Anti-rabies virus monoclonal antibodies

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

EMLc | ATC codes: Pending

Indication	Rabies ICD11 code: 1C82
Medicine type	Biological agent
List type	Core
Additional notes	Including quality-assured biosimilars
Formulations	**Parenteral > Locoregional injections > Intradermal:** 40 IU per mL in 1.25 mL vial (human) ; 40 IU per mL in 2.5 mL vial (human) ; 100 IU per mL in 2.5 mL vial (human) ; 300 IU per mL in 10 mL vial (murine) ; 600 IU per mL in 1 mL vial (murine) ; 600 IU per mL in 2.5 mL vial (murine) ; 600 IU per mL in 5 mL vial (murine)
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	Read more about patents.
Tags	Biological
Wikipedia	Anti-rabies virus monoclonal antibodies

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. The Committee considered that the availability of a range of alternative options for use in rabies postexposure prophylaxis (human RIG, equine RIG and ARV mAbs) on the EML and EMLc would facilitate access to treatment. The inclusion of ARV mAbs will potentially address some of the supply and production limitations currently experienced with hRIG and eRIG by increasing procurement options. It was also noted that ARV mAbs could be procured at lower cost than human RIG (but higher cost than equine RIG). The Committee noted that the clinical evidence supporting the use of ARV mAbs is from trials assessing rabies virus neutralizing activity, using an in vitro correlate of protection that has been accepted by WHO and regulatory agencies as a study endpoint in clinical trials of novel rabies vaccines or RIG products. The Committee also noted that there was no indication of an increase in mortality from postmarketing surveillance. The Committee acknowledged that evidence on efficacy and safety for use in children, the elderly or pregnant women was lacking, but was reassured by the technical unit that children were included in the trial populations, however the data had not yet been stratified. Moreover, the Strategic Advisory Group of Experts (SAGE) on Immunization recommended postmarketing surveillance of these products due to their potential adverse effects. The Committee noted that the 2018 WHO position paper on rabies encourages the use of ARV mAbs as an alternative to RIG and that having access to RIG and ARV mAbs may ensure adequate supply at the global level. The Committee also noted that WHO prequalification processes for monoclonal antibodies for infectious diseases are planned in 2022, to facilitate access to affordable and quality-assured products. Therefore, the Expert Committee recommended the inclusion of ARV mAbs (murine and human

formulations), including quality-assured biosimilars, on the core list of the EML and EMLc for use as part of rabies postexposure prophylaxis, in line with WHO recommendations.

Background

ARV mAbs have not previously been considered by the Expert Committee for inclusion on the Model Lists.

Public health relevance

Rabies is a preventable viral zoonotic disease and is 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, with severe sequelae in most (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 (RIG) and administration of modern tissue culture vaccines (3). Globally, an estimated 29.2 million people receive postexposure prophylaxis for rabies annually (1). Current WHO postexposure prophylaxis recommendations include thorough wound washing, rabies vaccination and infiltration of RIG (3). Historically, failure of postexposure prophylaxis in humans is rare when these treatments are performed promptly and properly, even after severe exposures (4–6). Since the introduction of modern cell culture vaccines and RIG in the late 1970s, no failures have been reported within enzootic developed countries, such as those in Europe and North America. When postexposure prophylaxis failures are reported in less developed countries, most reports are related to the lack of the use of RIG in bite victims. Historically, WHO recognized three classes of biological products as available for the passive immunization component of postexposure prophylaxis: human RIG (hRIG), intact equine RIG (eRIG) and highly purified fragments (F(ab′)2) produced from eRIG. Production capacity and cost limit the availability of these serum-derived polyclonal RIGs, with most less developed countries that have a high incidence of rabies reporting negligible use. Understandably, in less developed countries, cost is an important reason why RIG is not used during postexposure prophylaxis (7). For example, a study in India found that only 21 of 783 (2.7%) patients with bites where there was a risk of rabies virus being present were prescribed hRIG, and only 10 could afford to obtain the product (8). Survival outcome of these patients was not provided in this study. Other studies in India and Thailand have also shown that only 2–3% of patients with severe animal bites receive RIG (9,10). The inclusion of ARV mAbs in human postexposure prophylaxis is an opportunity for large-scale production of safe, effective, well characterized, dependable and uniform biological medicines, which would likely lead to lower long-term manufacturing costs (11).

Benefits

ARV mAbs were first produced during the late 1970s (12). Some ARV mAbs only recognized very distinctive epitopes on a given rabies virus variant. Other cross-reactive ARV mAbs, directed to the outer viral glycoprotein, more broadly neutralized global rabies viruses of public health relevance, and were shown to protect laboratory animals even after severe experimental viral exposure (13). After years of development, the first ARV mAbs to be used in humans was a mix of two such antibodies, CR57 and CR 4098 (together called CL184), which were shown to have broad neutralizing activity for many rabies virus isolates during preclinical research (14,15). Dose-ranging studies conducted in animals showed that a dose of 12 micrograms/kg in combination with vaccination was non-inferior to RIG and vaccination. Both phase I and II trials, conducted in India, Philippines and the United States of America, showed these ARV mAbs were safe and well tolerated, and had adequate levels of rabies virus neutralizing activity in all participants, with doses of CL184 of 20 IU/kg or 40 IU/kg. The product was withdrawn from further clinical development after changes in pharmaceutical company ownership. Thereafter, given the potential shown by CL184, other ARV mAbs, directed against the outer rabies virus glycoprotein, have proven to be an effective and safe option for use in postexposure prophylaxis, as an alternative to equine and human RIG (16). Several studies (published and unpublished) have shown ARV mAbs to have a similar effectiveness as RIG. A phase I simulated postexposure prophylaxis study in India of 74 adults found a single ARV mAb induced rabies

virus neutralizing activity comparable with a regimen containing RIG (17). A phase II/III, single-blind, randomized, non-inferiority study was conducted in India with 200 participants (adults and children > 5 years) with suspected WHO category III rabies virus exposures (18). Participants received either ARV mAbs or RIG (1:1 ratio) in wounds and, if required, intramuscularly on day 0, together with five doses of rabies vaccine on days 0, 3, 7, 14 and 28. The primary endpoint was the ratio of the day 14 geometric mean concentration of rabies virus neutralizing activity, as measured in ARV mAb recipients relative to RIG recipients. Of 199 participants, 101 received ARV mAbs and 98 received RIG together with at least one dose of vaccine. The day 14 geometric mean concentration ratio of rabies virus neutralizing activity for the ARV mAb group relative to the RIG group was 4.23 (97% confidence interval (CI) 2.59 to 6.94): geometric mean concentration of 24.9 IU/mL (95% CI 18.94 to 32.74) for ARV mAb recipients and 5.88 IU/mL (95% CI 4.11 to 8.41) for RIG recipients. No deaths from rabies were reported. Another phase III, multicentre, randomized controlled, non-inferiority study compared ARV mAbs plus vaccine to RIG plus vaccine in 308 participants with category III rabies virus exposure (19). Participants were randomized to receive either ARV mAbs (docaravimab and miromavimab) or hRIG, in a 1:1 ratio. The primary endpoint was comparison of responder rates between the two arms of the study, assessed as the percentage with rabies virus neutralizing antibodies titres ≥ 0.5 IU/mL on day 14. ARV mAbs were found to be non-inferior to hRIG, with 90.3% and 94.4% of participants, respectively, with antibody titres ≥ 0.5 IU/mL on day 14 (95% CI −0.02 to 0.10). No deaths or rabies cases were reported. A potential disadvantage is that polyclonal antibodies are thought to neutralize more lyssavirus variants than monoclonal antibodies (16). Researchers have attempted to address the reactivity of these biological medicines by using in vitro neutralization tests and various experimental animal models with a broad number of viral isolates to help provide reassurance of the extent of protection monoclonal antibodies provide compared with polyclonal antibodies. All ARV mAbs considered for human use have been shown to neutralize rabies virus in the geographical regions where trials were conducted, most significantly for canine rabies virus variants which cause most of the human deaths from rabies globally (14,20–23). Enhanced surveillance and pathogen discovery activities (using genomic sequencing) continue to characterize local viruses and coverage by available products to ascertain the public health relevance of lyssavirus antigenic diversity and neutralization coverage by existing monoclonal antibodies.

Harms

To date, no serious adverse events have been reported from the use of ARV mAbs in humans. Most reactions reported were mild to moderate in severity and resolved without sequelae in a short time (17–19,24). In a comparative clinical trial in India, 461 adverse events were reported, of which 83.7% were solicited events and 16.3% were unsolicited events (18). Of the 386 solicited events reported within the first 7 days of postexposure prophylaxis, 250 (64.8%) were injection site reactions (112 at the wound site, 40 at another site where any remaining RIG or ARV mAb was injected and 98 at the site of rabies vaccine injection). The other 136 (35.2%) solicited events were systemic reactions – 85 from 28 participants in the ARV mAb group and 51 from 20 participants in the RIG group. All solicited reactions were of mild to moderate severity, except for three events of redness, one event of pain and one case of fever (41.3 °C) which were assessed as severe – all were in the RIG group. Of the 75 unsolicited events reported from 57 participants during the 84-day study period, all were assessed as unrelated to the study treatment except for two: itching at a wound site in one participant in the ARV mAb group and pain at the injection site in one participant in the RIG group. The mean changes in haematology and chemistry parameters from day 0 to day 28 were comparable between the two groups. No antidrug antibodies were detected in any of the study participants.

Cost / cost effectiveness

Few data are available on the comparative costs and effectiveness of ARV mAbs. To date, only two ARV mAb products have been licensed and marketed in India, so prices from a wider range of settings are not available. Moreover, similar to RIG, the use of ARV mAbs usually occurs only once in a person’s life-time, after exposure but before illness onset. Therefore, any cost–effectiveness estimate is based only on the cost per case in light of the clinical event prevented, which is considered lifesaving with timely and appropriate postexposure prophylaxis. Postexposure prophylaxis is considered to be a cost-effective strategy to prevent deaths in people with WHO

category III exposure to rabies virus (25). The ability to pay for postexposure prophylaxis varies widely across the world. Studies on willingness-to-pay postexposure prophylaxis thresholds have been reported as US$ 1400 in United Republic of Tanzania (26) and US$ 2953 in the Philippines (27). In most less developed countries in Africa and Asia, availability of RIG is very limited and it varies greatly in price from US$ 15 to US$ 70 per vial (28). It is anticipated that the price of ARV mAbs will be in between the prices of hRIG and eRIG. For example, in India, an estimate for a routine course postexposure prophylaxis for an average-sized adult is US$ 285 for hRIG, US$ 55 for ARV mAbs and US$ 13 for eRIG.

WHO guidelines

WHO recommendations on anti-rabies postexposure prophylaxis are given in its rabies vaccine position paper and were last updated in 2018 (3). Use of ARV mAb products instead of RIG is encouraged, if available.

Availability

Two ARV mAb products are currently registered for use in humans. • 17C7 (also known as RAB1, SIIRMAB or Rabisheld), a homologous human ARV mAb for adult and paediatric use. It is licensed in India and is also registered for use in Bahrain, Chad, Democratic Republic of the Congo, Ethiopia, Georgia, Kazakhstan, Kenya, Kyrgyzstan, Mozambique, Nepal, Oman, Tajikistan, Tanzania and Uzbekistan. • M777-16-3/62-71-3 (docaravimab and miromavimab, also known as Rabimab, Twinrab), a heterologous mix of two murine ARV mAbs for adult and paediatric use. It is licensed in India. Two other ARV mAbs are currently under clinical and/or regulatory evaluation.

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