[9] and are available in Supplement 1 (study protocol) and Supplement 2 (SAP). The study was monitored by an independent data monitoring committee.

Eligibility Criteria

Patients were eligible for inclusion if they were older than 18 years of age, were intubated and mechanically ventilated, and had moderate or severe ARDS based on the Berlin definition.[1] The radiological and partial pressure of oxygen, arterial (Pao_2)/fraction of inspired oxygen (Fio_2) criteria had to be met within a 24-hour period, and the administration of the first dose of the study drug had to occur within 48 hours of the diagnosis of ARDS.

Major exclusion criteria were occurrence of invasive or noninvasive ventilation for more than 48 hours prior to the diagnosis of ARDS; an underlying diagnosis that could adversely affect survival, impair weaning from the ventilator, or compromise adherence to the protocol; administration of any form of IFN prior to study enrollment, or known hypersensitivity to natural or recombinant IFN or to any of the excipients; or use of any form of extracorporeal lung support.[9] Detailed enrollment criteria have been provided in Supplement 3.

To ensure appropriate enrollment, the medical monitors (P.N. or N.P.) confirmed the eligibility of every patient prior to randomization. The enrolling clinician had to match the patient's chest x-ray against a panel of unlabeled chest x-rays.[10] If the closest chest x-ray match corresponded to a chest x-ray inconsistent or equivocal for ARDS, the enrolling clinician could repeat the match using a new chest x-ray eventually available from standard clinical management until the time to diagnosis did not exceed 48 hours from the start of mechanical ventilation.

Severity of disease was assessed by the Acute Physiology and Chronic Health Evaluation (APACHE) II score (range, 0-71).[11]

Randomization and Study Drug

Randomization was performed with an automated, centralized computer-generated 24-hour randomization service. Patients were randomly assigned to study groups in a 1:1 ratio with the use of permuted blocks (block size, 2), stratification according to the severity of ARDS (moderate or severe), and country. All parties involved in the study remained blinded for the study treatment throughout the study. Patients received either intravenous 10-µg FP-1201-lyo (IFN-β-1a) or placebo once daily for 6 days. The placebo consisted of the same excipients as FP-1201-lyo, except IFN-β-1a. Administration of the first dose had to take place within 48 hours of ARDS diagnosis.

Study Measurements and Procedures

Apart from administration of the study drug, participating intensive care units (ICUs) were encouraged to manage patients according to best practice as expressed in the protocol.[9] Specifically, mechanical ventilation had to be provided using a lung-protective strategy.[12] Use of higher vs lower positive end-expiratory pressure, prone positioning, recruitment maneuvers, and extracorporeal lung support had to follow best evidence.[12,13] Weaning followed a predefined protocol.[12] Fluid management was unrestricted during episodes of shock, but for patients not in shock, a conservative fluid approach was recommended.[14] A recommendation was also given to avoid the use of glucocorticoids for the treatment of ARDS.[15]

Outcome Measures

The primary outcome was a composite end point incorporating 28-day survival and the number of ventilator-free days in patients at 28 days.[16] Ventilator-free days were scored as the

number of ventilator-free calendar days in those alive at day 28. For those who died within 28 days, the score was set at −1; for 28-day survivors, the score ranged between 0 (alive still on the ventilator at day 28) and 27 (alive and successfully extubated on day 1).[9]

Secondary end points (16 total) included all-cause mortality at 28 (and mortality in the ICU up to day 28 and mortality in hospital up to day 28), 90, and 180 days; organ failure–free days alive (mechanical ventilation–free days alive, renal support-free days alive, vasoactive support-free days alive, organ failure-free days alive) and ICU-free days alive within 28 days; the total number of days spent in the hospital; and the presence of neutralizing antibodies to IFN-β-1a at baseline and at day 28 and pharmacodynamic biomarker myxovirus resistance protein A (MxA, ng/mL),[17] a specific biomarker of IFN-β-1a activity. Organ function was assessed using Sequential Organ Failure Assessment (SOFA) scores (a score ranging from 0 to 4 for each organ system, where higher scores indicate more severe organ dysfunction).[18] Assessment of quality of life, respiratory functioning, and neurological functioning was scheduled at day 180, and these outcomes are not reported in this article.

Adverse events (serious and nonserious) occurring between informed consent and day 28 (definitions of adverse events are available in the protocol provided as Supplement 1) were recorded.

To assess biological activity of the study drug, an exploratory end point, soluble biomarker CD73 (ng/mL)[19] was measured during study days 1 through 14 with a previously developed enzyme-linked immunosorbent assay (described in Supplement 3). CD73 is the molecular target of IFN-β-1a.[19] Both MxA and CD73 range from 0 ng/mL upwards to a nonspecified maximum and have stable baseline values that may be affected by inflammatory and hypoxic insults.[18,19] The method for determining anti-IFN-β-1a antibodies is described in eMethods in the Supplement 3.

Sample Size Calculation

We planned to enroll 300 patients, providing 90% power and a 2-sided Mann-Whitney U test at the significance level of .05 assuming that (1) the mortality rate at 28 days is 30% in the control group and 15% in the IFN-β-1a group; (2) 20% of the patients survive but with no ventilator-free days in the control group; (3) patients receiving IFN-β-1a have 3 ventilator-free days more than patients treated with placebo (including the mortality difference); and (4) 5% of patients drop out and a further 4% of the remaining patients will not be evaluable for the primary efficacy analysis (PASS software version 11; NCSS LLC). The mortality of the active group was assumed to be around 10% according to the prior phase 2 study,[8] but was further increased to 15% to have a more conservative estimate. Similarly, the mortality of the control group was presumed to be around 35%,[1,3] but was further reduced to 30% considering that mortality in prospective randomized trials tends to be lower than in historical cohorts.

Statistical Analysis

All analyses were conducted in accordance with a predefined SAP unless otherwise specified.[9] The number of given study drug doses and major protocol violations blind to treatment allocation were verified to allow selection of patients for per-protocol analysis. Any resulting deviations from the planned analyses had to be justified and reported (blinded changes in the SAP prior to unblinded data analysis are in the final SAP available as Supplement 2). Missing data were not imputed for primary efficacy data.

Primary efficacy and adverse event analyses were conducted using the full analysis set (FAS) according to the received treatment. The FAS population consisted of all randomized patients who received at least 1 dose of the study drug. No statistical analyses were performed for adverse events between groups.

To determine differences in the treatment effect in the study population, we performed nonparametric analysis using the van Elteren test, adjusting for the country and ARDS severity according to the Berlin Definition.[16] To avoid type I error due to multiple comparisons of secondary end points, a hierarchical approach was used and end points in the hierarchy below a nonsignificant end point should be interpreted as exploratory only (testing hierarchy for the secondary end points presented in the eMethods in Supplement 3). Kaplan-Meier survival curves including log-rank test were used to assess mortality up to day 360.

For pharmacodynamic marker MxA and exploratory pharmacodynamic marker CD73, the difference between groups was analyzed as a change from baseline by analysis of covariance model with treatment, ARDS severity, and country as fixed effect factors, and baseline as a covariate.

For post hoc analyses, the associations of etiology of ARDS, APACHE II, SOFA score, ARDS severity, Pao_2/Fio_2 ratio, weight, vasopressor use, days taking vasopressors, sex, age, and prerandomization steroid use against 28-day mortality were explored, and the Breslow-Day test was used to test for interaction. Homogeneity of treatment effect was also assessed by calculating odds ratios (ORs) and associated 95% CIs by ARDS severity and by country and an analysis was also performed that included center as a random effect. A post hoc analysis of 28-day mortality was conducted using all randomized patients and imputing worst-case scenario for the randomized but not dosed patients (ie, patients in the IFN-β-1a group counted as deaths and placebo patients counted as survivors until day 28).

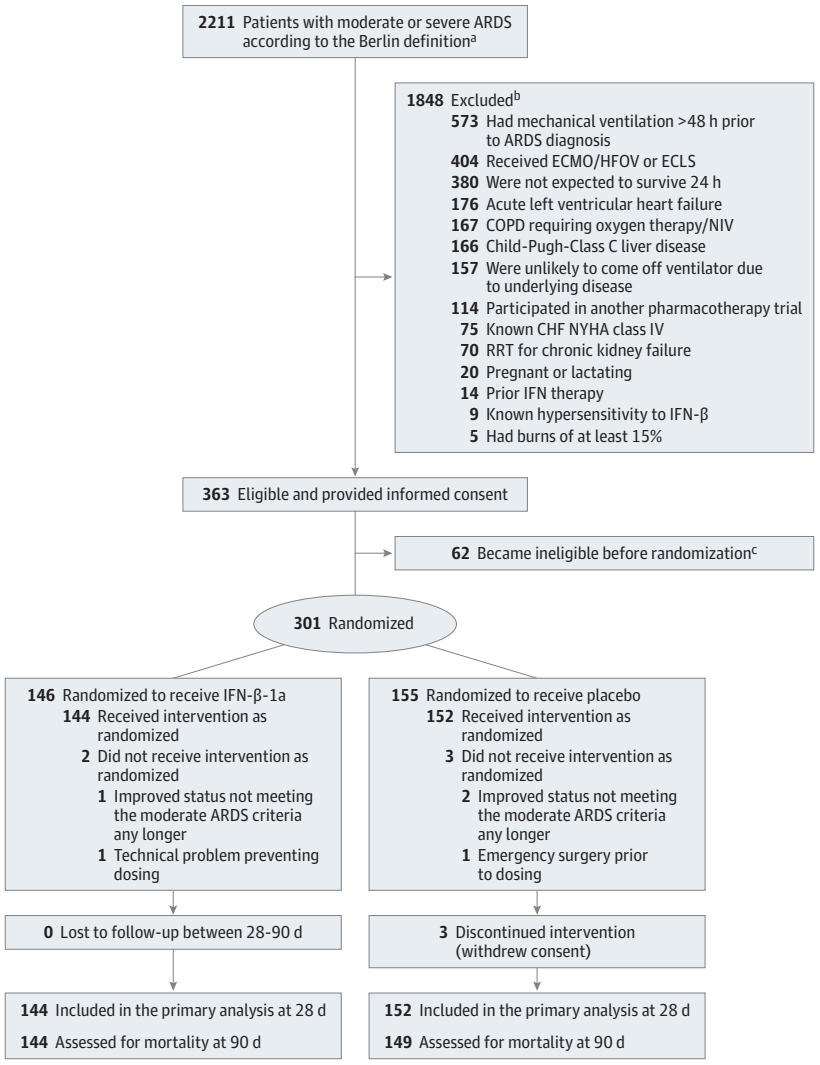
All data derivations, manipulations, and reporting procedures were done using SAS version 9.4 (SAS Institute) in a Windows 7 operating system. All statistical tests were performed as 2-sided and at a significance level of .05.

Results

Patients

Patients were enrolled between December 2015 and December 2017 at 47 of 74 available study sites. Of the 2211 patients with moderate or severe ARDS, 301 patients were randomized to receive IFN-β-1a or placebo. Five patients (2 in the IFN-β-1a group and 3 in the control group) were randomized but not dosed for the following reasons: 3 patients improved their status not

Figure 1. Recruitment, Randomization, and Analysis Population



ARDS indicates acute respiratory distress syndrome; CHF, chronic heart failure; COPD, chronic obstructive pulmonary disease; ECLS, extracorporeal life support; ECMO, extracorporeal membrane oxygenation; HFOV, high-frequency oscillatory ventilation; IFN, interferon; NIV, noninvasive ventilation; NYHA, New York Heart Association; and RRT, renal replacement therapy.

[a] Recruitment between December 2015 and December 2017.

[b] Exclusion criteria as recorded by the study sites (≥1 criteria may have been recorded for a single patient).

[c] Reasons for ineligibility not recorded at study sites.

meeting any more criteria for moderate ARDS; 1 patient was taken to emergency surgery before dosing; and 1 patient experienced a technical problem on computerized drug allocation program that prevented dosing. Primary analyses were conducted on the FAS (296 patients, of whom 144 received IFN-β-1a and 152 placebo; **Figure 1**; eFigure 1 in Supplement 3).

Adherence to the Protocol and Missing Data

The occurrence of significant protocol deviations was similar between the treatment groups (66 and 68 study patients in the active and placebo groups, respectively). There were no missing data for mortality and ventilator-free days at day 28 in the FAS population. No data were gathered from the 5 randomized patients (2 in the placebo group and 3 in the IFN-β-1a group) who did not receive study drug.

Demographic Variables and the Study Treatments

At baseline, 28 of 144 IFN-β-1a–treated patients (19.4%) had severe ARDS compared with 35 of 152 placebo-treated patients (23.0%) (**Table 1**). Baseline characteristics and concomitant treatments were comparable between the study groups (Table 1). A total of 44 patients (31%) in the IFN-β-1a group and 60 (39%) in the placebo group were taking corticosteroids at baseline.

During the 6-day treatment period, patients received a mean (SD) of 5.5 (1.3) doses of the study drug in the IFN-β-1a group and 5.7 (1.0) in the placebo group (eTable 1 in Supplement 3). Daily physiological parameters are presented in eTables 2-6 in Supplement 3.

Concomitant Treatment

During the first 28 days, neuromuscular-blocking agents (77.8% vs 75.5%), corticosteroids (54.2% vs 64.5%), renal replacement therapy (30.6% vs 35.5%), extracorporeal membrane oxygenation therapy (3.5% vs 3.3%), and prone positioning (43.1% vs 48.0%) were used in comparable proportions of patients in the IFN-β-1a and placebo groups, respectively (eTables 7-12 in Supplement 3).

Primary and Secondary Outcomes

The primary composite outcome measure of death and number of ventilator-free days at day 28 did not significantly differ between the IFN-β-1a and placebo groups (median, 10 days [interquartile range {IQR}, −1 to 20] vs 8.5 [IQR, 0 to 20], respectively; $P = .82$). Consistent results were observed in terms of ICU mortality, 28-day hospital mortality (outside the ICU), 90-day mortality, organ failure–free days, days alive without ICU care, and number of days in the hospital (**Table 2**). The Kaplan-Meier survival curves for mortality and ventilator-free days up to day 28 are presented in **Figure 2** (see also eFigure 2 for 360-day mortality and eTable 13 for demographic data and mortality in Supplement 3). A post hoc analysis of 28-day mortality among the 301 randomized patients and imputing worst-case scenario for the 5 randomized but not dosed patients (2 patients in the IFN-β-1a group counted as deaths and 3 placebo patients counted as survivors until day 28) showed similar results (eTable 14 in Supplement 3). One patient tested positive for neutralizing anti–IFN-β-1a antibodies at randomization and no positive patients were detected on the last study day in the ICU.

Adverse Events

The numbers of serious adverse events, adverse events, and patients with any serious and/or any adverse event were comparable between study groups (Table 2). In total, 265 study patients (89.5%) experienced adverse events during the study. Overall, the number and percentage of study patients experiencing at least 1 adverse event were similar in the treatment groups (131 patients [91.0%] in the IFN-β-1a group compared with 134 patients [88.2%] in the placebo group). In total, 74 patients (25%) experienced adverse events considered to be related to treatment during the study (41 patients [28.5%] in the IFN-β-1a group and 33 [21.7%] in the placebo group). The most common adverse events considered to be related to treatment were pyrexia (13 patients [9.0%]) and rhabdomyolysis (5 patients [3.5%]) in the IFN-β-1a group and pyrexia (5 patients [3.3%]) and transaminases increased (6 patients [3.9%]) in the placebo group (eTables 15-17 in Supplement 3).

Biological Effect

The median baseline level for MxA was 0 ng/mL (IQR, 0 to 0) and 0 ng/mL (IQR, 0 to 2.6) for the IFN-β-1a and placebo groups, respectively. Levels of MxA (eFigure 3 in Supplement 3) from days 1 through 14 were significantly different between the treatment groups (difference of baseline change between groups, 23.8 ng/mL [95% CI, 12.8 to 34.8]; $P < .001$). The median baseline level for CD73 was 0 ng/mL (IQR, 0 to 4.6) and 0 ng/mL (IQR, 0 to 5.3) for the IFN-β-1a and placebo groups, respectively. There was no significant difference between treatment groups for CD73 levels for study days 1 through 14 (difference, 0.7 ng/mL [95% CI, −1.1 to 2.4]; $P = .46$) (eFigure 4 in Supplement 3).

Post Hoc Analysis

Due to high use of corticosteroids at baseline (described in detail in eTable 8 in Supplement 3), we performed additional exploratory post hoc analyses revealing that mortality at day 28 (IFN-β-1a vs placebo) was 50.0% and 28.3% in patients taking corticosteroids at randomization (OR, 2.53 [95% CI, 1.12-5.72]) and 10.6% and 14.8% in patients not taking corticosteroids at randomization (OR, 0.78 [95% CI, 0.37-1.65]; $P = .04$

Table 1. Characteristics of the Patients at Baseline[a]

Characteristic	No. (%)	
	Interferon β-1a (n = 144)	Placebo (n = 152)
Age, y	58 (17)	58 (14)
Sex		
Male	102 (71)	91 (60)
Female	42 (29)	61 (40)
Predisposing diagnosis for ARDS		
Pneumonia	91 (63)	108 (71)
Sepsis	24 (17)	16 (11)
Aspiration	15 (10)	17 (11)
Trauma/burns (<15%)	4 (3)	3 (2)
Acute pancreatitis	6 (4)	5 (3)
Multiple transfusion	3 (2)	
Other[b]	1 (1)	3 (2)
APACHE II Score, mean (SD) [range][c]	22 (8.8) [4-44]	23 (7.7) [7-47]
SOFA score, median (IQR)[d]	9 (8-12)	10 (7-12)
Support at randomization		
Vasopressor support	113 (79)	119 (78)
Renal replacement therapy	10 (7)	14 (9)
Prone positioning	30 (21)	28 (18)
Neuromuscular-blocking agents	42 (29)	42 (28)
Corticosteroids	44 (31)	60 (39)
ARDS[e]		
Severe	28 (19)	35 (23)
Moderate	116 (81)	117 (77)
Ventilator settings before the first study drug dose		
Tidal volume, median (IQR), mL	417 (372-470)	423 (380-472)
Positive end-expiratory pressure, cm H_2O	10.6 (3.5)	10.3 (3.5)
Inspiratory pressure, cm H_2O	29.9 (6.8)	31.1 (7.6)
Time from diagnosis to first dose of the study drug, median (IQR), h	10 (4-24)	12 (5-24)

Abbreviations: APACHE II, Acute Physiology And Chronic Health Evaluation II; ARDS, acute respiratory distress syndrome; IQR, interquartile range; SOFA, Sequential Organ Failure Assessment.

[a] Continuous values are presented as mean (SD) unless otherwise indicated.

[b] Other predisposing diagnoses for ARDS were unknown in the interferon β-1a group (n = 1) and undetermined (n = 1), pneumonia induced by chemotherapy (gemcitabine) (n = 1), and postoperation (laparotomy) (n = 1) in the placebo group.

[c] APACHE II[11] scores were calculated based on variables recorded prior to randomization. An APACHE II score increase from 20 to 24 increases mortality risk from 20% to 26%.

[d] SOFA[17] scores were calculated based on variables recorded prior to randomization. SOFA score summary for the full analysis set population has been provided in detail in eTable 19 in Supplement 3. A SOFA score increase from 9 to 11 increases mortality risk from 20% to 26%.

[e] Severe ARDS was defined as partial pressure of oxygen, arterial (Pao_2)/ fraction of inspired oxygen (Fio_2) ≤100 mm Hg (≤13.3 kPa) with positive end-expiratory pressure ≥5 cm H_2O; moderate ARDS was defined as Pao_2/Fio_2 >100 mm Hg (>13.3 kPa) and ≤200 mm Hg (≤26.6 kPa) with positive end-expiratory pressure ≥5 cm H_2O.

Table 2. Primary and Secondary Outcomes[a]

	Median (IQR)			
	IFN-β-1a (n = 144)	Placebo (n = 152)	Absolute Difference (95% CI), %	*P* Value[b]
Primary Outcome				
Composite score: days alive and free of mechanical ventilation at 28 d (VFDsurv)[c,d]	10 (−1 to 20)	8.5 (0 to 20)	0 (−1 to 1)	.82
Secondary Outcomes				
28-d				
Mortality[c,d]	38 (26.4)	35 (23.0)	3.4 (−8.1 to 14.8)	.53
ICU mortality	37 (25.7)	35 (23.0)	2.7 (−8.8 to 14.1)	.62
Hospital mortality (outside ICU)	1 (0.9)	0	0.9 (−10.7 to 12.1)	.37
90-d Mortality	47 (32.6)	48 (31.6)	1.0 (−10.4 to 12.5)	.86
Days free of				
Mechanical ventilation[c,d]	10 (0 to 20)	8.5 (0 to 20)	0 (0 to 1)	.47
Renal support[d]	28 (0 to 28)	27 (1 to 28)	0 (0 to 0)	.72
Vasoactive support[d]	20 (0 to 25)	21 (1 to 25)	0 (−1 to 1)	.94
Any organ failure[d]	0 (0 to 0)	0 (0 to 0)	0 (0 to 0)	.15
Days alive without ICU care[d]	6 (0 to 16)	3.5 (0 to 15)	0 (0 to 0)	.34
No. of days in hospital	28 (23.5 to 28)	28 (22 to 28)	0 (0 to 0)	.70
Serious Adverse Events				
No. of serious adverse events	138	148	NA	
No. of patients with at least 1 serious adverse event	77 (53.5)	77 (50.7)	NA	
Adverse events leading to death	48 (33.3)	53 (34.9)	NA	
Adverse Events				
No. of adverse events	630	626	NA	
No. of patients with at least 1 adverse event	131 (91.0)	134 (88.2)	NA	

Abbreviations: ICU, intensive care unit; IQR, interquartile range; NA, not applicable (95% CI not calculated for differences of medians or for adverse events); VFDsurv, composite end point of mortality and alive and free from mechanical ventilation at day 28.

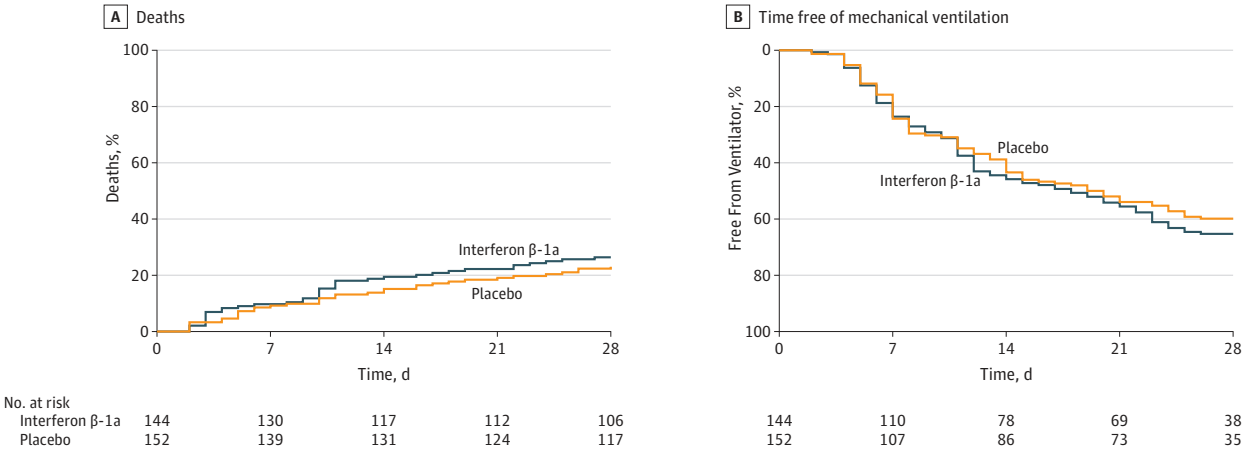
[a] Hodges-Lehmann estimation was used for calculation of the location shifts.

[b] *P* value is from Van Elteren test for VFDsurv; for other variables Barnard's exact test was used. A hierarchical testing strategy was used so that formal statistical significance (or lack thereof) could not be concluded beyond the first nonsignificant secondary outcome.

[c] Free of mechanical ventilation defined as at least 2 consecutive calendar days of unassisted breathing from randomization to day 28.

[d] Duration of days alive without organ support, ICU care, and hospital care calculated from randomization to day 28.

Figure 2. Days Alive and Free of Mechanical Ventilation



Death (A) and days free of mechanical ventilation (B) shown as proportion of patients over time from randomization to day 28. The median observation times for ventilator-free days were 18 days (interquartile range [IQR], 8-28) in the interferon β-1a and 19.5 days (IQR, 8-28) in the placebo group. The median observation times for survival to day 28 were 28 days (IQR, 24.5-28) in the interferon β-1a group and 28 days (IQR, 28-28) in the placebo group.

for interaction between baseline glucocorticoids and treatment group (Breslow-Day test for interaction) (eTable 18 and eFigure 5 in Supplement 3). The adjusted ORs for 28-day mortality by country are presented in eFigure 6 in Supplement 3. Additionally, statistical analyses examining the site effect are provided in eMethods in Supplement 3.

Discussion

In this international multicenter, double-blind, placebo-controlled, parallel-group, randomized clinical trial comprising patients with moderate or severe ARDS, IFN-β-1a

compared with placebo did not improve ventilator-free survival within 28 days.

This study was based on the strong biological plausibility of IFN-β-1a as a treatment for ARDS, given its ability to increase extracellular adenosine by activation of CD73 on epithelial and endothelial cells. Adenosine is one of the physiological regulators of endothelial cell permeability,[4] which also accelerates alveolar fluid reabsorption.[5] Administration of IFN-β-1a upregulates CD73 via de novo synthesis, prevents vascular leakage, and inhibits leukocyte recruitment in animal models.[6,7] Prior clinical data suggested efficacy for IFN-β-1a in ARDS. In a small phase 1/2 open-label nonrandomized study, an 81% reduction in 28-day mortality was observed in patients with ARDS treated with IFN-β-1a.[8]

In the current double-blind and randomized clinical trial, no significant differences in outcomes between the placebo and IFN-β-1a groups could be detected. Aside from lack of efficacy, one possible explanation is that the study was underpowered to detect any clinical benefit. Another possible explanation for these negative results may be in the extensive use of systemic corticosteroids in the trial, as previous experimental studies have shown that concomitant steroid treatment inhibits the effect of IFN-β-1a signaling through its transcription factors IRF3 and IRF9.[20,21] In the current study, there was evidence of decreased IFN-β-1a effect with no increase in soluble CD73 levels in IFN-β-1a–treated patients.

Although numbers of adverse events were comparable between study groups, it should be noted that in the IFN-β-1a group, 5 patients (3.5%) experienced treatment-related rhabdomyolysis. Because this clinical condition is rare in patients with ARDS, further studies are required to evaluate the role of IFN-β-1a in this clinical context. In addition, it is possible that the use of IFN-β-1a in combination with glucocorticoids was associated with increased mortality, which should be carefully considered in all future IFN-β-1a studies.

The major strength of the trial lies in its design and practices ensuring greater adherence to the Berlin definition in identifying critically ill adult patients with hypoxemia who were likely to have pulmonary edema caused by injury of the endothelial-alveolar barrier. To improve the reliability of the chest x-ray criterion for ARDS,[22,23] clinicians blindly associated the patient's chest x-ray with a set of radiograms previously defined as consistent, inconsistent, or equivocal for ARDS.[10] Inconsistencies were assessed and adjudicated by a medical monitor.

Limitations

This study had several limitations. First, the study may have been underpowered to detect a significant effect in 28-day ventilator-free survival because it relied heavily on an optimistic mortality assumption based on a small nonrandomized phase 1/2 trial. Second, in the primary composite outcome measure of death and number of ventilator-free days at day 28, mortality was assigned an arbitrary value of −1.[24] Ventilator-free days already incorporates mortality as 0, making the new score almost identical to ventilator-free days and giving only limited additional value to mortality. Third, the higher-than-expected use of glucocorticoids represents a potential limitation of the present study because glucocorticoids may interfere with the biological effect of IFN-β-1a.[20,21,25,26]

Conclusions

Among adults with moderate or severe ARDS, intravenous IFN-β-1a administered for 6 days, compared with placebo, resulted in no significant difference in a composite score that included death and number of ventilator-free days over 28 days. These results do not support the use of IFN-β-1a in the management of ARDS.

ARTICLE INFORMATION

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