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COMMENTARY

Commentary on the implications of safety and efficacy studies in pediatric patients with administration of human rabies immune globulin (HRIG)?

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ABSTRACT

The FDA strongly encourages rigorous safety and efficacy studies in all age groups for which vaccines and treatments for pervasive and severe diseases are intended. Until recently, there had been no safety and efficacy studies conducted in children for human rabies immune globulins. The publication," Safety, and efficacy of rabies immunoglobulin in pediatric patients with suspected exposure", Human Vaccines & Immunotherapeutics, 17:7, 2090–2096, was the first study that prospectively reviewed the use of KEDRAB® 150 IU/ml in 30 pediatric patients ages 0.5–14.9 years old. The results showed that 93.3% achieved RVNA titer >/ = 5 IU/ml, on day 14. Also, no participants reported a serious adverse event (SAE), or an adverse event (AE) leading to study discontinuation, and there were no deaths. The most common treatment emergent adverse events (TEAE) were injection-site pain. Currently there are 3 HRIG products on the US market, KEDRAB®, HyperRab® and Imogam® Rabies HT, but only KEDRAB® has published safety and efficacy data in a pediatric population. While it is common practice to prescribe medications for pediatric patients "off-label" there now exists one product with safety data in children. It is worth considering if this creates a higher medical liability for the prescriber and institution

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Introduction

"Having a safe and effective vaccine available for children in this age group is a priority for the agency and we're committed to a timely review of the data, which the agency asked Pfizer to submit in light of the recent Omicron surge," acting FDA Commissioner Janet Woodcock said in a statement. "Furthermore, children are not small adults. Because they're still growing and developing, it's critical that these vaccines are evaluated in well-designed and well-conducted clinical trials."[1]

As of 3 February 2022, the death toll from Coronavirus is **5,734,878**.[2] While this pandemic has been devastating and the rush to develop vaccines has been amazing, there would be no intention by the FDA to approve and/or distribute a vaccine to a pediatric population age 5–11 years old without proper safety and efficacy studies. The Pfizer-BioNTech pediatric vaccine was studied in three clinical trials in five different countries. Nearly 4,700 children aged 5–12 years old participated in these trials which included a placebo control. The results demonstrated that a reduced dose of 10 mcg was comparable to the 30 mcg dose for 16–25-year-old subjects. The safety data included predominately mild to moderate adverse effects with headache, fatigue, and fever most common. It is expected that other vaccine manufacturers will also have products for pediatric populations but will not be available for use even under an emergency use authorization (EUA) until their safety and efficacy studies are completed.[3]

Rabies is the oldest (2300 B.C.) and deadliest of all infectious diseases (59,000 deaths annually with a nearly 100% fatality rate),[4] yet surprisingly, until recently there have been no pediatric studies published on the safety and efficacy of human rabies immune globulin (HRIG) products. In the case of HRIG products in the USA, the registration trials have been in limited populations and of course with no placebo controls due to the nearly 100% fatal outcomes of clinical rabies. Therefore, the dosing (efficacy) has been the same for patients of all ages without regard to outcome and safety.

The Advisory Committee on Immunization Practices (ACIP) recommendation for dosing HRIG is 20 IU/kg independent of age[5] but this does not take into consideration that the size and number of bites in children are not smaller than they are in adults and the calculated volume of HRIG dictated by the dosing may not provide adequate volume for proper wound infiltration.[6]

The purpose of this review is to explore the implications of the first study on the safety and efficacy of HRIG in pediatric patients with suspected exposure to rabies.

Background

The goals of the Best Pharmaceuticals for Children Act (BPCA) and the Pediatric Research Equity Act (PREA) are to improve pediatric therapeutics through preclinical and clinical studies of drugs and biologics that are prescribed for children or that have the potential to benefit children. Ideally, such studies lead to the addition of useful information to the labeling of these products and then to the effective dissemination and application of that information to improve clinical care and child health.[7]

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In 2017, Kedrion Biopharma introduced KEDRAB® Human Rabies Immune Globulin (HRIG) to the US market for the prevention of rabies infections as a component of post-exposure prophylaxis (PEP). At that time there were two other HRIG products on the US market, Imogam® Rabies-HT and HyperRab® S/D. None of these products were indicated or had research studies for children and adolescents under the age of 17 years. Registrational trials for current HRIG products have, until recently, enrolled no pediatric subjects (HyperRAB® – 12 adults, KEDRAB® – 59 adults, Imogam-HT® – 32 adults)[8]

While all HRIG products are administered to patients under the age of 17 years, there are no published safety and efficacy studies to support such use.

According to the Centers for Disease Control and Prevention (CDC), an average of 59,000 patients are treated annually for rabies exposure and 40% of those treated are under the age of 15 years.[9] This means that roughly 22,000 children are treated for PEP annually in the USA without any safety data with the use of HRIG. Until recently deaths in the USA have been rare but in 2021, five deaths due to rabies were documented.[10]

The pediatric patient

There are several factors that make the pediatric patient unique compared to adults with regards to rabies exposure. Due to the shorter stature of the pediatric subject, the bite of the animal, especially from a dog, may be more likely to occur in the head or neck region which is highly innervated and requires precise neutralization with HRIG. The overall distance of these wounds to the CNS is considerably less than with hands or feet, and thus decreases the transit time for the virus to travel to the brain where damage may be irreversible.

Secondly, the average weight of a child under the age of 15 (45 kg)[11] is approximately half that of an average adult (90.8 kg).[11] Therefore, the standard dose of 20 IU/kg would only be approximately 900 IU or 6 ml for a child compared to 1500–1800 IU or 10–12 ml for an average male adult.

The bite size and number of bites of a rabid dog or fox may be the same for an adult or child and the need for complete neutralization of the wounds remains the same. The lower volume of HRIG (based on 20 IU/kg) can present a challenge if it is inadequate to treat all the wounds thoroughly. This issue is compounded if the HRIG product is double concentrated at 300 IU/ml, in which the total volume per dose for a child would only be 3 ml. If there were multiple or large wounds, the higher concentrated product may only be diluted back to the 150 IU/ml (one-half) concentration. In the case of HyperRab® the diluent must be 5% dextrose, and not 0.9% normal saline for compatibility purposes.[12] In the case of KEDRAB® the 150 IU/ml volume may be diluted 2–3 times with normal saline if necessary.[13] Imogam® Rabies-HT may also be diluted with normal saine if necessary.[13] The exact minimum effective concentration for neutralization of the rabies virus is unknown. Likewise, there is no evidence that a higher concentration than 150 IU/ml of HRIG is more efficacious than this original concentration.

Assuring proper POST EXPOSURE PROPYLAXIS (PEP)

While PEP may be 100% effective, improper PEP has been associated with clinical rabies and death. One aspect of PEP is assuring infiltration at the wound site(s) with sufficient HRIG to allow for passive immunization through viral neutralization.

The following steps are recommended to assure proper PEP with regards to HRIG administration:[14]

(1) After thorough cleansing of all the wounds and scratches with soap and water or a virucidal agent, observe the quantity, length, width, and depth of the wounds.
(2) The wound size and type may depend on the animal (e.g., bat, dog, cat, raccoon, fox, skunk). Check both sides of anatomical structure to be sure.
(3) Calculate the total dose of HRIG based on 20 IU/kg. (Note this dose is the same for adults and children, male or female.
(4) Estimate the volume necessary to properly infiltrate in and around all the wounds and exposure sites.
(5) The volume to be administered will depend on the concentration of the product 300 IU/ml or 150 IU/ml.
(6) When treating multiple wounds in small children, dilution of the 300 IU/ml product may be necessary before starting.[13]
(7) Draw the total dose into one syringe and move from wound to wound infiltrating each site while keeping track of total volume so as to not run out prior to thorough infiltration.

The following are frequently asked questions with HRIG administration:

(1) What happens if you run out of HRIG before all the wounds are treated?
   a. You cannot give additional HRIG beyond the total dose of 20 IU/kg as that may cause an inadequate vaccine (active) immunization response.
   b. By not infiltrating all of the wounds, you risk allowing the virus to replicate in the surrounding muscle tissue, and then travel through the neuronal junction to the CNS where it may cause clinical rabies and potentially a fatal outcome.
(2) What do I do with any excess HRIG if all the wounds are infiltrated but I still have remaining volume in the syringe?
   a. After thorough wound infiltration and there is remaining volume, the remainder is administered intramuscularly at anatomical sites distal from the vaccine injection. This facilitates indirect neutralization and passive immunity through the circulatory system.
   b. Never administer the HRIG and the vaccine from the same syringe.
(3) What do you do if you suspect rabies exposure but cannot identify any wounds?
   a. With bat exposures sometimes you cannot identify the puncture wounds, or the suspicion is not confirmed.

b. In this case 100% of the total dose 20 IU/kg will be administered intramuscular at sites distal from the vaccine administration site.

Safety and efficacy in the pediatric population

It is not unusual for licensed independent practitioners (LIP) to prescribe medications outside their indications or in the case of pediatrics, outside the age range studied. In the case of HRIG, the product Imogam® Rabies-HT has been on the US market since 2015 with an indication for "individuals suspected of exposure to rabies". There is no age range specified and there are no studies in the pediatric population.

HyperRab S/D® (original formulation 1974) recently was replaced on the US market in 2019 by HyperRab®. HyperRab® is doubly concentrated at 300 IU/ml, and it is manufactured differently than other HRIG products. HyperRab® includes caprylate as an antiviral for lipid-coated viruses instead of a solvent detergent. This is a newer product that is indicated for PEP for "all persons suspected of exposure to rabies," but safety and efficacy in pediatric patients has not been established."

KEDRAB® (Kedrion Biopharma), introduced on the US Market in 2017, is indicated for PEP in "persons of all ages". Safety and efficacy in children have now been established in children from 0.5–14.9 years of age with a 30-patient study (004) in which 28/30 patients achieved a rabies virus neutralizing antibody (RVNA) titer >/ = 5 IU/ml, the WHO recommended efficacy level, on day 14.

Safety and tolerability were assessed by monitoring local and systemic adverse events (AEs) and physical examination findings for the 14 days following 150 IU/ml HRIG administration. Monitoring for serious adverse events (SAEs) continued throughout the entire study. On day 14, blood samples were collected from participants for assessment of RVNA levels by rapid fluorescent focus inhibition testing. Thirty patients followed through to day 14 and were included in the analysis, but two were lost to follow-up on day 28. Fourteen participants (46.7%) were female, and 16 (53.3%) were male.

Safety

Throughout the study, no participants reported experiencing a SAE, or an AE leading to study discontinuation, and there were no deaths. The most common treatment emergent adverse events (TEAE) were injection-site pain (nine events).

Efficacy

Among the 30 suspected exposures to rabies, three (10.0%) were from animals that were subsequently confirmed rabid; the others were associated with uncaptured/untested or confirmed negative animals.

On day 14, 28 patients (93.3%) had RVNA titers ≥.5 IU/mL (mean ± SD of all participants: 18.89 ± 31.61; range: 0.21–153.62.

Two participants had RVNA titers <.5 IU/mL (0.4 IU/mL and 0.21 IU/mL). One of these participants was an 11-year-old girl whose RVNA titer was 0.4 IU/mL on day 14. The other was a 4-year-old boy with an RVNA titer of 0.21 IU/mL on day 14 who received PEP in response to possible rabies exposure from an animal subsequently confirmed positive for rabies. In this study, blood draw for RVNA titer was performed at day 14 and not repeated subsequently; thus, it remains possible that the two subjects that did not attain the cutoff by day 14 seroconverted by day 30.

Results of this study confirm the safety profile and efficacy of KEDRAB® in preventing rabies in pediatric patients when used as part of a PEP regimen. KEDRAB® was well tolerated with all AEs being mild in severity, and that included no SAEs. Therefore, the study authors concluded that KEDRAB® is appropriate for use as a lifesaving component of PEP in pediatric patients.

Safety and efficacy study implications

In a study published in 2004 by G.W. 't Jong et al in the Netherlands[14] it was noted that their results showed a high use of unlicensed and off-label use of respiratory drugs in children, while these are among the most used drugs in children. The current shortage of formulations and dosage forms appropriate for infants and toddlers, especially, must be resolved, and research on new and older drugs should include safety and efficacy studies in all appropriate pediatric age groups. The authors recommended that post-marketing surveillance of pediatric drug use should be intensified to increase the knowledge of safety and efficacy in a patient group, for which drug testing is restricted by ethical and practical boundaries.

The United States Food and Drug Administration (FDA) does not regulate the practice of medicine. In general, once the FDA approves a drug, licensed physicians may prescribe it for any purpose they consider medically appropriate.

Off-label prescribing occurs when a licensed independent practitioner (LIP) prescribes a drug that the FDA has approved to treat a different condition from which it was prescribed. This practice is legal and common. In fact, one in five prescriptions today are prescribed for off-label use.[15]

Lack of information with off-label drug use and outcomes may also put patients at a higher risk for medication errors, side effects, and unwanted drug reactions. It is important that the patient and LIP discuss the possible risks of using the drug and weigh them against the possible benefits.

There is debate about off-label drug use. Physicians emphasize that off-label prescribing has its place in medical practice, but they also admit that using a drug off-label may raise the risk of lawsuits should a patient have unwanted or bad side effects.

One implication of concern is that if there were an adverse reaction or medication event with a product not studied in the pediatric population while an alternative product with safety and efficacy data was available but not used, would that strengthen the case for litigation?

Another issue to consider with off-label drug use is reimbursement. Getting insurance plans to pay (reimburse) for off-label drug use may be a challenge. Many insurance companies **will not pay** for an expensive drug used in a way not listed in the approved drug label. They decline coverage on the grounds that its use is "experimental" or "investigational.[16]

In 2008, Medicare rules were changed such that more off-label uses of cancer treatment drugs would be covered.

In *U.S. v Caronia*, decided on 3 December 2012, a federal Court of Appeals panel in a 2–1 decision ruled that the promotion of prescription drugs by manufacturer's agents for off-label purposes is protected "free speech" under the First Amendment to the U.S. Constitution.[1] The FDA's prohibition against such practices was ruled unconstitutional. This decision, if it remains unchanged by any further appeals may have dramatic implications for the marketing of prescription pharmaceuticals.[17-19]

While pharmaceutical companies in the USA are strictly monitored for making false claims or minimizing adverse reactions as well as promotions outside the FDA indications, there appears to be a gray zone in the world of pediatrics. Most new medications come to market having primarily been studied in adult populations, with minimal studies in limited populations. The practitioner is left to their own risk and judgment to use these products in children without the benefit of safety and efficacy data. New formulations may become available with minimal study data and no regard for special populations.

While the prevention of rabies through PEP may be highly effective there still is no treatment for clinical rabies, with essentially a 100% fatality rate. There is no room for error in prevention protocols and understanding the safety and efficacy of special populations at highest risk is essential.

Conclusions

(1) Clinical trials to study the safety and efficacy of life-saving medications in pediatric populations is essential
(2) In February of 2021 Kedrion Biopharma published the results of their 30-subject pediatric study that established the safety and efficacy of KEDRAB® for PEP in rabies risk exposures
(3) The data from this study are valuable to establish both safety and efficacy for KEDRAB® in the populations studied from 0.5 -14.9 years of age in males and females.
(4) Even though it is customary practice to use medicines "off-label" when there are no established indications or studies available, the risks and liabilities are potentially greater to prescribers and institutions when using alternative products to those with established safety and efficacy data.
(5) While the practice of prescribing "off-label" products is not considered illegal and the promotion of such products has been considered free speech, the BPCA and PREA both encourage safety and efficacy studies.
(6) Both the Joint Commission (TJC) and the Centers for Medicare and Medicaid Services (CMS) encourage the use of products that are FDA indicated or have published literature supporting their safety and efficacy.
(7) The critical nature of HRIG administration must be considered since rabies is nearly 100% fatal once it becomes symptomatic but is nearly 100% preventable with appropriately administered post-exposure prophylaxis.

Disclosure statement

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References

1. https://www.businessinsider.in/science/news/pfizer-biontech-ask-fda-to-authorize-two-dose-covid-19-vaccine-for-children-under-5/articleshow/89286495.cms.
2. https://www.worldometers.info/coronavirus/coronavirus-death-toll/.
3. https://www.nejm.org/doi/full/10.1056/nejmoa2116298.
4. https://en.wikipedia.org/wiki/Rabies.
5. Manning SE, Rupprecht CE, Fishbein D, Hanlon CA, Lumlertdacha B, Guerra M, Meltzer MI, Dhankhar P, Vaidya SA, Jenkins SR, et al. Human rabies prevention--United States, 2008: recommendations of the advisory committee on immunization practices. MMWR Recomm Rep. 2008;57(RR–3):1–28.
6. Wilde H. Failures of post-exposure rabies prophylaxis. Vaccine. 2007;25(44):7605–09. doi:10.1016/j.vaccine.2007.08.054.
7. https://www.fda.gov/drugs/development-resources/pediatric-research-equity-act-prea.
8. Hobart-Porter N, Stein M, Toh N, Amega N, Nguyen H-B, Linakis J. Safety and efficacy of rabies immunoglobulin in pediatric patients with suspected exposure. Hum Vaccines Immunother. 2021;17(71):2090–96. doi:10.1080/21645515.2020.1854000.
9. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6613553/.
10. https://www.everydayhealth.com/rabies/people-died-of-rabies-in-the-us-the-most-in-a-decade/.
11. https://www.cdc.gov/nchs/fastats/body-measurements.htm.
12. https://www.hyperrab.com/documents/2533658/2533707/Prescribing+Information+HyperRAB+300.pdf/813095ad-a0b7-48fd-b3a8-c531d418e148?t=1617208717698.
13. Siegel J. Rabies immune globulin: ensuring administration safety. Pharm Pract News Spec Ed. Sept.12,2019:47–52.
14. Jong GT, Eland IA, Sturkenboom M, van den Anker J, Stricker B. Unlicensed and off-label prescription of respiratory drugs to children. Eur Respir J. 2004 ;23(2):310–13. doi:10.1183/09031936.04.00015404.
15. https://www.ahrq.gov/patients-consumers/patient-involvement/off-label-drug-usage.html#:~:text=Off%2Dlabel%20prescribing%20is%20when,are%20for%20off%2Dlabel%20use.
16. https://www.cancer.org/treatment/treatments-and-side-effects/treatment-types/off-label-drug-use.html.
17. US Pharm. 2013;38(1):40–42. https://www.uspharmacist.com/article/off-label-promotion-is-free-speech.
18. kedrab.com/KEDRAB-prescribing-information.pdf.
19. Sanofi Pasteur SA Rabies Immune Globulin (Human) USP heat treated Imogam rabies HT (package insert) Marcy L'Etoile 2018 Google Scholar, https://www.fffenterprises.com/assets/downloads/product-information/sanofi-pasteur/pi-IMOGAM-RABIES-HT.pdf.