Pulmonary delivery of anti-ricin antibody: From the bench to the clinic

Ricin is a potent toxin, with a strong potential to be used as a biological weapon due to its worldwide availability, ease of production in large quantities, and thermal stability. Inhalation of ricin is likely to be the intended route for acts of bioterrorism, because ricin is easily dispersed as an aerosol. Inhalation of ricin is the most lethal route of exposure, causing diffuse pulmonary edema and an increase of air-blood barrier permeability, leading to alveolar flooding and ultimately to death in a few days. Several approaches have been proposed to treat pulmonary ricin poisoning. These include prophylactic immunization with vaccines and post-exposure treatment with therapeutic antibodies, but none of these approaches are currently approved [1].

Post-exposure administration of neutralizing anti-ricin monoclonal antibodies (mAbs), delivered locally into the lungs, was effective in animals [1]. The intravenous route does not deliver a sufficient amount of mAbs to the respiratory tract. Although rapid diagnosis of ricin poisoning is currently available, optimization of inhalation to efficiently and rapidly deliver active mAbs directly into the lungs has not been developed.

The paper in this issue by Dr. Nathalie Heuzé-Vourc’h, her team and an international public-private consortium describes the development of a unique drug delivery system delivering a therapeutic monoclonal antibody (IgG 43RCA-G1) deep into the lungs to treat pulmonary ricin intoxication [2]. After developing a high-affinity neutralizing anti-ricin scFv antibody, the Heuzé-Vourc’h group modified it as a full length IgG close to human IgG to optimize for use in humans. Then, they tested its efficacy in vivo, in a murine lung challenge model of ricin intoxication [3] and determined the therapeutic window using local delivery. They showed that IgG 43RCA-G1 rescued 100% of the mice for up to six hours after intoxication following direct delivery to the lungs, which is sufficient for intoxicated individuals to seek treatment and receive the antibody.

The next step consisted of developing a drug delivery system to deliver IgG 43RCA-G1 by inhalation in humans. Successful inhalation depends on the performance of the device to efficiently deliver the drug to the target site, here the alveoli. The Heuzé-Vourc’h group was able to reduce the aerosol particle size and maximize delivery deep into the lung. It was necessary, however, to stabilize IgG 43RCA-G1 during the mesh nebulization and to facilitate its delivery under operational conditions. Thus, the Heuzé-Vourc’h group developed a dry-powder formulation of IgG 43RCA-G1 that would be reconstituted prior to nebulization in an adapted solution containing surfactants to avoid mAb aggregation. The aerosol characteristics and drug deposition of the drug delivery system was tested in vitro and in vivo to evaluate its performance to deliver the IgG deep in the lung. The predicted lung and alveolar depositions were remarkably higher than in other previous studies. Lung depositions in non-human primates further supported the in vitro data and revealed that the anti-ricin antibody accumulated for at least 6 h in the airways, which is consistent with the therapeutic window of the drug.

The paper by the Heuzé-Vourc’h group is important as it describes the first drug delivery system as a medical countermeasure against ricin as a weapon, providing a major breakthrough in the fields of aerosol therapy, defense against biological weapons, and respiratory mAbs. Numerous drug candidates have been developed with promising in vitro and in vivo results, but most of them do not reach the clinic. This is simply because transposition to humans always presents unanticipated important issues, including low drug stability, lack of drug safety, and difficulty in drug delivery. The Heuzé-Vourc’h team designed their study with the ultimate human use in mind, i.e., to predict how the drug delivery system will work in humans. Such a strategy is critical for accelerating the transfer of this novel drug delivery system from the bench side to the clinic. It is time for the drug delivery researchers to pay more attention to developing drug delivery systems for clinical use. The Journal of Controlled Release is committed to provide a forum for disseminating such research efforts.

References


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