Therapeutic antibodies for infectious diseases

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First, for rare or emerging diseases, such as Ebola, pandemic influenza or MERS-CoV, demonstrating proof of concept in clinical trials is difficult. The small number of patients, the unpredictable outbreaks and epidemiology and the high fatality associated with the ethical challenges of conducting randomized clinical trials, are obstacles when evaluating mAbs as a treatment for such diseases. Therefore, alternative regulatory pathways for product licensure are needed. However, many countries do not have mechanisms in place for such pathways and there is no framework in place for testing, licensure and use of mAbs. In addition, consensus on acceptable clinical endpoints and definition of conditions under which mAbs would be used, are lacking. Therefore, we need disease-specific well-characterized animal models to demonstrate proof of concept and even efficacy for these diseases.

Second, for fatal diseases, such as rabies, where highly effective polyclonal antibodies are available, but short in supply, conducting randomized controlled trials present ethical and logistical challenges. Therefore, researchers need alternative study designs to evaluate mAbs against such diseases. Furthermore, polyclonal antibodies are conceived to neutralize more virus strains than mAbs. Researchers need to address the breadth of protection of these mAbs. Using in vitro neutralization methods and animal models with a broad number of viral isolates could help provide reassurance of the breadth of protection given by mAbs compared to polyclonal antibodies.

Third, when several mAbs are under development against the same disease, but with different product profiles, such as affinity, protective dose and route of administration, health agencies and donors might have difficulty selecting which product(s) to fund. Furthermore, there exists a challenge when comparing mAbs products due to the lack of international reference preparations.

Fourth, high costs may limit access, especially to those in low-resource settings. Although the production costs of mAbs have been reduced over the last decade, the cost is still high (about 100 United States dollars per gram), especially if several grams are needed for treatment. The number of grams required will differ greatly depending on the target pathogen. Methods to decrease the cost include enabling lower doses by increasing the affinity of the mAbs or changing the production system to increase yields and/or decrease the cost of goods. Targeted use in high-risk individuals may present a cost-effective strategy.

Fifth, for several disease targets, investors and people working with product development need clarity on whether public health agencies will procure and use the new therapeutics or postexposure prophylactics. Without a known market, biotechnology companies are hesitant to invest in mAb research and development. We therefore need alternative financing models, such as advanced market commitments. To ensure that mAbs reach populations who need them the most, the WHO prequalification programme could facilitate the establishment of procurement mechanisms.

Finally, the use of approved mAbs products for persistent infections and/ or mutating pathogens is of concern. As with other drugs, antimicrobial resistance to mAbs is a potential threat. However, this threat may be overcome by targeting highly conserved epitopes or by using antibody cocktails containing more than one mAb. Postmarketing guidelines to monitor mAbs efficacy would also be required.

In conclusion, mAbs have a potential to address a wide range of infectious diseases and development pathways need to be clearly defined to facilitate the licensure of these products. Regulatory agencies, biotechnology companies, public sector research agencies and funders must together implement a multisectoral approach to ensure adequate financing, clear regulatory guidance and policies to support the development, approval and use of mAbs. Such an ap-
Monoclonal antibodies for infectious diseases

Erin Sparrow et al.

Approach extends beyond mAbs to other therapeutic products with difficult clinical pathways and uncertain markets. Global strategies, such as the WHO research and development Blueprint and other initiatives, will be essential for product development progresses.

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