Scientific Basis for Approval of Human Rabies Immune Globulin in Combination with Rabies Vaccine

FDA Workshop: Developing Rabies Monoclonal Antibody Products as a Component of Rabies Post-Exposure Prophylaxis

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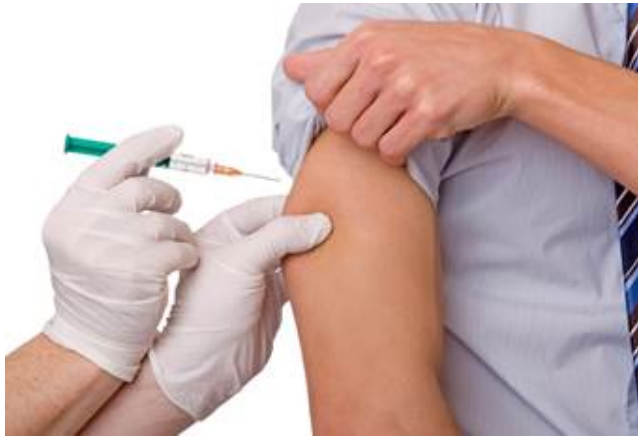
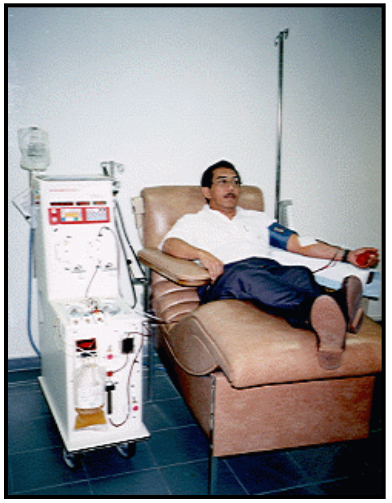
“My comments are an informal communication and represent my own best judgment. These comments do not bind or obligate FDA.”

Human Rabies Immune Globulin (HRIG)

- First US license on June 12, 1974
- Manufactured from Source Plasma, collected at US licensed plasma centers
- Donors are hyperimmunized with US-licensed rabies vaccine
- Plasma is pooled and purified by fractionation to Immune Globulin [i.m.]
- Licensed for use in combination with rabies vaccine, for post-exposure prophylaxis

HRIG Manufacturing



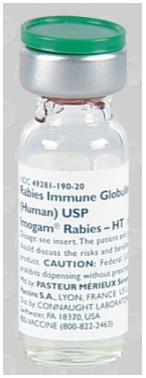


Plasma donation

Donor vaccination

Plasma

Fractionation (Cohn 6/Oncley 9)



Hyperab
1974

CUTTER FACSIMILE9 DON'T USE

14-7608-021
(Rev. June 1974)

RABIES IMMUNE GLOBULIN (HUMAN) Hyperab™

DESCRIPTION

Rabies Immune Globulin (Human)–Hyperab™ is a sterile solution of antirabies gamma globulin (IgG) concentrated by cold alcohol fractionation from plasma of donors hyperimmunized with rabies vaccine. Hyperab™ globulin is a 16.5% ± 1.5 solution of gamma globulin from venous blood in 0.3M glycine, preserved with 1:10,000 Thimerosal (a mercury derivative). Its pH is adjusted with sodium carbonate. The product is standardized against USA Standard Antirabies Serum. The USA unit of potency is equivalent to the International Unit (IU) for rabies antibody.

ACTION

The usefulness of preformed rabies antibody in preventing rabies in man when administered immediately after exposure was dramatically demonstrated in a group of persons bitten by a rabid wolf in Iran[1,2]. Similarly beneficial results were later reported from the USSR[3]. Studies coordinated by WHO helped determine the optimal conditions under which antirabies serum of equine origin and rabies vaccine can be used in man[4,5,6,7]. These studies showed that serum can interfere to a variable extent with the active immunity induced by the vaccine, but that this interference could be minimized by booster doses of vaccine 10 and 20 days after the end of the usual 14- or 21-dose series.

The utility in man of antirabies serum of equine origin has not, however, been realized without penalty: an overall rate of 16.3% was reported for serum sickness following antirabies serum, and this rate steadily rose with increasing age, being especially marked in the group over age 15[8]. Only a preparation of human origin would prevent this side effect, while preserving the benefit of preformed rabies antibody in severely exposed patients.

Attempts to prepare rabies immune serum or globulin of human origin were made by others [9,10,11]. Their preparations were subpotent, however, but they served to demonstrate the feasibility of the approach.

More recently, the preparation of lots of rabies immune globulin (human) of adequate potency was reported by Cabasso et al.[12]. In carefully controlled clinical studies, this globulin was used in conjunction with rabies vaccine of duck-embryo origin (Lilly Laboratories, Indianapolis, Indiana) [Cabasso et al. [12]; Loofbourow et al.[13]]. These studies determined that a human globulin dose of 20 International Units/kilo (IU/kilo) of rabies antibody given simultaneously with the first vaccine dose resulted in amply detectable levels of passive rabies antibody 24 hours after injection in all subjects receiving it, and produced minimal, if any, interference with the response to 14 daily doses of the vaccine followed by 2 booster

Vaccine +/- Rabbit RIG for Rabies Prevention

- Subjects – Victims of rabid wolf attack in Iran, August 1954
- Treatments in head wound subjects
  - Vaccine – phenolized rabies-infected sheep brain
  - Rabbit anti-rabies serum (Lederle); 0.65 mL/kg i.m.
- Mortality in subjects with head/neck wounds
  - Vaccine only, 3/5 (60%)
  - Vaccine + Rabbit anti-rabies serum (1-6 doses), 1/13 (7.7%)

Baltazard et al. Practical test of antirabies serum in bites by rabid wolves. Bull WHO 1955; 13:747-72.

Early serum anti-Rabies antibody levels in Iranian Study Subjects

Habel K and Koprowski H. Laboratory data supporting the clinical trial of antirabies Serum in persons bitten by a rabid wolf. Bull WHO 1955; 13: 773-79.

TABLE II. NEUTRALIZING ANTIBODY LEVELS IN SERA OF PATIENTS EXPOSED TO HEAD AND NECK BITES OF RABID WOLF—SERIES A, TREATED WITH TWO DOSES OF SERUM AND COMPLETE COURSE OF VACCINE

Patient No.	Out-come	Antibody titres on days after start of treatment *																
		0	1	3	4	5	6	7	8	10	13	15	19	21	25	29	33	41	53
A1	S	0	8	+		22		+		22		22		22		5		+	12
A2	S	0	13	+		32		+		22		22		12		6		+	3
A3	S	0	tr			13		+		66		30		76		191		+	76
A4	S	0	tr	+			32	+		22		22		12		6			tr
A5	S	0	6	+		112		+		10		17		22		22		+	8
27 **	S	0			19		38		99	112	99	+	30		32		22		

TABLE III. NEUTRALIZING ANTIBODY LEVELS IN SERA OF PATIENTS EXPOSED TO HEAD AND NECK BITES OF RABID WOLF—SERIES B, TREATED WITH ONE DOSE OF SERUM AND COMPLETE COURSE OF VACCINE

Patient No.	Out-come	Antibody titres on days after start of treatment *													
		0	1	3	5	7	10	12	15	17	19	21	29	41	53
B1	S	0	6	+	22	+	6		tr			8	tr	tr	13
B2	D	0	tr	+	20	+	tr	tr	tr	tr	tr				-
B3	S	0	6	+	10	+	6		5			5	13	6	
B4	S	0	tr	+	8	+	13		18			6	8	+	13
B5	S	0	0	+	15		13		tr			5	tr		
B6	S	0	tr	tr	6	tr	8		8			30	67		112

TABLE IV. NEUTRALIZING ANTIBODY LEVELS IN SERA OF PATIENTS EXPOSED TO HEAD AND NECK BITES OF RABID WOLF—SERIES C, TREATED WITH COMPLETE COURSE OF VACCINE ONLY

Patient No.	Out-come	Antibody titres on days after start of treatment *													
		0	1	3	5	7	10	15	19	21	25	29	33	41	45	53
C1	D	0	0	0	0	0	0	0	22	50	85	66				
C2	S	0	0	0	0	0	0	0	tr	5	13	6		19		5
C3	D	0	0	0	0	0	0	0		0	0					
C4	D	0	0	0	0	0	0	0	tr		18	27	22	15	89	18
C5	S	0	0	0	0	0	0	0				0		0		0

S = Survived D = Died of rabies

* The figures shown are the reciprocals of the serum dilutions, representing the 50% end-point in the neutralization test against 8-46 LD_{50} of virus.

** Patient 27 received six injections of serum and a complete course of vaccine

\+ = Virus neutralized by undiluted serum; no titration of antibodies done

tr = Partial neutralization of virus at a dilution of less than 1:5 of serum

Rabies Immunoglobulin WHO Standard Provenance (mouse neutralization titers)

- International Standard for Anti-rabies serum, 1955[1]
  - Equine serum
  - 86.6 IU/ampule
- First International Standard for Rabies Immunoglobulin, 1984[2]
  - HRIG, purchased by FDA as a standard preparation, filled by WHO
  - Collaborative study – calibrated against Anti-rabies serum WHO standard
  - 59.0 IU/ampule
- Second International Standard for Rabies Immunoglobulin
  - HRIG product, donated to WHO by Behringwerke AG
  - Collaborative study – calibrated against 1st Rabies Immunoglobulin standard
  - 30 IU/ampule[3]

[1] WHO Expert Committee on Biological Standardization. Eighth Report. WHO Tech Rep Ser 1956; 108:11.

[2] Fitzgerald et al. A collaborative study to establish an international standard for Rabies immunoglobulin of human origin. J Biol Stand 1985; 13: 327-333.

[3] Lyng, J. Calibration of a replacement preparation for the International Standard for Rabies immunoglobulin. Biologicals 1994; 22: 249-55.

Clinical studies in healthy volunteers of Cutter Hyperab in support of licensure (Cutter Hyperab)

- University of California, Davis (Cabasso et al)
  - HRIG + Duck embryo vaccine (DEV)
    - HRIG 10, 20, or 40 IU/kg i.m.
    - Vaccine daily x 14 doses, boost on d23, d33
  - HRIG only - 40 IU/kg i.m.
  - DEV only (as with HRIG)
- CDC (Hattwick et al)
  - HRIG + DEV
    - DEV (1 mL) daily x 14 doses, boost (1 mL) d23 or 24, d33 or 34 ("14 + 2")
    - DEV (2 mL) daily x 7 doses, then 1 mL daily x 7 doses, boost d23 or 24 and d33 or 34 (21 + 2")
  - HRIG only - 40 IU/kg i.m.
  - DEV only, both regimens (as with HRIG)

Optimal HRIG dose permits early rise in titers, minimal vaccine inhibition

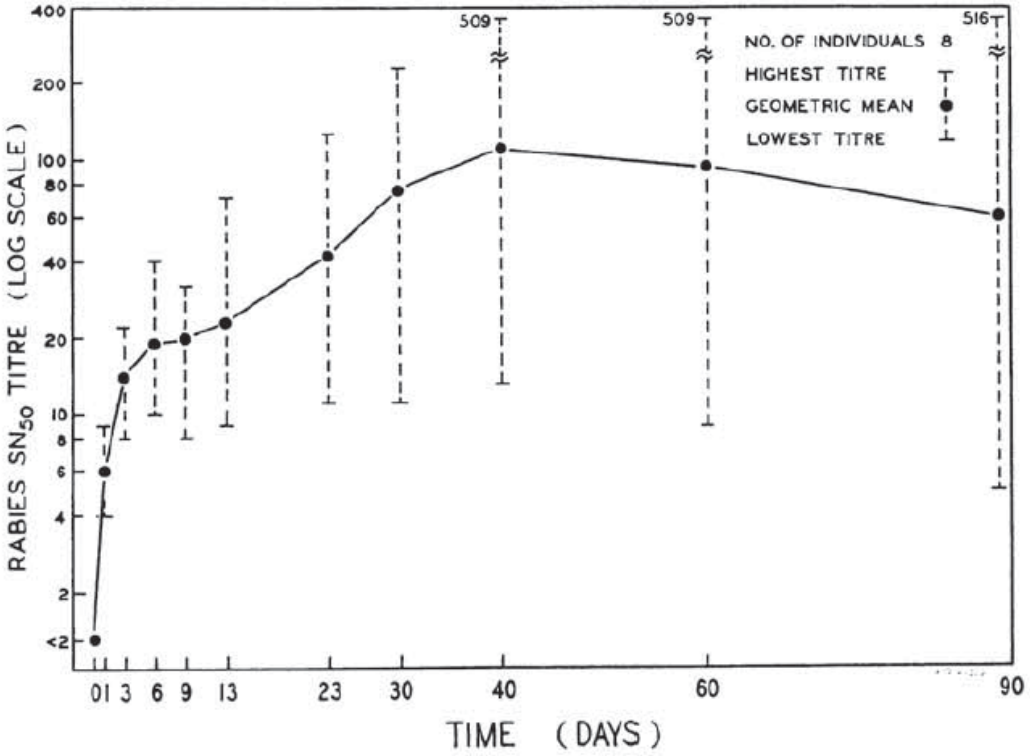


Fig. 4. Serum-neutralizing antibody response (SN_{50}) in group D subjects after the administration of rabies immune globulin (human) (RIGH) and a course of rabies vaccine of duck-embryo origin (DEV); the dosage of RIGH was 20 IU/kg.

Cabasso et al. Rabies Immune Globulin of Human Origin: Preparation and dosage Determination in non-exposed volunteer subjects. Bull WHO 1971, 45:303-5.

NIH/Division of Biologics Standards Review of March 16, 1972

"Controlled clinical studies reported in support of this license application have demonstrated that when used as recommended at the rate of 20 units per kilogram of body weight in man and in conjunction with the Eli Lilly duck embryo rabies vaccine given as recommended, a rapid rise in neutralizing antibody results without interfering with later antibody inducement by the vaccine No known prevention of rabies exists with the exception of circulating neutralizing antibody. Because there is no known treatment for rabies once symptoms develop, controlled clinical studies of efficacy cannot be done in man. Therefore neutralizing antibody produced in recipients of this product without interference with antibody production by vaccine is accepted as ample evidence of efficacy."

Considerations

- Clinical trial of heterologous RIG in rabies outbreak in Iran, and case series with HRIG in USSR
  - Small studies
  - Varying serum/IG doses within studies
  - Results favor passive immune therapy particularly for level III exposures (wounds to head/neck)
  - Pharmacokinetic data in humans suggest that early anti-rabies antibody titers favor survival
- Animal studies support passive immune therapy
- Equine RIG (ERIG) associated with serum sickness
- "Rigidly controlled field trials in man are not possible" (Federal Register 1980, Vol. 45 No. 74, p. 24570)
- Benefit/risk of treatment with HRIG

Subsequent HRIG Licensure

- Imogam-HT licensed 4/27/1984
- Licensure based on literature supporting concept of passive immune therapy

+

PK study

Imogam 20 IU/kg + Rabies Vaccine (Imovax)

Rabies vaccine only

Imogam only

HRIG (Imogam) Clinical Study Results

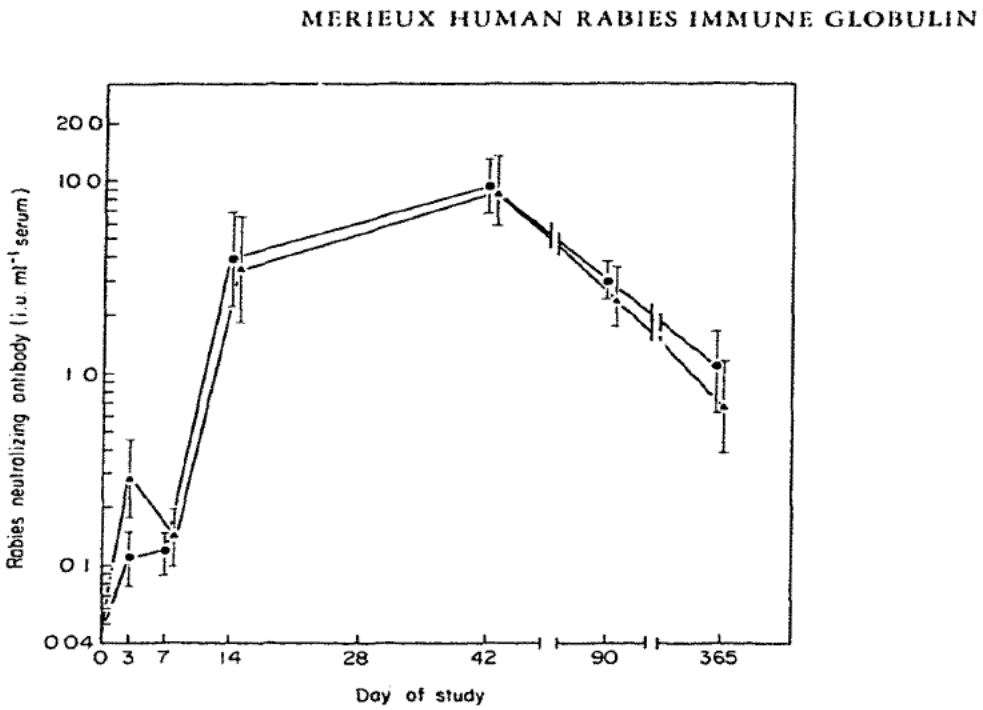


Fig. 2. Rabies antibody titres following administration of biologicals in group C and E. Coded as: ●, Group C, 20 i.u. kg^{-1} M-HRIG and 1 dose of M-HDCV on days 0, 3, 7, 14, 28; ▲, Group E, 44 i.u. kg^{-1} M-HRIG and 1 dose of M-HDCV on days 0, 3, 7, 14, 28. Vertical bars indicate GMTs with 95% confidence limits.

Helmick et al. A clinical study of Merieux human rabies immune globulin. J Biol Stand 1982; 10: 357-67

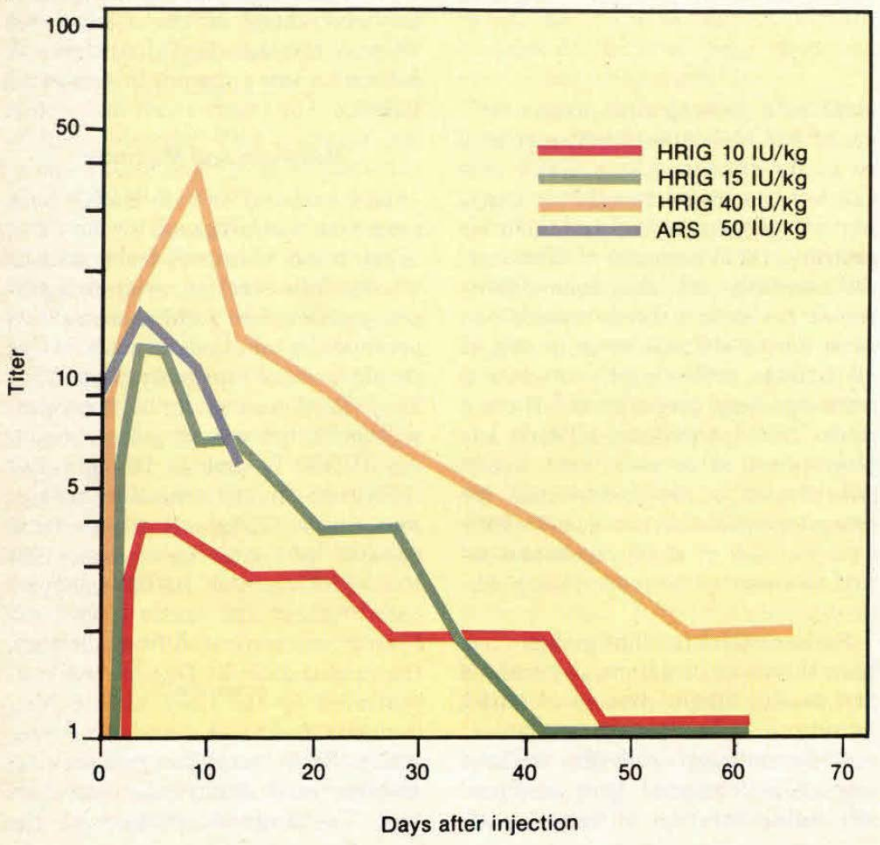
Observations

- Clinical field studies are relatively limited, but experience with licensed HRIGs suggests failures are very rare
- HRIG products given at 20 IU/kg do not yield “protective” titers (0.5 IU/mL for vaccines)
  - Serum measurements may not reflect tissue levels achieved with recommended infiltration of wounds with HRIG
  - Vaccine antibody response may be a correlate of cellular immune responses
- HRIG delays (but does not prevent) rabies in animal studies suggesting slowing but not elimination of rabies entry into the nervous system
  - Most animal models have short incubation compared to humans
- Onset of antibody action (earlier) and duration (half life) are likely to be important considerations for monoclonal antibody effectiveness

Thank You!

HRIG vs. ERIG

Rabies serum neutralizing antibody titers after injection of 10-, 15-, or 40-IU/kg doses of human rabies immune globulin (HRIG) or 50 IU/kg of equine antirabies serum (ARS), (from Atanasiu et al[12]). Titers indicated as numeral 1 equal titers of less than 2.



408 JAMA, Jan 28, 1974 • Vol 227, No 4

Antiserum Dose in Iranian Clinical Trial of Rabbit anti-rabies serum + vaccine

Test Serum LD50 1:1060

International

Standard LD50 1:952

Habel K and Koprowski H. Laboratory data supporting the clinical trial of antirabies Serum in persons bitten by a rabid wolf. Bull WHO 1955; 13: 773-79.