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Short Communication

Monoclonal antibodies for rabies post-exposure prophylaxis: A paradigm shift in passive immunization

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Abstract

An estimated 59000 people die of rabies every year in the world. Passive immunization forms an important component of rabies Post-Exposure Prophylaxis (PEP), in Category III exposures,and sometimes in Category II exposures. Presently Rabies Immunoglobulins (RIGs) of human and equine origin are being used in most partsof the world, for passive immunization. However, overall, less than 10% of patients with category III exposuresare receiving passive immunization due to economic and technical reasons including shortage and often limited supply of RIGs. Although plasma derived RIGs have proven to be highly efficient in conferring protection after rabies exposure, the limited access, high cost and often short supply of RIGs are major constraints. Therefore, a search for a replacement to plasma derived RIGs has been strongly encouraged by the WHO since 1990. The development and availability of rabies monoclonal antibodies in recent years is a positive sign. This short note elaborates the importance of Rabies monoclonal Antibodies (RmAb) in rabies PEP and its potential role in improving availability, accessibility and affordability of biologicals for passive immunization in order to reduce human mortality due to rabies in resource poor endemic countries.

Introduction

Rabies is 100% fatal, but it is also a 100% preventable disease. In humans, rabies prevention is achieved by either pre- or post-exposure prophylaxis. Unfortunately, an estimated 59,000 people die of rabies every year in the world, and most of them are from Asia and Africa [1]. It is alarming to note that over 40% of rabies deaths occur in children aged under 15 years [2]. Dogs are responsible for 99% of human rabies cases. Dog bite is the primary reason for seeking rabies Post-Exposure Prophylaxis (PEP).

Rabies Post-Exposure Prophylaxis (PEP) includes the first aid treatment of the wound and the administration ofrabies vaccine alone or in combination with rabies immunoglobulin (RIG) for category II or III exposures, respectively [3]. In particular, patients with category III exposure and severely immunocompromised people with category II exposure, should receive RIG administered into or around the wound site along with rabies vaccination [2]. One of the main barriers to effective PEP is the availability, accessibility and affordability of rabies immunoglobulin in high burden rabies endemic countries.

In general, three classes of rabies immunoglobulins are available for passive immunization; human rabies immunoglobulin (hRIG), equine rabies immunoglobulin (eRIG) and highly purified F('ab) 2 fragments produced from eRIG. The dose of hRIG recommended by the WHO is 20 IU/kg body weight; for eRIG and F(ab')2 products, the recommended dose is 40 IU/kg body weight. Both rabies vaccine and rabies immunoglobulin are listed on the WHO Model List of Essential Medicines, a list of minimum medicine needs for a basic health care system and some countries have included it in the National list of essential medicines [4,5].

Burden of passive immunization

Globally an estimated 29.2 million people undergo rabies PEP each year and our experience shows that at least one third of them may fall under category III bite [1]. Rabies immunoglobulin is are in short supply globally and it has

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been estimated that only 1–10% of category III patients recommended to receive it, actually receive RIG as a part of PEP [6,7]. Although RIGs have proven to be highly efficient in conferring protection after rabies exposure, the limited access, high cost and often short supply of RIGs in low and middle income, rabies endemic countries have hampered efforts to reduce the rabies death toll. WHO and international partners are working together to achieve zero human rabies deaths by 2030 and equitable access of RIG to rabies endemic countries may be a major impediment to achieve the desired goal of zero human deaths due to rabies by 2030.

Limitations of RIGs

The supply and use of hRIG is limited to high income countries due to high cost and limited production, as finding human donors is becoming difficult. On the other hand, the supply and use of eRIG is limited to low income rabies endemic countries. It is comparatively cheap as it can be produced using low cost technology. However, its production is also difficult due to the discontinuation by many producers and ethical and animal welfare issues which have surfaced in recent years. The safety and quality of eRIGs have been improved considerably through introduction of a highly purified product, i.e. F(ab')2 eRIG but reliable and regular supply is an issue. Unfortunately, many medical practitioners have textbook knowledge of eRIG and they are reluctant to use eRIG, due to fear of anaphylactic shock, although purification methods have greatly improved and the risk of side effects is now minimal.

A general drawback of plasma derived polyclonal RIGs is that there is batch to batch variation affecting efficacy and relatively short shelf life [2]. There are quality concerns about some products as there is no WHO prequalification system for RIG [8]. Another drawback is that most of the virus-specific antibodies in RIGs are non-neutralizing and only a small proportion of the many antibodies are pathogen specific which may affect efficacy [9,10]. Moreover, anti-rabies vaccination and plasma derived RIGs do not confer protection against infection with all non-rabies virus (RABV) lyssavirus species [11]. There is a potential risk of transmission of bloodborne infection and/or diseases. Thus, a search for a replacement to plasma derived RIGs has been strongly encouraged by the WHO.

Ideas to action in search of rabies monoclonal antibody (RmAb)

Since monoclonal antibodies were first generated in 1975, using the hybridoma technology, they have been instrumental for a wide range of applications in research, diagnosis and therapy of cancer, as well as in inflammatory and infectious diseases [12]. Considerable preclinical research for development of RmAb had been done for many decades by WHO Collaborating Centers and academic institutions and WHO has been playing an important role in translating ideas into action. RmAbs have been considered as a viable and promising option to address the limitations of plasma derived RIGs.

A WHO expert consultation held in Philadelphia, USA in 1990 recommended to promote the development of "cocktail" RmAbs for PEP considering limitations of polyclonal plasma derived RIGs [13]. WHO organized a consultation on ''Rabies Monoclonal Antibody Cocktail for Rabies Post Exposure Treatment" in 2002, elaborating a plan of action for the selection, evaluation and technology transfer of rabies monoclonal antibodies [14]. In the light of advancement in RmAb development, a "WHO meeting on monoclonal antibodies against rabies and evaluation of mechanisms to improve access to other blood-derived Immunoglobulins" was held in 2017 which discussed challenges to approval and use of RmAbs and identified possible solutions to ensuring access [15].

Advantages of RMabs

The transition from RIG to monoclonal antibody-based PEP has been strongly recommended by the WHO with the aim of achieving an adequate supply, a reduction in the production costs, a reduction in adverse reaction risks, and the availability of consistently active batches. More rapid industrial production capability with consistent quality of RmAb is a greater advantage to meet a global demand in immunobiologicals. In addition, as monoclonal antibodies come in the form of a concentrated product, they can be more useful and effective than RIGs for infiltration into and around the wounds, which is in line with WHO recommendation for passive immunization [2]. RMab is much cheaper than HRIG. In future, if the production of RMabs is scaled up, based on the demand, it may be available at a competitive price, when compared to ERIG or Fab'2 products. Another advantage may derive from formulation studies to develop RmAbs in lyophilized form that would allow long-term storage as well as convenience of supply to rural areas.

RmAbs could offer an equally efficacious, more affordable, more accessible, more standardized and safer alternative to plasma derived RIGs [16].

Selection of RMabs

Nearly all approved monoclonal antibodies are of the IgG isotype and, predominantly, of the IgG1 subclass. It is of paramount importance to identify the combination of neutralizing monoclonal antibodies that bind to different antigenic sites on the RABV G protein and are able to broadly neutralize both RABV and non-RABV lyssavirus isolates in order to reduce potential risk of PEP failure. The best characteristics for a cocktail of rabies virus neutralizing antibodies are as follows: (i) high potency, (ii) recognition ofdistinct non-overlapping antigenic sites and (iii) high breadth ofreactivity for complete coverage of field rabies virus isolates [9].

Availability of RmAb

The Indian pharmaceutical industries are in the forefront of innovation, technology transfer and commercially viable economical production including rabies mAbs.

A cocktail of two human RmAbs (CR57 and CR4098) was developed by Crucell, the Netherlands and evaluated preclinically and phase I and II clinical trials were conducted in India and other countries [16,17].

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The two component monoclonal antibodies recognise non-overlapping and non-competing epitopes on antigenic sites I and III of Rabies Virus Glycoprotein. The product was reported to be broadly neutralizing many rabies isolates in *in vitro* studies [18,19]. Unfortunately, further product development was abandoned, despite having promising pre-clinical and clinical trial results.

The Serum Institute of India Pvt. Ltd.(SIIPL) has been playing a proactive role in innovation, technology transfer and mass production of immunobiological. The SIIPL and MassBiologics, USA, signed an agreement in 2006 to further develop rabies mAb (RMAB1) in India which took almost a decade to materialize into commercial production of rabies mAbs. Broadly neutralizing monoclonal antibody 17C7 was generated by transgenic mice that express human immunoglobulin genes 'Rabishield' is the first RmAb manufactured by the Serum Institute of India Pvt. Ltd. which was licensed in India in 2016 and launched in 2017. The product is a single human IgG1 type RmAb that binds to a conformational epitope of the rabies glycoprotein [20]. The product was found to be safe and demonstrated non-inferiority to HRIG The WHO SAGE also noted that this product would serve as an important learning process for future RmAbproducts [8].The recommended dose is 3.33 IU/kg. As far as the cost is concerned, for a person weighing 60 kg, the cost of this product is about 18% of the cost of HRIG. The post-marketing surveillance data will be valuable to make policy informed decision.

'Twinrab' is the first 'cocktail' RmAb produced by Zydus Cadila which was licensed in 2019 and marketed in 2020 in India. It combines two murine mAbs which bind to different epitopes on the rabies glycoprotein. The RmAbs were donated from two WHO Collaborating Centres for Rabies, i.e. Animal Diseases Research Institute, Canada (RmAb: M777-16-3) and the Centres of Disease Control and Prevention, USA (RmAb:62-71-3). WHO transferred the technology to Zydus Cadila under a material transport agreement (MTA) which includes a commitment from the manufacturer to sell any resulting product at affordable prices to the public sector of developing countries [16]. Twinrab was found to be a safe and effective alternative to hRIG. The recommended dose of 'Twinrab' is 40 IU/kg [21]. When compared to hRIG, for a person weighing 75 kg, the cost of Twinrab is about 20% of the cost of HRIG.

Conclusion

An important step towards ensuring that RmAbs are used is that the WHO formal position paper on rabies vaccines now includes recommendations for the use of monoclonal antibody products in PEP [22]. Non-discriminatory, universal and equitable access to quality assured RmAb for passive immunization is need of the time. Introduction of commercially available RmAb is a first step and a number of regulatory and quality assurance measures should be taken to improve accessibility and affordability of RmAbs globally. RmAb is a highly purified and concentrated biological product which is produced with a consistent potency under standardized production practices. Therefore, RmAb is to be considered under WHO prequalification scheme to provide quality assurance of product to Member States and partner agencies such as UNICEF and GAVI as they may be interested in supply and logistic arrangements of RmAbs for low- and middle- income countries, in order to contribute to the global campaign for achieving zero human deaths due to rabies by 2030. In other words, mass production and accessibility of rabies specific monoclonal antibodies through international partnership and reduction in the number of deaths are now realistic goals [11].

Way forward

As RmAb products are now approved in some countries, it is of paramount importance that access in other rabies endemic countries be facilitated. Clear criteria and mechanisms need to be established for regulatory approval, including clinical trial design and acceptable end-points for RmAb [14]. WHO should facilitate a joint assessment with regulatory agencies of recently licensed RmAbs in combination with risk management plans that include data collection protocols [16]. Not all rabies endemic countries have quality control systems in place and RmAb is a new product and it will be necessary to establish and accelerate a WHO prequalification scheme to ensure uptake from Member States as well as international partners. It will also facilitate registration and licensing of RmAb by the drug regulatory authorities for use in rabies PEP.

It is expected that RmAb will replace conventional RIGs in future as there are limiting factors for the production and use of RIGs for passive immunization. Consumer purchase price of RmAbs will be an important consideration for countries to introduce it. The price of RmAb will go down once it will be widely used for passive immunization, which is noticeable in India. National authorities should create an enabling environment (education, inclusion in essential medicine list, regular supply) for use of RmAb for passive immunization in category II (conditional) and category III (mandatory) cases in national PEP guidelines as recommended by WHO. Similarly, a registry should be maintained to monitor the clinical use of RmAb products [8].

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