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

Donor vaccination → Fractionation (Cohn 6/Oncley 9) → Plasma donation
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 Iran1-2. Similarly beneficial results were later reported from the USSR3. Studies coordinated by WHO helped determine the optimal conditions under which antirabies serum of equine origin and rabies vaccine can be used in man4,5,6,7. 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 158. 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 others9,10,11. 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%)

Early serum anti-Rabies antibody levels in Iranian Study Subjects

Habel K and Koprowski H.
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 1\(^{st}\) Rabies Immunoglobulin standard
  – 30 IU/ampule\(^3\)

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

![Graph showing serum-neutralizing antibody response (SN₅₀) 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.]

“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
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.

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 Atanasii et al\textsuperscript{12}). Titers indicated as numeral 1 equal titers of less than 2.
Antiserum Dose in Iranian Clinical Trial of Rabbit anti-rabies serum + vaccine

Test Serum LD50 1:1060

International
Standard LD50 1:952