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ORIGINAL ARTICLE

Safety and Varicella Outcomes in In Utero–Exposed Newborns and Preterm Infants Treated With Varicella Zoster Immune Globulin (VARIZIG): A Subgroup Analysis of an Expanded-Access Program

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Background. Infants exposed to varicella zoster virus (VZV) in utero ≤5 days before or ≤48 hours after delivery and preterm infants are at high risk for varicella complications. An expanded-access program assessed varicella outcomes after administration of varicella zoster immune globulin (human) (VARIZIG) in a real-world setting.

Methods. In this open-label, expanded-access program, high-risk infants received ≤125 IU/10 kg of VARIZIG (NCT00338442). VZV outcomes and safety were assessed.

Results. There were 43 newborns exposed to VZV in utero and 80 preterm infants exposed to VZV; >80% received VARIZIG within 96 hours of reported exposure. When varicella outcomes were available, varicella occurred in 7 of 38 (18%) in utero–exposed newborns and zero of 65 preterm infants. Varicella-related complications were reported in 3 in utero–exposed newborns (3 with >100 lesions, 1 each with encephalitis and pneumonia). Adverse events were reported for 16% of in utero–exposed newborns and 25% of preterm infants, but few were considered related to VARIZIG. There were no deaths attributable to varicella or VARIZIG.

Conclusions. Varicella incidence and morbidity were low in in utero–exposed infants and zero in preterm infants who received prophylactic VARIZIG. There were few VARIZIG-related safety concerns.

Keywords. hyperimmune globulin; passive immunization; postexposure; preterm; varicella.

Varicella zoster virus (VZV) results in approximately 100 000 cases of varicella and >1 million cases of herpes zoster each year in the United States [1–3]. Infants born to pregnant women who develop varicella within 5 days before delivery or within 48 hours after delivery are at risk for severe neonatal varicella [4–6]. This increased risk is due to several factors: lack of protective transplacental VZV antibodies in the few days after maternal VZV infection, impaired cellular immune response, and a high transplacental viral load transferred to the fetus [4, 6, 7]. Preterm infants are at a higher risk for invasive disease and varicella complications due to age-related impairment in cellular immune responses, as well as insufficient opportunity to acquire maternal immunoglobulin G antibodies prior to their premature birth, as these antibodies are transplacentally transferred from the mother to infant during the second and third trimesters of pregnancy [8–10].

Passive immunization during the incubation period of varicella can prevent or attenuate varicella and its complications. Over the past 60 years, clinicians have used generic immune serum globulin and hyperimmune serum globulin containing high titers of VZV-specific antibodies to prophylax immunocompromised and high-risk individuals exposed to varicella [11–16]. After the most commonly used preparation of varicella zoster immune globulin (VZIG) was discontinued in 2006, a replacement was developed. Varicella zoster immune globulin (human) (VARIZIG, Saol Therapeutics, Roswell, Georgia) is recommended for postexposure prophylaxis to prevent or attenuate varicella in high-risk individuals, including (1) infants who are <28 weeks' gestational age, (2) infants weighing <1000 g, (3) hospitalized neonates ≥28 weeks' gestational age whose mothers lack immunity to varicella, and (4) infants whose mothers develop varicella within 5 days before delivery or within 48 hours after delivery [17–19]. The Centers for Disease Control and Prevention recommends that VARIZIG be administered as

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soon as possible after VZV exposure, ideally within 96 hours, but up to 10 days after exposure [18]. Levin et al have recently reported on results from an expanded-access program that assessed the incidence and severity of VARIZIG in a real-world setting in several high-risk populations, including infants aged <1 year [20]. Given the limited published information with VARIZIG, we report here a more detailed analysis of clinical and safety outcomes in subgroups of infants exposed to VZV in utero or of preterm infants.

METHODS

This was an open-label, expanded-access program in which infants received ≤125 IU/10 kg of VARIZIG administered intramuscularly, ideally within the first 96 hours postexposure, but up to 10 days postexposure (NCT00338442). The initial protocol allowed for infants weighing <5 kg to receive a reduced VARIZIG dose (≤62.5 IU). Participants in the full expanded-access program were physician-identified high-risk individuals who had been exposed to varicella or herpes zoster, including immunocompromised children and adults, pregnant women, healthy nonimmune adults, and infants [20]. For the current analysis, we further assessed varicella outcomes and safety metrics of VARIZIG administered to infants who were stratified into 2 subgroups: newborns born to mothers who developed VZV infection within 5 days before birth or within 48 hours after birth and preterm infants (<28 weeks' gestation). Infants were followed from initial VARIZIG administration with 3 additional visits through a maximum of 42 days to determine the incidence and severity of varicella and any varicella-related complications (eg, pneumonia, encephalitis, or mortality). Per study definition, varicella cases were considered severe when the lesion count was >100. Parent/caregiver-reported and investigator-reported adverse events (AEs) were included in the safety evaluation. Additional study design details have been previously reported [20].

This study was conducted in accord with the Good Clinical Practice Guidelines as defined by the International Conference on Harmonisation, the Declaration of Helsinki, and/or all applicable federal and local regulations and institutional review boards, as appropriate. All infants had parent/caregiver-provided written informed consent.

RESULTS

Participants

Forty-three newborns exposed to VZV in utero and 80 preterm infants were enrolled in the study (Table 1). In utero–exposed newborns had a mean age of 2.2 (standard deviation [SD], 2.21) days at enrollment, were relatively evenly distributed between males and females, and 42% were Hispanic/Latino newborns. Newborns had a mean weight of 3.2 (SD, 0.82) kg. The mean age for preterm infants at the time of exposure was 36.4 days, with half (51%) of preterm infants aged <1 month and 13 (16%) aged 1 to <2 months. The majority of preterm infants were female (59%) and white (55%). The mean weight of preterm infants at the time of exposure was 1.9 (SD, 0.93) kg.

Table 1. Baseline Demographics

Characteristic	In Utero–Exposed Newborns (n = 43)	Preterm Infants (n = 80)
Age at VARIZIG administration, d		
Mean (SD)	2.2 (2.21)	36.4 (34.11)[a]
Median	1.0	27.5
Range	0–9	1–180
Sex, No. (%)		
Female	23 (53)	47 (59)
Male	20 (47)	33 (41)
Race, No. (%)		
White	11 (26)	44 (55)
Hispanic or Latino	18 (42)	14 (18)
Black or African American	4 (9)	15 (19)
Asian	5 (12)	2 (3)
Not reported/declined/other	5 (12)	5 (6)
Weight, kg		
Mean (SD)	3.2 (0.82)	1.9 (0.93)
Median	3.3	1.8
Range	1.0–4.7	0.5–5.7

Abbreviations: SD, standard deviation; VARIZIG, varicella zoster immune globulin, human.
[a]Forty-one preterm infants (51%) were aged <1 month, 15 (19%) were 1 to <2 months old, 13 (16%) were 2 to <3 months old, 9 (11%) were 3 to <4 months old, and 2 (3%) were 4–6 months old.

VZV Exposure

Nearly all (99%) preterm infants were exposed to VZV in a hospital setting (Table 2). Most (60%, n = 26) in utero–exposed newborns were exposed to varicella (maternal infection), although 14% (n = 6) were exposed to herpes zoster (maternal infection); 26% (n = 11) of in utero–exposed newborns did not have the specific type of VZV infection specified in their case report form. The preterm infant group reported similar rates of exposure to varicella or herpes zoster; 42% of preterm infants did not have the type of VZV infection specified in their case report form (Table 2). The duration of exposure in preterm infants reported by providers ranged from <15 minutes to 5 days, with 35% exposed for >12 hours, 25% exposed for 3–12 hours, and 31% exposed for <3 hours (14% were exposed for <1 hour). Duration of exposure for in utero–exposed newborns could not be calculated.

Varicella Outcomes

More than 80% of infants in each subgroup received VARIZIG within 96 hours of either delivery (if in utero exposure) or contact exposure (if preterm infants) (Table 2). For infants with available varicella outcome data, the incidence of varicella was 18% (7/38) for in utero–exposed newborns and 0% (0/65) for preterm infants (Figure 1). Maternal varicella infection led to varicella in 7 of 23 (30%) in utero–exposed newborns, whereas maternal

Table 2. Exposure and Administration Details

Characteristic	In Utero–Exposed Newborns (n = 43)	Preterm Infants (n = 80)
Source of VZV exposure		
In utero	43 (100)	0
Hospital	0 (0)	79 (99)
Household	0 (0)	1 (1)
Type of VZV exposure[a]		
Varicella	26 (60)	26 (33)
Herpes zoster	6 (14)	20 (25)
Not specified	11 (26)	34 (42)
Timing of administration[b]		
≤96 hours postexposure	37 (86)	71 (89)
>96 hours[c] postexposure	6 (14)	8 (10)
Unknown	0 (0)	1 (1)
Concomitant antiviral prophylaxis		
Did not receive	32 (74)	77 (96)
Did receive	11 (26)	3 (4)

Data are presented as No. (%).
Abbreviation: VZV, varicella zoster virus.
[a]For in utero–exposed newborns, the type of VZV exposure refers to the maternal VZV infection.
[b]Timing of administration is calculated based on initial report of exposure. For in utero–exposed infants, this was considered to have occurred at birth or prior to birth.
[c]Timing of administration was >96 hours (up to 10 days) postexposure.

herpes zoster infection did not result in varicella in the 6 newborns exposed to maternal herpes zoster in utero. Three newborns exposed in utero developed varicella-related complications; all 3 had >100 lesions, 1 developed encephalitis, and 1 developed pneumonia. No preterm infants developed varicella-related complications. Information on varicella outcome was not available for 5 in utero–exposed infants and 15 preterm infants. Nine infants weighing <5 kg received ≤62.5 IU of VARIZIG; of these infants, 7 did not develop varicella and 2 were lost to follow-up. One preterm infant was considered to be underdosed, having received 14 IU for a 1.2 kg infant; this preterm infant did not develop varicella.

Approximately one-quarter (28%) of in utero–exposed newborns received concomitant acyclovir prophylaxis, compared with only 4% of infants in the preterm group. If administered, concomitant acyclovir prophylaxis was begun on the day before or the day of VARIZIG administration in 72% of infants. Overall, 7 patients only received acyclovir prophylaxis for 2 or fewer days, presumably until VARIZIG was administered, whereas 7 others received acyclovir for a range of 4–9 days. Among the in utero–exposed newborns treated with acyclovir prophylaxis, 1 of 11 developed varicella; this newborn developed >100 lesions. In comparison, the remaining 6 in utero–exposed newborns who developed varicella did not receive acyclovir prophylaxis; 2 of these newborns had varicella-associated complications (1 had >100 lesions and pneumonia, 1 had >100 lesions and encephalitis).

Safety

Overall, 22% of infants experienced an AE, of which 16% were in utero–exposed newborns and 25% in preterm infants (Table 3). Only 2 of these AEs were considered possibly related to VARIZIG.

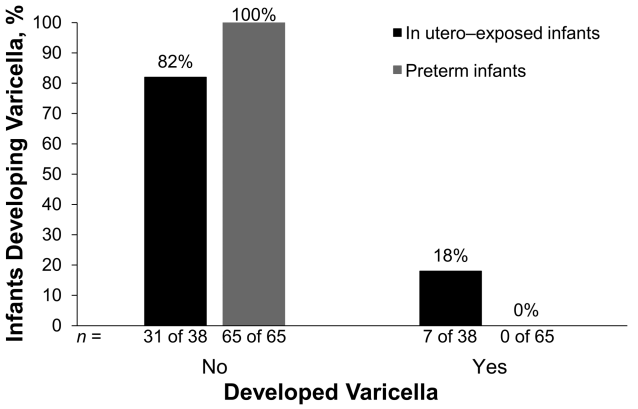

Figure 1. Incidence of varicella in each infant subgroup. Only those with varicella outcome data are depicted; varicella outcome was not available for 5 in utero–exposed infants and 15 preterm infants.

Twelve percent of in utero–exposed newborns experienced 5 serious AEs (4 were cases of varicella), of which 1 case of varicella was labeled by an individual investigator as an AE possibly related to VARIZIG (ie, a lack of VARIZIG efficacy). Nine percent of preterm infants experienced 20 serious AEs, of which 1 seizure was considered possibly related to VARIZIG. There were 2 deaths reported, both of which occurred in premature infants (23 and 25 weeks' gestation) and were caused by bronchopulmonary dysplasia and intraventricular hemorrhage; both deaths were considered unrelated to VARIZIG or varicella.

Table 3. Safety of VARIZIG (Varicella Zoster Immune Globulin [Human])

Preferred Term	In Utero–Exposed Newborns (n = 43)	Preterm Infants (n = 80)
AEs		
Participants, No. (%)	7 (16)	20 (25)
Total AEs, No.	13	58
AEs related to VARIZIG		
Participants, No. (%)	1 (2)	1 (1)
Participants with related AEs, No. (%)		
Seizure	…	1 (1)
Varicella	1 (2)	…
Serious AEs		
Participants, No. (%)	5 (12)	7 (9)
Total serious AEs, No.	5	20
Total related serious AEs, No.	1	1
All related serious AEs, No. (%)[a,b]		
Seizure	…	1 (2)
Varicella	1 (2)	…
Deaths, No. (%)	…	2 (3)

Abbreviations: AE, adverse event.
[a]In the in utero–exposed population, the following serious AEs were considered unrelated to VARIZIG: pneumonia (n = 1), varicella (n = 3).
[b]In the preterm infant population, the following serious AEs were considered unrelated to VARIZIG: bronchopulmonary dysplasia, pneumonia, staphylococcal sepsis, thrombocytopenia (each in 2 participants); and coagulopathy, condition aggravated, seizure, cytomegalovirus infection, disseminated intravascular coagulation, intraventricular hemorrhage, metabolic acidosis, necrotizing enterocolitis, pulmonary hemorrhage, sepsis, and urinary tract infection (each in 1 participant).

DISCUSSION

Despite high levels of varicella vaccination in most communities, varicella still occurs, and the incidence of varicella is likely to remain problematic if nonmedical vaccination exemption rates consistently increase nationwide [21]. Moreover, herpes zoster prevalence has not yet been significantly affected by universal varicella vaccination or supplemental zoster vaccination [22]. As such, VZV remains a threat to high-risk populations.

Prior to the availability of passive immunization, case studies reported that newborns exposed to VZV in utero exhibited a high incidence of clinical infection (24%) and death (31%) [4]. A subsequent retrospective report using passive immunization with VZIG (discontinued in 2006) indicated that 62% of in utero–exposed newborns exhibited symptomatic rash after exposure to varicella, with no varicella-related deaths [7]. For comparison, in immunocompromised children treated with VZIG, the VZV infection rate was 60.4%, with varicella pneumonia occurring in 6.1% of those who developed varicella [16]. In the current analysis, the risk of transmitting varicella to these in utero–exposed newborns was high, and prophylactic administration of VARIZIG may have prevented or attenuated varicella infection in these patients. It is noteworthy that 7 of 38 in utero–exposed newborns still developed varicella, of which 3 were complicated cases (2 with visceral involvement), although there were no varicella-associated deaths. Passive immunization was conceptually designed to work by neutralizing the VZV in vivo; VARIZIG has high titers of neutralizing antibody. However, VZV is highly cell-associated (in the tissue and blood) and can spread directly from cell to cell [23], thus potentially avoiding the neutralizing antibodies introduced by passive immunization. This raises the possibility that the administered antibody can function by arming nonspecific cells of the innate immune system, such as natural killer cells or monocytes [24–26]. It is possible that in the 7 breakthrough cases of varicella, the newborns not only lacked antibody but also innate cellular components of the immune system. This theory could be the basis for future research.

A limitation of our study is that detailed data regarding VZV exposure are lacking in many cases. Although some preterm infant exposures to VZV may have been minimal, it is unknown if each exposure was significant enough to cause varicella. However, investigators determined whether each exposure necessitated VARIZIG administration, which is how VARIZIG is used in clinical practice. As such, we are limited by relying on each investigator's definition of a significant VZV exposure. It may be that in this cohort, preterm infant exposure to VZV is not as concerning as previously thought due to intrinsic host factors, or that VARIZIG provided protection against VZV infection. As previously noted, of the in utero–exposed newborns with known outcome data, all of the cases of varicella occurred when the mother had varicella (n = 7/23), not herpes zoster (n = 0/6). Although the small number of newborns in these groups limits the conclusions about risk by VZV infection type, it is likely that transplacental passage of maternal antibodies conferred some protection to the subset of infants born to mothers with herpes zoster.

Most in utero–exposed newborns and preterm infants did not receive antiviral prophylaxis concomitant with VARIZIG, while 5% (n = 6/123) received antiviral treatment after developing varicella. In utero–exposed newborns had the highest percentage of concomitant antiviral prophylaxis (28%). However, antiviral prophylaxis was most often given within the first few days of exposure (ie, immediately after birth or when exposure was first reported) while the physician was waiting for receipt of VARIZIG. Often antiviral prophylaxis was discontinued after only 2 days. This use of acyclovir prophylaxis deviates from a report demonstrating a reduced incidence of varicella when acyclovir is given 6–10 days after exposure for 7 days compared with failure of acyclovir prophylaxis that was administered in the first few days after exposure [27].

This analysis has additional limitations. Because of this expanded-access program, which assessed the use of VARIZIG in a real-world setting, there was no control treatment and there was a large amount of missing data measurements. This study did not always distinguish the type of VZV exposure, so the true proportion of varicella vs herpes zoster exposures in each group is unknown. Furthermore, each physician determined whether the exposure qualified for prophylaxis, which probably led to the inclusion of cases with limited exposure and risk of varicella.

CONCLUSIONS

These data demonstrate safety in the newborn and preterm infant population, and show that for a variety of exposure types and times, the incidence of varicella and varicella-related complications was similar regardless of the timing of administration of a single dose of intramuscular VARIZIG.

Notes

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Potential conflicts of interest. M. J. L. has served as a consultant and/or scientific advisor for Merck, GlaxoSmithKline, and Saol Therapeutics, and has received research support from Merck and GlaxoSmithKline. J. M. D. has been a consultant and/or scientific advisor for Saol Therapeutics. A. A. G. has a service contract from Merck for laboratory studies of complications of live attenuated VZV vaccines.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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