An Analysis of Time to Improvement in Oxygenation in Japanese Preterm and Late Preterm or Term Neonates With Hypoxic Respiratory Failure and Pulmonary Hypertension

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ABSTRACT

Purpose: We analyzed data from an ongoing registry to determine time to improvement in oxygenation in preterm and late preterm or term neonates with hypoxic respiratory failure and pulmonary hypertension receiving inhaled nitric oxide (iNO) in Japan.

Methods: Registry neonates received iNO ≤7 days after birth (February 26, 2010, to October 9, 2012). Efficacy and safety profile data were collected up to 96 h after iNO initiation and, if necessary, every 24 h thereafter and before iNO discontinuation. Patients were stratified by gestational age (GA), oxygenation index (OI), and shunt direction at baseline.

Findings: Data were evaluated for 1106 neonates (431 with a GA <34 weeks and 675 with a GA of ≥34 weeks). Sixty percent of patients had improved OI; rates were similar for those with GAs of <34 versus ≥34 weeks (61% vs 59%). Overall, mean time to improvement was 11.4 h and tended to be shorter in the groups with a GA <34 weeks versus ≥34 weeks (9.2 vs 12.9 h). Thirty percent of responding neonates required >1 h to achieve improvement in oxygenation. Neonates with higher baseline OI had the greatest decrease in OI during the first hour of treatment. The mortality rate was higher among iNO-treated patients with a baseline OI ≥25 versus those with OI ≥15 to <25 (25% vs 12%; $P = 0.0073$).

Implications: iNO treatment provided acute, sustained improvement in oxygenation in neonates with GAs <34 and ≥34 weeks; 70% of patients had improvement within 1 h, but the remaining 30% took >1 h to respond. Initiation of iNO at lower OIs was associated with reduced mortality compared with higher OI. (*Clin Ther*. xxxx;xxx:xxx) © 2019 The Authors. Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

Key words: hypoxic respiratory failure, inhaled nitric oxide, preterm neonate, pulmonary hypertension.

INTRODUCTION

Inhaled nitric oxide (iNO; INOmax®, INO Therapeutics LLC, Hazelwood, MO) is a selective, potent dilator of pulmonary vasculature that is inactivated when rapidly combined with hemoglobin, leading to minimal systemic effects.[1–4] Treatment with iNO improves oxygenation, as reflected in improvements in partial pressure of arterial oxygen (PaO_2) and oxygenation index (OI), and reduces the need for extracorporeal membrane oxygenation in term and near-term neonates with hypoxic respiratory failure (HRF) and pulmonary hypertension (PH).[5–7] On the basis of the findings from key clinical studies, iNO is indicated in the United States, Europe, and Australia/New Zealand for term and near-term (gestational age [GA] >34

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weeks) neonates with HRF associated with clinical or echocardiographic evidence of PH in conjunction with ventilatory support and other appropriate agents.[4,8,9] In Japan, use of iNO is indicated for improvement of HRF with concurrent PH in neonates with GAs >34 weeks; however, the government payer system does not limit its use based on age.[10] Some randomized controlled studies in preterm infants have found a benefit of iNO treatment in reducing the risk of chronic lung disease and/or death,[11–13] whereas others have not.[14–17] Nevertheless, consensus statements from the National Institutes of Health,[18] as well as the American Heart Association and American Thoracic Society,[19] concluded that the use of iNO in some preterm neonates, particularly those with PH or lung hypoplasia, may be beneficial.[18]

An ongoing registry of preterm and late preterm or term neonates with HRF and PH in Japan is being conducted to assess the safety and efficacy profiles of iNO treatment in everyday clinical practice. This registry represents the largest dataset currently available on the use of iNO in a preterm neonatal population with HRF and PH. Previously reported results from an analysis of changes in OI over time and survival stratified by GA (<34 and ≥34 weeks) found that iNO improved oxygenation as effectively in the preterm group as in the term and near-term neonate group without having a negative effect on survival rates[20] The objective of the current analysis was to determine the time to improvement in oxygenation parameters in neonates with HRF and PH while receiving treatment with iNO.

PATIENTS AND METHODS

Overview of Registry, Patients, and iNO Treatment

This ongoing registry was designed to capture efficacy and safety profile data for all neonates with HRF and PH in Japan who received iNO beginning February 26, 2010.[20] Neonates with cardiac disorders who were dependent on right-to-left shunts were excluded from the analysis based on contraindications listed in the Japanese product labeling.[10,20] Neonates who started iNO >7 days after birth also were not included in the registry according to the reimbursement policy in Japan.

Clinicians in the registry were encouraged to use iNO according to the product labeling in Japan.[20] In accordance with the reimbursement policy in Japan, treatment with iNO was initiated within 7 days of birth at a concentration of 20 ppm at a fraction of inspired oxygen concentration (FiO_2) of 1.0. After 4 h from the start of administration, the dose of iNO could be reduced to 5 ppm once PaO_2 was >60 mm Hg or pulse oximetry arterial oxygen saturation was >92%.[20] With iNO maintained at 5 ppm, the FiO_2 was to be gradually reduced until the PaO_2 was >70 mm Hg at an FiO_2 of 0.4–0.6.[20] When discontinuing iNO administration, the dose was gradually reduced to 1 ppm. During iNO administration at 1 ppm, if no change in oxygenation was observed, iNO administration was discontinued after raising the FiO_2 by 0.1 and remained off if there was no deterioration in oxygenation. If oxygenation worsened, iNO was resumed at 5 ppm and discontinuation of iNO was reconsidered after 12–24 h.[20]

The program was conducted through Air Water Inc. (Tokyo, Japan) in accordance with Ministerial Ordinance No. 171 of the Ministry of Health, Labor and Welfare and other related governmental regulations, and the registry protocol was approved by the institutional review board at each participating center.

Data Collection

Enrollment in the registry will be open through 2018; data included in this report were collected from February 26, 2010, to October 9, 2012.[20] Data from the registry were collected according to the clinicians' clinical use of iNO (ie, all patients in the registry received iNO).[20] Data were collected immediately before administration of iNO, at 1, 4, 12, 24, 48, 72, and 96 h after initiation of iNO, every 24 h thereafter (if necessary), and just before discontinuation of iNO.[20] Clinicians provided data on patient background information and medical history, prior drugs and therapies, systemic blood pressure, echocardiography, chest radiography, PaO_2, pulse oximetry arterial oxygen saturation, blood methemoglobin, inspired nitric oxide concentration, inspired nitrogen dioxide concentration, mechanical ventilation information, OI, laboratory test findings, concomitant drugs and therapies, and adverse events.[20]

Statistical Analysis

Data for the current analysis were compiled and summarized using descriptive statistics (eg, mean, SD,

Table I. Baseline demographic and clinical characteristics.[a]

Characteristic	All Patients (N = 1106)	GA <34 weeks (n = 431)[b]	GA ≥34 weeks (n = 675)[b]
GA, mean (SD), wk	34.1 (6.2)[c]	27.1 (3.5)	38.6 (1.9)
Postnatal age, mean (SD), h	14.5 (22.1)[c]	10.1 (15.6)	17.4 (25.0)
Sex			
Male	602 (54.4)	220 (51)	382 (57)
Female	504 (45.6)	211 (49)	293 (43)
Weight at birth, mean (SD), kg	2.134 (1.031)[c]	1.043 (0.593)	2.832 (0.520)
Underlying disease			
Respiratory distress syndrome	259 (23.4)[c]	229 (53.1)	30 (4.4)
Meconium aspiration syndrome	144 (13.0)[c]	2 (0.5)	142 (21.0)
Congenital diaphragmatic hernia	116 (10.5)[c]	6 (1.4)	110 (16.3)
Idiopathic	84 (7.6)[c]	26 (6.0)	58 (8.6)
Pneumonia/sepsis	70 (6.3)[c]	40 (9.3)	30 (4.4)
Other	423 (38.2)[c]	125 (29.0)	298 (44.1)
Missing	10 (0.9)[c]	3 (0.7)	7 (1.0)
Duration of iNO treatment, mean (SD), h	120.4 (245.5)	85.2 (132.3)	142.9 (295.2)
Reason for administration of iNO			
Treatment of HRF associated with PH	1096 (99.1)	429 (99.5)	667 (98.8)
Other	10 (0.9)	2 (0.5)	8 (1.2)
Complications or conditions[d]			
None	439 (39.7)	195 (45.2)	244 (36.1)
Lung hypoplasia	263 (23.8)	79 (18.3)	184 (27.3)
Congenital heart disease	119 (10.8)	22 (5.1)	97 (14.4)
Multiple abnormalities	55 (5.0)	16 (3.7)	39 (5.8)
Other	397 (35.9)	180 (41.8)	217 (32.1)

GA = gestational age; HRF = hypoxic respiratory failure; iNO = inhaled nitric oxide; PH = pulmonary hypertension.
[a] Data are presented as number (percentage) of patients unless otherwise indicated.
[b] GA data were missing for 8 patients.
[c] $P < 0.0001$ for GA <34 versus ≥34 weeks from an analysis of variance for continuous variables and χ^2 tests for categorical values.
[d] Patient could have >1 condition.

median percentages, and ranges) and stratified by GA (<34 and ≥34 weeks), presence of lung hypoplasia, and direction of shunt (ie, bidirectional, right-left, left-right, and no shunt). Analyses of individual parameters were based on the number of evaluable neonates for each parameter; not every neonate had evaluable data for every parameter. For the purposes of this analysis, the OI was calculated as follows: mean airway pressure × FiO_2 × 100/PaO_2. Improvement, or positive response, in oxygenation was defined as a 10% decrease from baseline in OI or a 10% increase from baseline in PaO_2.

RESULTS

Patients

Data were compiled for a total of 1114 neonates; 1106 were included in the subgroup analyses, of whom 431 neonates had a GA <34 weeks, 675 had a GA ≥34 weeks, and 8 had missing GA data (Table I).[20] As expected, significant differences were

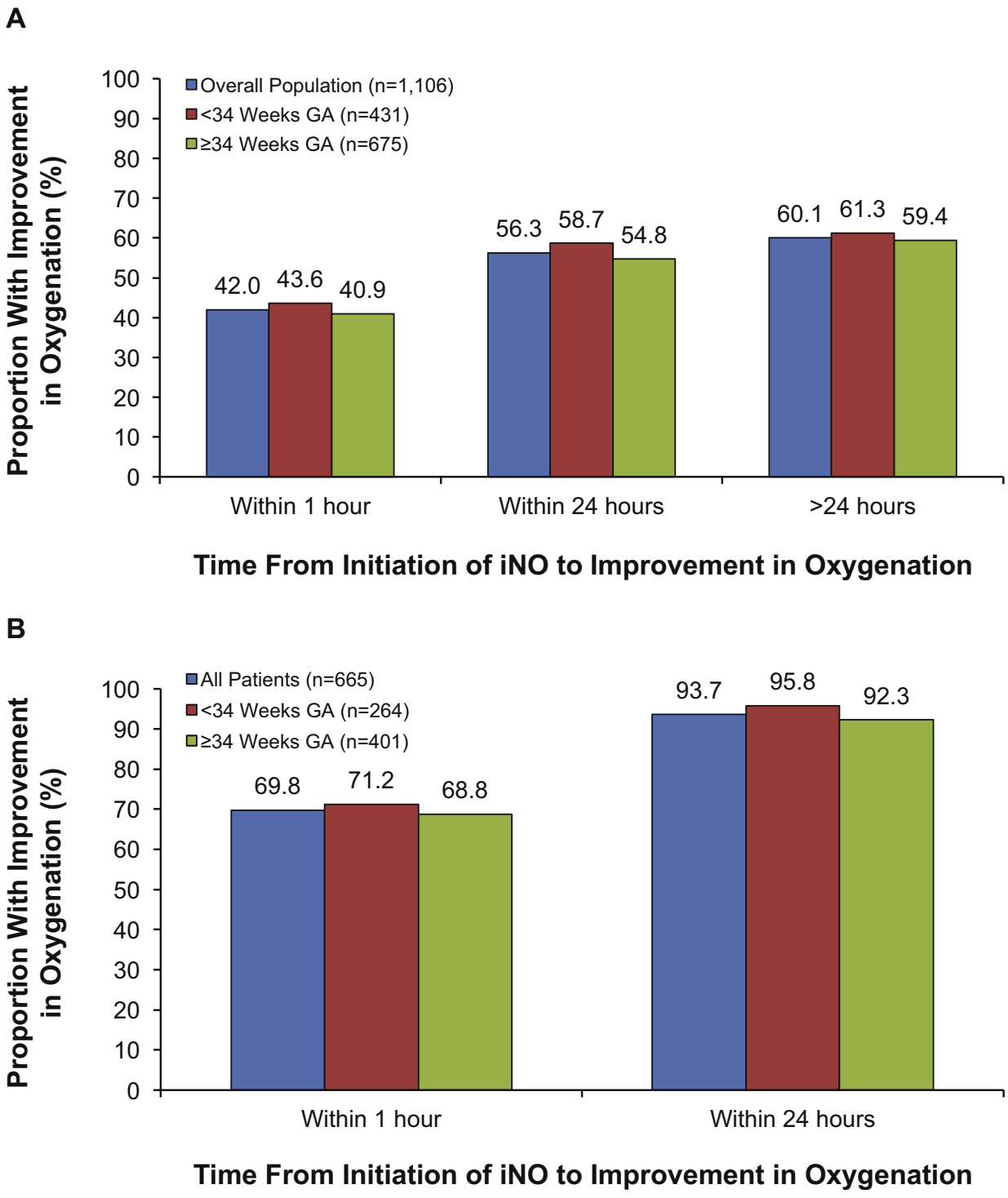

Fig. 1. (A) Cumulative proportion of patients with improvement in oxygenation in the overall population and GA subpopulations. (B) Timing of improved oxygenation among patients showing improvement in oxygenation. Improvement in oxygenation was defined as either a 10% decrease from baseline OI or a 10% increase from baseline in PaO_2. GA = gestational age; iNO = inhaled nitric oxide.

noted between the GA groups in mean age, GA, and birth weight, as well as the proportions of neonates with underlying disease and complications at baseline. The prevalence of pneumonia or sepsis and respiratory distress syndrome was higher in the group with GAs <34 weeks, whereas the prevalence of congenital diaphragmatic hernia and meconium aspiration syndrome was higher in the group with GAs ≥34 weeks. The mean (SD) duration of treatment was 5.0 (10.3) days in the overall population and was significantly shorter in neonates with GAs <34 weeks (3.5 [5.5] days) compared with those with GAs ≥34 weeks (6.0 [12.3] days; $P = 0.0001$).

Improvement in OI

Overall, 665 patients (60%) had an improvement in oxygenation while receiving iNO treatment: 264 of 431 (61%) in the GA <34 weeks group and 401 of 675 (59%) in the GA ≥34 weeks group (Figure 1A). The mean (SD) time to improvement in oxygenation among patients who had improvement during iNO treatment was 11.4 (27.6) hours; the median (range) time to improvement was 1.0 (1.0−504.0) hour. The mean time to improvement in the subgroups stratified by GA or direction of shunt is given in Table II.

Among the neonates whose oxygenation improved, 201 of 665 (30%) did not have improvement until after 1 h of iNO treatment. Results in the GA subgroups were similar; 76 of 264 neonates (29%) with GA <34 weeks and 125 of 401 neonates (31%) with GA ≥34 weeks required >1 h of iNO treatment to respond (Figure 1B). Data on time to improvement were available for 123 patients with lung hypoplasia who had improvement in oxygenation during iNO; of these, 87 (70.7%) had improvement within 1 h and 110 (89.4%) had improvement within 24 h. Of the 42 neonates with GAs <34 weeks and lung hypoplasia, 30 (71.4%) had oxygenation improvement within 1 h and 41 (97.6%) had improvement within 24 h compared with 57 (70.4%) and 69 (85.2%), respectively, in the GA ≥34 weeks subgroup (n = 81) with lung hypoplasia. When patients were stratified by direction of shunt, similar proportions experienced improvement in oxygenation within 1 h, within 24 h, and after 24 h following iNO initiation compared with the overall population (Figure 2A); fewer neonates with bidirectional shunt had improvement within 1 h compared with those who had right-left shunt (40.4% vs 48.8%; $P = 0.0129$). Among those who experienced improvement in oxygenation, patients with a bidirectional or left-to-right shunt were most likely to require >1 h of iNO treatment before they experienced improvement in oxygenation (Figure 2B).

Changes from baseline in OI over time for patients with available data in the GA <34 weeks group (n = 156) and the GA ≥34 weeks group (n = 261) stratified by baseline OI are shown in Figure 3A and B, respectively. Subgroups with higher baseline OI values had the most marked decrease in OI during the first hour of iNO treatment; OI values continued to decrease over time in these subgroups through the >24-h assessment. The proportions of patients who had evaluable data and experienced OI >40 at any time point or died are summarized in Table III, stratified by baseline OI. The mortality rate was significantly higher in the baseline OI ≥25 group (24.8%) compared with the baseline OI ≥15 to <25 group (12.1%; $P = 0.0073$) and the baseline OI <15 group (8.9%; $P < 0.0001$).

Table II. Time to improvement in oxygenation.

Category	Time to Improvement, Mean (SD), h
All patients with improvement during iNO treatment (n = 672)	11.4 (27.6)
GA <34 weeks (n = 264)	9.2 (15.0)
GA ≥34 weeks (n = 401)	12.9 (33.4)
Bidirectional shunt (n = 273)	11.7 (18.1)
Right-to-left shunt (n = 301)	9.9 (32.4)
Left-to-right shunt (n = 44)	20.2 (33.7)
No shunt (n = 31)	12.4 (38.9)

GA = gestational age; iNO = inhaled nitric oxide.

DISCUSSION

The results of this analysis indicate that similar proportions of neonates with GAs <34 weeks and ≥34 weeks treated with iNO had improvement in oxygenation and a similar mean time to improvement. Among those who experienced

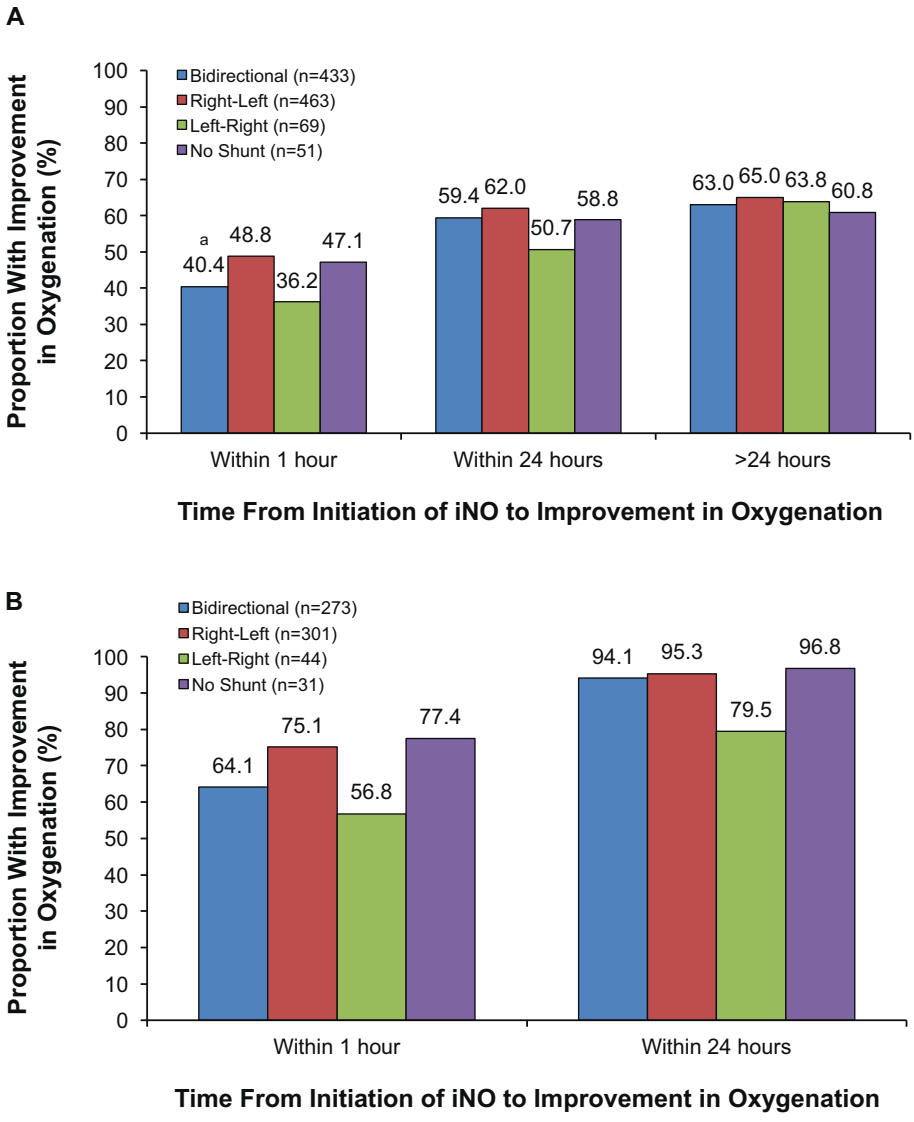

Fig. 2. (A) Cumulative proportion of patients with improvement in oxygenation in the overall population, stratified by direction of shunt. [a]$P = 0.0129$ vs the right-left shunt group within 1 h. (B) Timing of improved oxygenation among patients showing improvement in oxygenation, stratified by direction of shunt. Improvement in oxygenation was defined as either a 10% decrease from baseline OI or a 10% increase from baseline in PaO_2. iNO = inhaled nitric oxide.

improvement in oxygenation while receiving iNO treatment, approximately 70% had improvement within the first hour after initiation of iNO and 94% had improvement within 24 h, with a small proportion (6%) requiring >24 h of iNO treatment. Similar rates were observed for neonates with GAs <34 weeks and lung hypoplasia at baseline compared with those with GAs ≥34 weeks with lung hypoplasia at baseline. Neonates with a left-to-right shunt appeared to take longer to achieve improvement in oxygenation (mean, 20.2 h) than those who had a bidirectional shunt (mean, 11.7 h), right-to-left shunt (mean, 9.9 h), or no shunt (mean, 12.4 h).

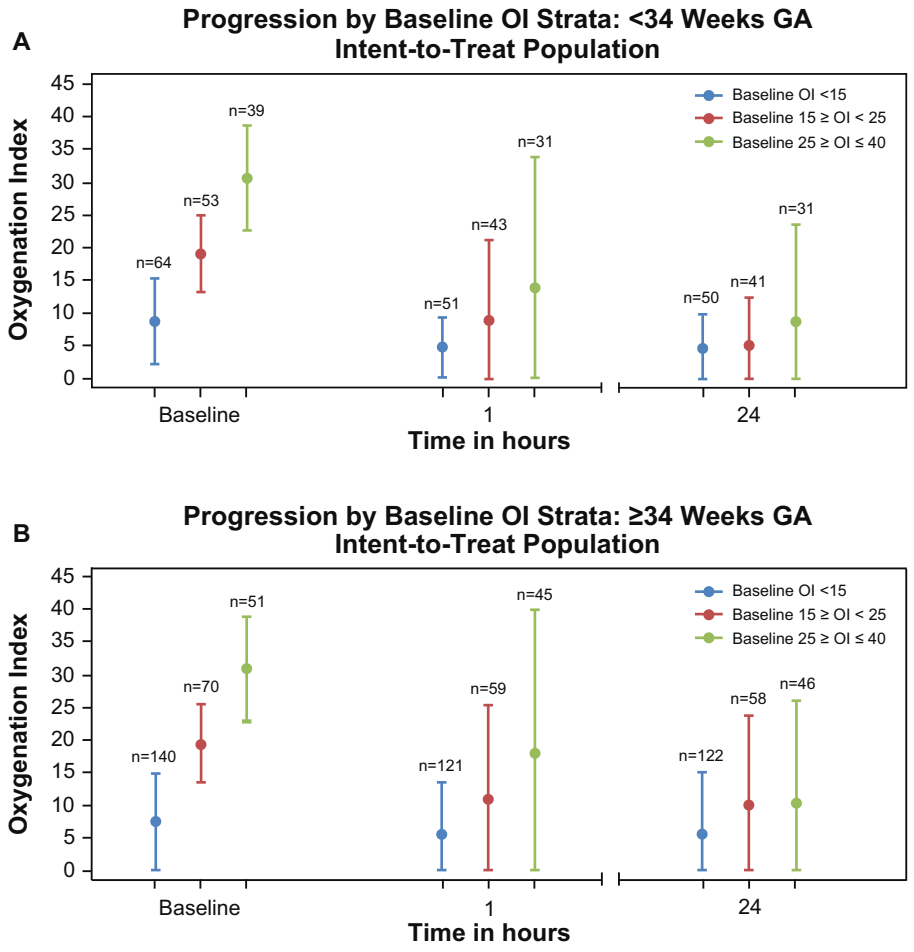

Fig. 3. (A) Progression of OI over time in the GA <34 weeks group, stratified by baseline OI category. (B) Progression of OI over time in the GA ≥34 weeks group, stratified by baseline OI category. Patients who died and patients with baseline OI >40 are excluded. Lower confidence bounds <0 are shown as zero. GA = gestational age; OI = oxygenation index.

These data on the rapid action of iNO for improvement in oxygenation are consistent with clinical studies of iNO in neonates with GAs >34 weeks with HRF and PH. Davidson et al[5] reported statistically significant improvement in PaO_2 and a mean decrease in OI of 14% within 30 min of iNO exposure. In the Neonatal Inhaled Nitric Oxide Study, the mean PaO_2 increased by 58.2 mm Hg within 30 min after initiation of iNO compared with a 9.7-mm Hg increase in the patients who received placebo ($P < 0.001$); a significantly greater change in OI was also observed with iNO compared with placebo (–14.1 vs 0.8; $P < 0.001$).[7] Interestingly, our results suggest that some patients may require longer exposure to iNO than others, and duration of treatment may be an important factor in determining its effectiveness in a subset of patients with HRF and PH. Of the 665 neonates who achieved improvement in oxygenation while receiving iNO, 30% did not improve until after they were exposed to iNO for >60 min. In addition, results from this current analysis of outcomes in the neonates stratified by baseline OI suggest there may be a survival benefit associated with initiation of iNO at lower OI levels; neonates who received iNO when OI was between 15 and 25 had a much lower mortality rate than those

Table III. Proportions of patients with evaluable data who experienced OI >40 at any time point after baseline or who had died, stratified by baseline OI.[a]

Category	Baseline OI <15 (n = 225)	Baseline OI ≥15 to <25 (n = 141)	Baseline OI ≥25 to ≤40 (n = 129)
OI >40 at any time point	11 (4.9)	8 (5.7)	29 (22.5)[b,c]
Death	20 (8.9)	17 (12.1)	32 (24.8)[b,d]
Died or OI >40 at any time point	21 (9.3)	18 (12.8)	39 (30.2)[b,e]

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OI = oxygenation index.
[a] *P* values were from Fisher exact tests; 104 patients with evaluable data had a baseline OI >40 (data not given in the table).
[b] $P < 0.0001$ vs the baseline OI <15 group.
[c] $P < 0.0001$ vs the baseline OI ≥15 to <25 group.
[d] $P = 0.0073$ vs the baseline OI ≥15 to <25 group.
[e] $P = 0.0005$ vs the baseline OI ≥15 to <25 group.

who had a baseline OI ≥25. This observation is consistent with data reported in a previous analysis by Konduri and Kim,[21] who recommended that iNO treatment be initiated at an OI of approximately 20, before the occurrence of severe respiratory failure in neonates with PH. On the basis of the data compiled in the present study, it appears that early initiation of iNO (OI <25) and adequate duration of iNO exposure (at least 1 h) may be associated with clinically meaningful improvements in iNO-treated neonates. However, more study is needed. Because the purpose of the registry is to collect data on the efficacy and safety profiles of iNO in real-world clinical use, our data set did not include an untreated control group, and the analyses did not account for the potential effect of treatment interventions other than iNO on the observed outcomes.

Previously reported safety profile data from the registry have indicated that severe intraventricular hemorrhage occurred in more neonates in the GA <34 weeks group compared with the GA ≥34 weeks group,[20] which is an expected finding associated with GA.[22,23] No neonatal necrotizing enterocolitis was reported in either age group, and the highest observed mean methemoglobin levels were similar in both groups. These observations regarding the safety profile of iNO in preterm neonates are consistent with consensus guidelines.[18,24] This ongoing registry in Japan provides an opportunity to collect adverse drug reaction reports in a country where underreporting, particularly for expected adverse events, has been documented.[25] Observational registry data are inherently limited by the presence of confounding factors, such as missing data and/or variations in clinical practice across different sites. Nevertheless, the data from this registry provide valuable information regarding the real-world use of iNO in clinical practice.

In conclusion, 60% of neonates had improvement in oxygenation while receiving iNO therapy, and the proportions of neonates with GAs <34 weeks who had improvement in oxygenation during iNO treatment was similar to neonates with GAs ≥34 weeks; the mean time to improvement was also similar in both age groups. Oxygenation improvement did not occur until after at least 60 min of iNO exposure in 30% of the responding neonates, suggesting that early discontinuation of iNO may compromise efficacy in a subset of patients. These data also suggest that initiation of iNO treatment before OI reaches 25 is important for improving survival compared with initiation at a higher OI.

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CONFLICT OF INTEREST

William D. Rhine has received travel expense reimbursement from Mallinckrodt Pharmaceuticals to attend and present a scientific poster at the 2018 International Conference on Clinical Neonatology. Jim L. Potenziano and Shannon Escalante are employees of and stockholders in Mallinckrodt Pharmaceuticals. Hajime Togari and Satoshi Suzuki are members of the advisory board for the INOflo Post Market Surveillance Study in Japan for Mallinckrodt Pharmaceuticals and have served as speakers for Mallinckrodt Pharmaceuticals, receiving honoraria and travel expense reimbursement. The authors have indicated that they have no conflicts of interest regarding the content of this article.

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The study was designed by William D. Rhine and Jim L. Potenziano. The principal investigator was William D. Rhine. The study investigators were Hajime Togari and Satoshi Suzuki. Hajime Togari and Satoshi Suzuki enrolled patients. Collection and assembly of data was performed by Shannon Escalante and Jim L. Potenziano, and Hajime Togari and Satoshi Suzuki (for original collection of data, not assembly). All authors participated in data analysis and interpretation, manuscript preparation, manuscript review and revisions, and final approval of manuscript.

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