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Review

Passive immunization for influenza through antibody therapies, a review of the pipeline, challenges and potential applications

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ABSTRACT

The Global Action Plan for influenza vaccines (GAP) aims to increase the production capacity of vaccines so that in the event of a pandemic there is an adequate supply to meet global needs. However, it has been estimated that even in the best case scenario there would be a considerable delay of at least five to six months for the first supplies of vaccine to become available after the isolation of the strain and availability of the candidate vaccine virus to vaccine manufacturers. By this time, the virus is likely to have already infected millions of people worldwide, causing significant mortality, morbidity and economic loss.

Passive immunization through broadly neutralizing antibodies which bind to multiple, structurally diverse strains of influenza could be a promising solution to address the immediate health threat of an influenza pandemic while vaccines are being developed. These products may also have a role in seasonal influenza as an alternative to other options such as antivirals for the treatment of severe acute respiratory illness due to influenza.

This article provides an overview of the current clinical pipeline of anti-influenza antibodies and discusses potential uses and the challenges to product development.

Contents

Abbreviations: bNAb, broadly neutralizing antibody; GAP, Global Action Plan for influenza vaccines; mAb, monoclonal antibody; ICTRP, International Clinical Trials Registry Platform.

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1. Introduction

Both influenza A and influenza B viruses cause seasonal epidemics in humans. Seasonal influenza vaccines contain attenuated strains of influenza A and influenza B viruses. The subtypes contained within seasonal influenza vaccines can vary from year to year due to minor changes in the genetic makeup of the viruses known as antigenic drift. Antigenic drift occurs on a continuous basis as the influenza virus replicates and is the reason why lifelong immunity does not occur following natural infection. Twice per year the World Health Organization (WHO) issues recommendations on the composition of seasonal influenza vaccines for the northern and southern hemispheres. Influenza A viruses also have the potential to undergo major genetic changes, known as genetic shift, which can cause pandemics.

In order to mitigate the spread and severity of an influenza pandemic multiple strategies are needed. Vaccines may remain one of the best defences against a pandemic, however the need for the vaccine to be made specifically to the pandemic strain, and the time needed for vaccine production means that there is a delay of several months before vaccines would be available to the general population [1]. It is likely that by this time the virus will have spread to infect millions of people worldwide bringing with it significant mortality and economic loss [2,3]. Such a delay in vaccine availability was experienced during the 2009 pandemic (A(H1N1) pdm09) with the virus identified in April and Candidate Vaccine Virus available to manufacturers in May, but the first vaccines not ready for distribution until October that year [4]. One strategy undertaken by several Governments is to stockpile "pre-pandemic" vaccines against avian subtypes such as H5N1 or H7N9. However, there are uncertainties about what the next pandemic strain will be and whether stockpiled vaccines would be efficacious against it [5,6]. While "universal vaccines" that could protect against any influenza strain would avoid this delay in vaccine availability, such products are still very far from reality. A further limitation is that with active immunization with vaccines, there would also be a delay of about two weeks between immunization and development of protective immunity.

The Global Action Plan for Influenza Vaccines (GAP) was created to address global concerns about access to pandemic influenza vaccines. The third objective of GAP was to promote research and development of improved influenza vaccines. Since then, some progress has been made in the development of novel influenza vaccines and production technologies and there are several innovative vaccines approved or in development [7,8]. A truly "universal" influenza vaccine would ideally confer lifelong immunity for all influenza subtypes and be unaffected by antigenic drift and shit. However, major barriers to the development of "universal" influenza vaccines are: a lack of consensus on the primary clinical endpoint to be achieved; a lack of correlates of protection to measure success; and the extensive and costly efficacy trials anticipated [7]. Taking into consideration the challenges to development of universal influenza vaccines, the WHO Product Development for Vaccines Advisory Committee has considered the improvement of seasonal influenza vaccines to be more feasible and advised WHO to develop preferred product characteristics for seasonal vaccines to improve the breadth, quality and duration of protection [9].

During the last decade there has also been extensive research on monoclonal antibodies for passive immunization against influenza. Such products could be used as pre- or post-exposure prophylaxis to prevent or reduce symptoms or in the treatment of severe influenza infection.

Passive immunization with recombinant antibodies presents an alternative strategy that could be implemented early in the pandemic to mitigate the impact of the virus while vaccines are being manufactured. If such products were broad spectrum and targeted conserved regions of the influenza A virus their efficacy may not be affected by antigenic drift or shift, meaning that the same products could be used from year to year in seasonal epidemics and be stockpiled for use in pandemics.

There are several advantages of monoclonal antibodies over vaccines including a potentially easier and more feasible research and development (R&D) pathway than universal vaccines, and a rapid onset of protective immunity. However, these advantages have to be contrasted with a higher cost, limited production capacity and the relatively short duration of protection.

In addition to bridging the gap between the start of the pandemic and vaccine availability, recombinant antibodies may also offer a promising alternative to other antiviral treatment options such as oseltamivir, which have shown limited efficacy in treating patients with influenza [10]. Furthermore, such products may also be a potential therapy for severe influenza caused by circulating seasonal strains of influenza A. Their use as a treatment during seasonal epidemics would ensure an annual market for manufacturers, leading to the establishment of facilities and sustainable production lines to be called upon in the event of a pandemic.

After ten years the GAP is coming to a close and a consultation with global stakeholders will mark its end in November 2016. When reviewing the progress under objective three of the GAP, stakeholders should look beyond progress made in vaccine development to consider also the development of recombinant antibodies for passive immunization against influenza.

Here we review the current pipeline of recombinant anti-influenza antibodies in clinical development, discuss some of the challenges to their product development, licensure and use, and discuss their public health potential and potential cost-effectiveness. The article also presents unresolved questions for developers and regulatory authorities to consider.

2. Methods

To determine the current pipeline of influenza antibodies in clinical development, a review of Clinical Trials.gov and of the WHO International Clinical Trials Registry Platform (ICTRP) was conducted on 8 January 2016 using the keywords "Monoclonal AND Influenza". The search yielded clinical trials for eight different monoclonal antibody products. To obtain more information regarding preclinical and clinical trial results, mode of action, dosing, efficacy and target product profiles literature and web reviews were conducted. To obtain published articles in scientific journals a literature review in PubMed using the candidate drug name was conducted. To obtain grey literature such as abstracts from conferences and press releases a review of manufacture's websites, Google Scholar and Google was then conducted for each of these candidate drugs.

3. Results

We identified eight different monoclonal antibody candidate products registered to be currently or have been in clinical development (Table 1). All products have undergone in vitro testing and in vivo evaluation in animal models. No products have made it beyond the phase 2 clinical trial stage. All products are expressed through mammalian cell lines and administered intravenously. All products are targeted against influenza A and reported to be broad spectrum across various subtypes of the virus. The majority of products are being developed by companies that are US based or owned. A summary of the information on the state of development for each of the eight products found in the public domain is presented below in alphabetical order.

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