Equine rabies immunoglobulin

Section: 19. Immunologicals > 19.2. Immunologicals > Sera, immunoglobulins and monoclonal antibodies

EMLc | ATC codes: J06BB05

Indication	Rabies ICD11 code: 1C82
Medicine type	Biological agent
List type	Core
Formulations	**Parenteral > Locoregional injections > Intradermal:** 150 IU per mL in vial ; 200 IU per mL in vial ; 300 IU per mL in vial ; 400 IU per mL in vial
EML status history	First added in 2021 (TRS 1035)
Sex	All
Age	Also recommended for children
Therapeutic alternatives	The recommendation is for this specific medicine
Patent information	Patents have expired in most jurisdictions Read more about patents.
Tags	Biological
Wikipedia	Equine rabies immunoglobulin

Expert Committee recommendation

The Expert Committee acknowledged the public health need for effective interventions for rabies postexposure prophylaxis, noting that the case fatality of rabies infection is almost 100% after the onset of clinical symptoms and that access to rabies postexposure prophylaxis is still inadequate in many settings where rabies is endemic. The Expert Committee noted that efficacy of eRIG is similar to hRIG and that adverse events are minimal with available purified eRIG preparations. The Expert Committee also noted that eRIG is recommended in WHO's 2018 rabies vaccine position paper approved by the Strategic Group of Experts on Immunization and that the price of eRIG is considerably lower than for hRIG. Therefore, the Expert Committee recommended that purified eRIG be included on the core list of the EML and EMLc for use as part of rabies postexposure prophylaxis, in line with WHO recommendations and based on a favourable benefit-to-harm ratio. The Committee considered that eRIG will provide a valuable alternative option to hRIG, at a lower cost, and increase procurement options.

Background

The 2019 Model Lists include only human rabies immunoglobulin (Section 11.2.1 Human immunoglobulins). Rabies immunoglobulin (without specification of human or equine) has been included on the Model Lists since 1992. In 2013, the listing was changed to specify human rabies immunoglobulin, thereby excluding eRIG.

Public health relevance

Rabies is a preventable viral zoonotic disease and a neglected tropical disease. It is responsible for an estimated 59 000 human deaths annually, mostly in countries in Africa and Asia (1). Most human rabies cases result from dog bites. After the onset of clinical symptoms, the disease is almost always fatal. Survival from clinical rabies has been documented in only 15 cases, mostly with severe sequelae (2). While rabies control depends heavily on

prevention of canine rabies by mass vaccination, postexposure prophylaxis of humans who have been bitten by an animal is a highly effective preventive intervention. After a bite exposure, postexposure prophylaxis involves the combined use of extensive wound washing, infiltration of rabies immunoglobulin and administration of modern tissue culture vaccines (3). The role of RIG in passive immunization is to provide neutralizing antibodies at the site of exposure before patients start producing vaccine-induced antibodies.

Benefits

Purified eRIG is highly effective, as evident after decades of clinical use (4). A 2013 study compared the neutralization effectiveness of reduced eRIG and hRIG in cell culture and in mice: in vitro, neutralization of rabies virus by eRIG and hRIG were identical, while in vivo, full protection was conferred by both eRIG and hRIG (5). Moreover, no vaccine was administered to those animals that received RIG, yet the experimental groups that received at least 0.025 IU/100 microlitres of either eRIG or hRIG showed 100% survival, compared with 100% mortality in the control group. Today, modern eRIG is highly purified and enzyme-refined and contains over 85% antigen-binding immunoglobulin fragments – F(ab′)2 (6–8). Although these F(ab′)2 fragments may have a shorter half-life in vivo than intact immunoglobulin, these fragments have a higher specificity and instances of antigen-binding reactions, and therefore efficacy is preserved (8). The relative efficacy of eRIG is strongly supported, especially considering the price and scarcity of hRIG and the nearly 100% case-fatality of clinical rabies.

Harms

Long-standing biomedical data support the relative safety of eRIG in human rabies postexposure prophylaxis (9). In the past, crude horse serum and unpurified eRIG were associated with serum sickness, anaphylaxis and other severe adverse reactions (5). Through techniques such as heat treatment, pepsin digestion and enzyme refinement, the immunoglobulin crystallizable fragment (Fc) is removed and the nonspecific protein content of the purified serum is reduced to less than 3% (10). As the Fc fragment in unpurified eRIG is responsible for direct complement activation and anaphylactic reactions, the high F(ab′)2 content and low Fc proteins allow for increased safety and specific activity (5,8). This eRIG treatment has been shown to be safe for pregnant women, as the F(ab′)2 immunoglobulin fragments do not cross the placenta (11). Studies to date suggest that severe adverse reactions with eRIG, such as serum sickness and anaphylaxis, are infrequent (12). Other adverse events tend to be mild, not life-threatening and easily resolved, such as local pain, redness, induration, fever and pruritus (8,10–16). Clinical studies show that the incidence of anaphylaxis with eRIG is similar to that associated with the use of penicillin (17).

Cost / cost effectiveness

In general, all RIGs are relatively expensive and not readily available. The cost per dose of eRIG is reported to range between US$ 25 and US$ 50, while the cost per dose of hRIG is between US$ 100 and US$ 250 (20). For example, in Cambodia, eRIG costs between US$ 20 and US$ 30 per dose. In comparison, a Cambodian farmer’s monthly salary is between US$ 60 and US$ 80 (21). Thus, a dose of RIG can consume up to half a month’s salary. The high cost of RIG compared with income also exists throughout Africa and Asia (5,21,22). This difference is even wider for hRIG, and thus it is impractical for use in areas with limited financial resources (23). Based on available data and experience of use for postexposure prophylaxis, eRIG is considered to be a safe and effective alternative in the many areas where hRIG is unavailable or unaffordable (24,25).

WHO guidelines

WHO recommendations on the use of RIG in postexposure prophylaxis are given in the rabies vaccine position paper and were last updated in 2018 (3). Changes were based on functional use, mainly in that the dose of RIG is now determined taking account of the anatomical feasibility of administration in and around the affected area instead of on the patient’s total body weight. WHO recommends the use of RIG as part of postexposure prophylaxis in immunologically naive individuals with category III rabies virus exposure, defined as single or multiple transdermal bites or scratches, contamination of mucous membrane or broken skin with saliva from

animal licks, exposures due to direct contact with bats (severe exposure). RIG is not indicated for previously immunized individuals. RIG should be administered only once, preferably at, or as soon as possible after, the start of postexposure prophylaxis. RIG should not be given after day 7 following the first rabies vaccine dose, because circulating antibodies will have begun to appear. In almost all cases, the amount of RIG administered is based on the location and extent of the lesions, where the rabies virus is localized after exposure. For small wounds, the maximum quantity of RIG that is anatomically feasible should be administered. Only the maximum dose of RIG is still assessed by body weight (e.g. 20 IU/kg for hRIG and 40 IU/kg for eRIG). Skin testing before eRIG administration should not be done because it is unreliable in predicting adverse effects. However, the treating physicians should be prepared to manage anaphylaxis, which, although rare, could occur during any stage of RIG administration. Since the introduction of the current recommendations, the amount of RIG to administer is estimated to be on average 40% of the quantity that was previously required based on body weight alone (16,18,19). Hence, these recommendations are expected to have a net positive effect on the cost of human rabies prophylaxis for patients and governments.

Availability

Currently, eRIG has regulatory approval mostly in less developed countries in Africa, Asia and Central and South America, and in other countries including Brazil, China, India and Thailand. Availability is irregular, and depends in part on equine stocks, local animal welfare concerns and production limitations.

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