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Research Article

Rabies-Monoclonal Antibody - A Perspective

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A B S T R A C T

Rabies is an acute viral zoonotic disease that affects the central nervous system (CNS) of all warm-blooded animals, including mammals. Research studies and experience from across the world have demonstrated that appropriate administration of a combination of (a) local wound treatment, (b) anti-rabies vaccination and (c) passive immunization have proved to be quite effective in preventing the occurrence of rabies. As far as passive immunization is concerned, polyclonal plasma-derived rabies immunoglobulins (RIG) pose a number of limitations with scarce supply, high cost, etc. amongst many others. On the contrary Rabies Monoclonal Antibodies (R-mAb) are much cheaper, permit longer-term storage, etc. and hence could offer a more standardized, accessible, affordable and equally efficacious and safer alternative to RIG. Accordingly, this article has tried to throw light on the transition from RIG to monoclonal antibody-based Post Exposure Prophylaxis (PEP) which has been recommended by the WHO strongly. The advantages, limitations and future scope of R-mAb have been discussed at length to give a comprehensive idea about this novel invention in the field of medicine.

Keywords: Anti-Rabies Vaccination, Post-exposure Prophylaxis, Rabies Immunoglobulin, R-mAb

Introduction

Rabies is an acute viral zoonotic disease that affects the central nervous system (CNS) of all warm-blooded animals, including mammals and is found in more than 150 countries and territories. As there is no treatment available to save those affected, the disease is invariably fatal. But with the presently available different rabies immunobiologicals i.e. anti-rabies vaccines (ARV) and rabies immunoglobulins (RIG), the disease is almost 100% preventable. Globally, approximately 59,000 deaths occur due to this disease annually and dogs are the primary vectors in almost 99% of the cases.[1,2] From India alone there are about 1/3rd i.e. approx. 20,000 deaths are due to human rabies and 97% of them are caused due to dogs.[3,4]

The Current scenario of health and Rabies in India

Rabies is 100% fatal hence animal bites (dog, cat and wild carnivores) should be considered a “medical emergency” and post-exposure prophylaxis (PEP), which is life-saving, should be administered immediately post the animal bite incident.[5] Research studies and experience from across the world have demonstrated that appropriate administration of a combination of (a) local wound treatment, (b) anti-

rabies vaccination and (c) passive immunization, has been proved to be quite effective in preventing the occurrence of rabies. All three components of treatment are equally important since rabies has been found to occur if one of the elements has been omitted.[6]

There has been an increased demand for an anti-rabies vaccine in the country since a considerable number of people suffer dog bites. As secondary vaccines, ARVs are procured by the state government in most of cases which often face resource scarcity. Moreover, during the past few years, there have been consistently low levels of production of rabies biologicals in the public sector hence there have been frequent shortages of anti-rabies vaccines and equine rabies immunoglobulin (ERIG) for post-exposure prophylaxis. The export of rabies biologicals by the private sector in India requires evaluation and regulation under the realm of national vaccine security, regular stockouts in the domestic area and the long-term goal of achieving human rabies-free India by 2030.[7]

The burden of Passive Immunization

Globally, an estimated 29.2 million people are subjected to rabies post-exposure prophylaxis annually and data from various sources has demonstrated that at least 1/3rd of them come under category III bite.[8]

There is a shortage of supply of RIG globally and as per estimates of all the category III patients recommended to receive RIG, hardly 1%-10% actually receive rabies Immunoglobulin as a part of the post-exposure prophylaxis.[9]

While rabies immunoglobulins have proven to be quite efficient in giving protection after an incident of animal bite and rabies exposure, factors like limited accessibility, high cost and scarce supply of rabies immunoglobulins in the low-middle income and rabies endemic countries have hindered the efforts to cut down the rabies death toll. The World Health Organization and several other international organizations are working collaboratively in achieving zero human rabies deaths by the year 2030 and ensuring equitable access to rabies vaccines and immunoglobulins to rabies endemic countries, the paucity of which may be a big hindrance to achieving the desired target.[10]

Rabies Immunoglobulins

In general, for passive immunization, there are three classes of RIGs available viz. (a) equine rabies immunoglobulin (eRIG), (b) human rabies immunoglobulin (hRIG) and (c) highly purified F('ab) 2 fragments produced from equine rabies immunoglobulin (eRIG). 20 IU/kg body weight is the recommended dose of hRIG by the WHO. 40 IU/kg body weight is the recommended dose by the WHO for F(ab')2 and eRIG products.[11,12]

The Journey of Rabies Monoclonal Antibody (RmAb)

In 1990, an expert consultation by WHO held in Philadelphia, USA recommended the development of "cocktail" RmAbs for Post Exposure Prophylaxis taking into account the limitations of the polyclonal plasma-derived rabies immunoglobulins.[13] A consultation on ''Rabies Monoclonal Antibody (RmAb) Cocktail for Rabies Post Exposure Treatment" was organized by the WHO in 2002 which elaborated an action plan for the selection, evaluation and transfer of technology of RmAbs.[14]

In 2017 a "WHO meeting on monoclonal antibodies against rabies and evaluation of mechanisms to improve access to other plasma-derived Immunoglobulins" was organized in light of the advancement in rabies monoclonal antibodies development that discussed various challenges and roadblocks to approval and routine use of rabies monoclonal antibodies and identified potential solutions and explanations for ensuring access.[15]

Limitations posed by Rabies Immunoglobulin

The supply and usage of human rabies immunoglobulin (hRIG) are restricted to high-income countries because of the limited production and high cost, as finding human donors are getting tougher and production capacity is limited. The technology was developed in the USA and the WHO facilitated technology transfer to India, China and other potential countries with innovative pharmaceutical industries.

While on the other hand, the supply and usage of equine rabies immunoglobulin (eRIG) are restricted to low- and middle-income rabies endemic countries. An eRIG is relatively cheaper since it can be manufactured through low-cost technology. But its production is also challenging because of the discontinuation by many manufacturers due to animal welfare and ethical concerns which have come up in recent years.

Unfortunately, quite a lot of medical practitioners have limited or textbook knowledge of equine rabies immunoglobulin (eRIG) and are reluctant to use it from the fear of anaphylactic shock, even though purification methods have improved significantly and there is minimal risk of side effects.

A common hindrance of the plasma-derived polyclonal rabies immunoglobulin is there due to a variation from batch to batch that affects the efficacy and the relatively short shelf-life. Since there is no WHO pre-qualification system for rabies immunoglobulin (RIG) there are concerns regarding the quality of certain products.[16] Another hindrance is the majority of the virus-specific antibodies in rabies immunoglobulins are actually non-neutralising

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and of the many antibodies, only a limited proportion are actually pathogen-specific which might affect the efficacy. [17]

Furthermore, ARV and the rabies immunoglobulins derived from plasma don't provide protection against infection with all lyssavirus species.[18] There lies a possible risk of contagion of blood-borne infection / diseases. Hence, a hunt for an alternative to plasma-derived Rabies Immunoglobulins has been strongly urged by the WHO.

Advantages of Rabies Monoclonal Antibodies (RMabs)

The transition from rabies immunoglobulin to monoclonal antibody-based Post Exposure Prophylaxis (PEP) has been recommended by the WHO strongly with the aim to:

- Lower the production costs
- Get an adequate supply
- To ensure availability of consistently active batches
- Lower the adverse reaction risks

In order to meet global demand in immunobiologicals, rapid industrial production capability along with the consistent quality of rabies monoclonal antibodies is quite relevant. Additionally, monoclonal antibodies can be much more effective than rabies immunoglobulins for wound infiltration since they come in the form of a concentrated lyophilized product which is in accordance with the WHO recommendation for passive immunization.[19] Rabies monoclonal antibodies is much cheaper as compared to HRIG. In the near future, if the production of rabies monoclonal antibodies is scaled up, depending on the demand, it might actually be available at a very competitive price as compared to Fab'2 products or ERIG. Another advantage may be that developing RmAbs in lyophilized form would actually permit storage for the longer-term and make supplying to rural areas convenient. As compared to plasma-derived rabies immunoglobulins, rabies monoclonal antibodies could offer a more standardized, more accessible, more affordable and equally efficacious and safer alternative.[20]

Availability of RmAb

The pharmaceutical industries in India are in the foreground of innovation and commercially viable economical production including rabies monoclonal antibodies.

The Serum Institute of India manufactured the first RmAb known as 'Rabishield' which was licensed in the country in 2016 and eventually launched in 2017. Single human IgG1 type rabies monoclonal antibody is the product that binds to a conformational epitope of the rabies glycoprotein.[21]3.33 IU/kg is the recommended dose for 'Rabishield'. For a 60 kg weight person 'Rabishield' would cost around eighteen percent of the cost of HRIG.

The Zydus Cadila produced the first 'cocktail' rabies monoclonal antibodies known as 'Twinrab'. It was licensed and marketed in India in 2019 and 2020 respectively. This combines two murine mAbs that bind to discrete epitopes on the rabies glycoprotein.[22] The recommended dose for 'Twinrab 'is 40 IU/kg. For a 75kg weight person, this product would cost around twenty percent of the cost of HRIG. In other words, there is marginal cost variation between single and cocktail RmAb as compared to hRIG which may be even less costly in the future.

Safety Profile of Rabies Monoclonal Antibody

Rabies monoclonal antibody is manufactured through recombinant DNA technology and is appropriate for wide-scale production that will ultimately overcome the shortage of the HRIG and ERIG as these are dependent on humans and animals. Rabies monoclonal antibodies have nil safety concerns as compared to plasma-derived immunobiologicals. Rabies monoclonal antibody doesn't require skin sensitivity testing and can directly be administered which will save the physicians' time without any fear of adverse reactions. Rabies monoclonal antibody is an IgG-1 monoclonal antibody that has improved safety with nil transmission of blood-borne pathogens, has no limit to the production capacity with consistency in the production, contains well-defined and well-characterized potency and is less copious to administer locally.[23]

Challenges and Concerns posed by R-Mabs

Although rabies mAbs have been developing domestically and globally, their fast clinical progress is challenging. Although many of the candidate Rabies monoclonal antibodies have reached clinical trials, only two products have gained approval in India. Early clinical studies are relatively uncomplicated in humans, but the high cost of production, trial conducting activities and cost of post-marketing surveillance may be too high for developers to bear. An additional challenge is to track the outcome of the suspected exposures to further determine the efficacy of the rabies mAbs and to compare the efficacy of mAbs in patients bitten by lab-confirmed animals and the end-point confirmation of both results.[24]

To date, none of the MAbs are listed in the U.S., European, British or International Pharmacopeia. Further, the EMA, FDA, Health Canada, the Australian Government and the Japanese Pharmaceuticals and Medical Devices Agency have not yet approved any of the MAbs. Further, in India, the PSUR (periodic safety update reports) period of R-mAbs is still in the completion phase and its reports are still to be evaluated at the national level.[25] India with the highest burden of rabies definitely requires newer modalities for the management of animal bite however the current studies undertaken by different institutes with support

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from industry needs to be weighed by independent bodies in India to ascertain the effectiveness and safety of MAbs in light of recent evidence in India which can guide the policymakers on the mass scale use of MAbs.

Way forward

- Sustainable and mass-scale production of eRIG and hRIG with consistency in quality of rabies immunoglobulin is questionable which is complicated by animal welfare and ethical concerns. Therefore, mass production and the use of RmAb is the need of the hour
- Since rabies monoclonal antibody products have now been approved in some select countries, it becomes critical to facilitate access in other rabies endemic countries as well. For this, a clear set of criteria and mechanisms are required to be set up for regulatory approvals and also cover clinical trial design and satisfactory end-points for Rabies monoclonal Antibody.[14] The result of post-marketing surveillance of RmAbs in India will be critical for regulatory approval
- A joint assessment of recently licensed RmAbs with regulatory agencies should be facilitated by WHO along with risk management plans which also cover data collection protocols[20]
- Quality control systems are not there in place for all rabies endemic countries and since RmAb is a novel product it will be important to set up and speed up a WHO pre-qualification scheme for ensuring intake from the Member States along with international partners
- Since there are confining factors for the production and usage of Rabies Immunoglobulins for passive immunization, it is a possibility that rabies monoclonal Antibodies may replace conventional Rabies Immunoglobulins in the near future
- The affordability of rabies monoclonal Antibodies by consumers will be a critical factor for the countries to introduce RmAb. But as the demand will increase the cost will come down to an affordable range
- Once RmAb starts to be widely used/ adopted for passive immunization it will be cheaper which has been noticed in India due to competitive price among manufacturers
- An enabling environment should be created by national authorities (through proper education, getting it included in the essential medicine list, steady supply) for the use of rabies monoclonal antibodies for passive immunization under category II (conditional) and category III (mandatory) cases according to the National Post Exposure Prophylaxis (PEP) guidelines as per WHO recommendation

To conclude, the human rabies monoclonal antibodies produced by recombinant technology are secure and safe for PEP and will obviate the problems around the availability, safety and purity of passive immunization and will be efficacious in preventing rabies.

Highlights

- Rabies, a fatal disease, is preventable with prompt post-exposure prophylaxis (PEP)
- Rabies monoclonal antibodies (R-mAbs) produced by recombinant technology are efficacious
- R-mAbs have nil safety concerns as compared to plasma-derived immunobiologicals
- R-mAb offer a more standardized, accessible, affordable and safer alternative to RIG
- Transition from RIG to R-mAbfor PEP is strongly recommended by the WHO

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