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Review

Monoclonal antibodies as anti-infective products: a promising future?

E. Pelfrene [1, *], M. Mura [1], A. Cavaleiro Sanches [2], M. Cavaleri [1]

[1)] *Office of Anti-infectives and Vaccines, Human Medicines Evaluation Division, European Medicines Agency, London, UK*
[2)] *Quality Office, Human Medicines Research & Development Support Division, European Medicines Agency, London, UK*

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ABSTRACT

Background: The paucity of licensed monoclonal antibodies (mAbs) in the infectious diseases arena strongly contrasts with the ready availability of these therapeutics for use in other conditions.
Aims: This narrative review aims to assess the potential of monoclonal antibody-based interventions for infectious diseases.
Sources: A review of the literature via the Medline database was performed and complemented by published official documents on licensed anti-infective mAbs. In addition, ongoing trials were identified through a search of the clinical trial registration platform ClinicalTrials.gov.
Content: We identified the few infections for which mAbs have been added to the therapeutic armamentarium and stressed their potential in representing a readily available protection tool against biothreats and newly emerging and reemerging infectious agents. In reviewing the historical context and main features of mAbs, we assert a potentially wider applicability and cite relevant examples of ongoing therapeutic developments. Factors hindering successful introduction of mAbs on a larger scale are outlined and thoughts are offered on how to possibly address some of these limitations.
Implications: mAbs may represent important tools in treating or preventing infections occurring with reasonably sufficient prevalence to justify demand and for which existing alternatives are not deemed fully adequate. Future initiatives need to address the prohibitive costs encountered in the development process. The feasibility of more large-scale administration of alternative modalities merits further exploration. In order to ensure optimal prospect of regulatory success, an early dialogue with competent authorities is encouraged. **E. Pelfrene, Clin Microbiol Infect 2019;25:60**

Introduction

In 2017, bezlotoxumab became the second monoclonal antibody authorized for use throughout the European Economic Area directed against an infectious agent. It targets *Clostridium difficile* toxin B, and as such aims to prevent recurrences of the infection in adults at high risk of repeated bouts [1]. This follows a much earlier EU regulatory approval of palivizumab (in 1999), which is administered to prevent serious lower respiratory tract disease requiring hospitalization caused by respiratory syncytial virus (RSV) in children at high risk for the disease [2]. Licensing of these two monoclonal antibodies (mAbs), nearly two decades apart, illustrates the gap to date in clinical development of this therapeutic tool against infections. This is consistent with the experience of other regulatory authorities, such as the US Food and Drug Administration (FDA), which granted similarly phrased labels in the United States for both products [3,4]. Additionally, the FDA recently licensed ibalizumab as a rescue therapy in heavily treatment-experienced adults with multidrug-resistant HIV-1 infection and also previously approved raxibacumab (in 2012) and obiltoxaximab (in 2016), both intended for treatment of inhalational anthrax (in combination with appropriate antibacterial medicines) and for prophylaxis when alternative therapies are not available or are not appropriate [5–7]. The latter two products were assessed by FDA according to its 'Animal Rule,' largely relying on efficacy data generated in a relevant animal model [8–10]. In general, the use of mAbs is viewed as an attractive biodefense measure, countering deliberate threats [11]. The technology platform may also offer a rapid protection against newly emerging and reemerging infectious agents when no other treatment or prophylaxis is available. Witness to this, for example, is the ongoing research in mAbs to treat patients with Middle East respiratory syndrome [12]. The

* Corresponding author. E. Pelfrene, European Medicines Agency, 30 Churchill Place, London E14 5EU, UK.
E-mail address: eric.pelfrene@ema.europa.eu (E. Pelfrene).

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experimental use of a tobacco plant–derived mixture of mAbs (ZMapp) during an Ebola virus disease outbreak in western Africa provides an additional example in this respect [13,14].

Interestingly, the paucity of currently licensed mAbs in the infectious diseases arena strongly contrasts with the ready availability of these therapeutics for use in other conditions, mainly oncology and chronic inflammatory or rheumatic afflictions. Indeed, for these disease areas, mAbs globally generate a sizeable yearly income [15]. This narrative review revisits the potential applicability of mAbs in targeting infections and outlines their prospects for successful therapeutic development.

Methods

We undertook a search on Medline Complete regarding trials and reviews for antibody-based therapeutics in infectious diseases. The terms used in different combinations were as follows: 'therapeutic antibodies,' 'monoclonal' and 'infectious diseases,' as well as pathogen-specific terms. The results were limited to English-language reports and surveyed documents published from January 2008 to March 2018. Our methodology was further complemented by published official documents on anti-infective mAbs licensed to date by EU and US regulatory authorities. Some of the trials were identified through a search of the clinical trial registration platform ClinicalTrials.gov.

Main features

Historically, immune sera were used to treat or prevent infectious diseases before the availability of vaccines and antibiotics, with polyclonal sera (hyperimmune sera) still being used against conditions such as rabies, diphtheria, tetanus and botulism [16]. These sera are typically administered when rapid protection is required, following known exposure in an unvaccinated individual (or vaccination is nonexistent) or when previously acquired immunity has waned. As with hyperimmune sera, mAbs can be deployed irrespective of preexisting immune protection status and equally may benefit the immunocompromised host [17,18]. However, they avoid some of the disadvantages attributed to sera derived immunoglobulins, such as potential (exceedingly low) transmission of infectious hazards and batch variability [19].

Over the years, monoclonal antibody engineering has evolved. The first licensed monoclonal antibody, OKT3, indicated to prevent acute kidney transplant rejection, used a murine hybridoma technique [20,21]. Early commercial successes with mAbs were limited, however, by the availability of suitable myeloma cell lines. Also, occurrence of adverse immune reactions, by provoking a human anti-mouse antibody response, is a recognized setback for use of the technique. To limit such unwanted effects whilst also enhancing effector function, chimeric (mouse–human) antibodies first replaced murine hybridomas and more recently humanized (i.e. antibody structure containing less than 10% nonhuman sequences) and fully human mAbs have been developed [19,21]. New expression tools became available, such as phage display libraries, transgenic mice, Chinese hamster ovary (CHO)-based biomanufacturing and highly scalable plant technology, as well as the possibility to produce mAbs using human B cells isolated from subjects in convalescence or after vaccination [22–25].

Thus, current methods have made production more efficient, and importantly, the use of human and humanized mAbs poses fewer safety concerns as opposed to older techniques and serum therapy [19,26]. With exquisite specificity being the hallmark, mAbs generally harbour a low potential for off-target adverse reactions [27], although it makes them vulnerable to escape mutants, potentially rendering this therapeutic measure ineffective [28]. Hence, this drawback justifies the development of mAbs cocktails, with the antibody constituents binding to different epitopes [27,29]. Also, alternative antibody formats have been engineered, simultaneously addressing different targets involved in pathophysiologic processes. As such, bispecific antibodies aim to ensure enhanced potency and breadth of protection [30–32]. Other developments include antigen-binding (Fab) fragments, single chain variable fragments (ScFv) and pairs linked in different ways, as to create formats combining optimal size, half-life, activity and safety [25,33], as well as novel delivery systems such as antibody–antimicrobial conjugates and radioimmunoconjugates [34,35]. Effector functions can be modified: Fc domain changes may enhance the affinity to Fc receptors on phagocytic cells, NK cells and B cells, and hence enforce antibody-dependent killing, whilst mutations leading to increased binding affinity for neonatal Fc receptor (FcRn) contribute to an extended half-life of the antibody [25].

Applicability

In principle, mAbs could target a wide range of biologic agents, encompassing bacterial and viral pathogens, fungi and associated toxins, with their action exerted either directly (e.g. preventing cell entry or neutralizing toxins) or via indirect mechanisms (e.g. modulating inflammatory responses or promoting opsonic phagocytosis) [26,34,36].

Bacterial targets

To date, licensed antibacterial mAbs target exotoxins, with the antigen–antibody complexes primarily removed via the reticuloendothelial system [1,6,7,34]. Instead, mAbs may bind to structural cell surface components (proteins and exopolysaccharides), with subsequent direct bactericidal clearance or immune system dependent cytotoxicity (antibody or complement dependent) [34]. In this regard, the pharmacodynamic mode of action varies amongst the candidate products currently under development [34].

Notwithstanding previous disappointment in translational research [37], activities which target *Staphylococcus aureus* and *Pseudomonas aeruginosa* are the most developed so far (B. François et al., 'Safety and tolerability of a single administration of AR-301, a human monoclonal antibody, in patients with severe pneumonia caused by *Staphylococcus aureus:* first in man trial,' abstract 1992, paper presented at European Congress of Clinical Microbiology and Infectious Diseases 2017) [34,38].

Indeed, in an era of increased awareness and intensified effort to mitigate the antimicrobial resistance threat, mAbs may offer a welcome addition to the therapeutic toolkit [39]. Although unlikely to compete directly with conventional antimicrobials in treating serious bacterial infections, mAbs might act synergistically if both measures are administered concurrently. To date, promising results to that effect have been shown in animal models [40,41]. Further on, antibody administration is expected to provide less selective pressure for cross-resistance and may preserve the gut microflora [34,42]—an important consideration in view of our expanding knowledge on the role of the human gut microbiome in both health and disease [43]. Nevertheless, the success for a wide introduction of mAbs in treating established bacterial infections will be largely dependent on ready and specific pathogen identification. This necessitates further investment and research into validated point-of-care rapid diagnostics (e.g. PCR-based and fluorescence in-situ hybridization technologies), allowing prompt targeted therapy [44].

Also, because the effect of a single dose can last for one to a few months, the use of recombinant antibodies as prophylaxis could

theoretically allow for a decrease in conventional antimicrobial usage. Hence, in recent efforts, clinical development programmes intend to demonstrate that mAbs against bacterial pathogens will protect at risk patients (e.g. prevention of *S. aureus* ventilator-associated pneumonia in colonized, mechanically ventilated patients in the intensive care unit) (ClinicalTrials.gov NCT02940626, NCT02296320) [44].

Viral targets

mAbs may provide a broad neutralizing, potent activity against highly conserved viral epitopes. Alternatively, the antibodies can target receptors and coreceptors located on host cells [19]. With research still in infancy, mAbs which recognize virally infected cells and induce antibody-dependent cytotoxicity may offer an additional mechanism of action [45].

Hitherto, mAbs have been licensed as HIV rescue therapy in adults and as an RSV infection preventive in high-risk children [5,2]. Whilst ibalizumab targets the conformational epitope of the CD4 T-cell receptor, blocking cell entry by HIV-1, other candidates under development, either also target host antigens or alternatively directly bind HIV-1 antigens [46–48]. Research further includes the promise of bispecific and trispecific broadly neutralizing antibodies [31,49]. With regard to RSV, palivizumab interferes with virus attachment and fusion by binding RSV F protein [50]. Presently RSV research is focused on extending the half-life of RSV mAbs, aiming to protect infants throughout their first RSV season with a single dose administration [51].

Other currently studied viral targets include influenza, Ebola and Zika [36]. Recent viral outbreaks have brought a heightened awareness to prepare against emerging infections [36]. For such threats, mAbs could potentially be indicated as treatment of infected individuals and could as well provide targeted prophylaxis for individual protection and transmission interruption (possibly changing the dynamics of a nascent epidemic) [52]. For example, within the context of ongoing product development targeting influenza, for which promising results were obtained in ferret models and early clinical development, broadly neutralizing mAbs might be suitable at the emergence of a pandemic outbreak, at least for specific at-risk groups such as exposed contacts and healthcare professionals [52–54]. In that scenario, they could be used to bridge the time gap before availability of strain-specific vaccines [55].

Replacement of polyclonal antibodies

With a potential to provide a comparably efficacious product, the replacement of currently indicated hyperimmune sera by mAbs deserves to be explored, taking into account feasibility issues related to their clinical development [16]. For example, in the face of periodic outbreaks of diphtheria in various world regions, a global short supply of equine diphtheria antitoxin provides new impetus in developing a suitable monoclonal antibody alternative [56]. So far, though, activities have been most advanced in respect to rabies, for which at least two different products are considered [19]. For one of these, a single human monoclonal antibody (SII-RMAb), a recently completed noninferiority controlled trial concluded it as a potential safe and potent alternative to human rabies immunoglobulin-containing postexposure prophylaxis regimen [57].

Challenges and perspectives

As illustrated by the ongoing efforts, anti-infective mAbs constitute a thriving focus of research, but in order to become a success, multiple challenges need to be overcome.

First, technical barriers remain. For instance, proper selection of bacterial targets remains fraught with uncertainties: highly conserved outer membrane proteins may be masked and hence unavailable for binding with antibodies; conversely, epitopes located on exopolysaccharides are typically not conserved (i.e. different serotypes exist), posing limitations to the effectiveness of a targeting single monoclonal antibody [34]. Moreover, bacterial defence mechanisms developed in response to host immunoglobulins (e.g. production of antibody degrading proteinases) can impede the success of antibody-based therapy. For viral infections, a single lasting treatment is hampered in the face of multiple strains, rapid evolution and selection of escape mutants [36]. In addition, for some pathogens, viraemia often peaks before appearance of symptoms [58,59]. In these circumstances, rapid point-of-care diagnostics may be fundamental to the success of the intervention, allowing prompt therapy initiation in those most at risk of developing serious illness [36,60].

Second, regulatory product approval pathways are not well optimized for emerging threats. Indeed, a small number of patients and unpredictable outbreak dynamics may impede the conduct of confirmatory controlled clinical trials. Also, human challenge studies can provide supportive evidence of protection for only a limited number of conditions [61,62]. In the absence of adequate risk mitigation, such an approach is not expected to be feasible for most of the emerging infections [63,64]. Alternatively, however, for those threats lacking sustained human-to-human transmission, assessment could be based mainly on data obtained from animal challenge studies and on pharmacokinetic/safety evaluation of the product in healthy volunteers, on the condition that animal models can be established that are sufficiently representative of human disease [8,65]. The availability of protocols to test the effectiveness and safety of the therapeutic in the field at the time of an outbreak would then probably constitute a condition to the licensing.

Third, business models and potential markets do vary depending on the disease target, but on the whole, investment and product development are hindered by lack of clarity on how to position the use of mAbs amongst preventive and therapeutic options [27]. Uncertainties remain—for instance, in selecting appropriate trial endpoints and delineating populations best suited to the intervention [16]. Additionally, development is constrained by high investment expenses amidst unsure future returns. Appropriate pricing is considered a prerequisite for market success, and hence increased streamlining, optimization and innovative processes (e.g. Quality-by-Design) may exert downward pressure on costs. Moreover, research into new delivery methods should be expanded and intensified, ensuring convenient administration to a large number of people. This may entail the development of novel intramuscular and inhalation formulations. In this respect, DNA plasmid-delivered mAbs produced by muscle cells *in vivo* are singled out as a potential way to circumvent some of the limitations in immunoglobulin G administration [66]. Next-generation mAbs might offer further opportunities, even allowing a single product to target multiple pathogens [67,68]. From a regulatory viewpoint, tools are available in the European Union to ensure a swift evaluation process and early access to the market, including specific scientific guidance or dedicated advice to companies (Table 1) [69]. In this regard, obtaining and complying with European Medicines Agency's scientific advice has shown to be predictive of regulatory success [70].

Concerning emerging infections, broad stakeholder engagement (with national and international public health agencies, private sector, funding organizations and regulatory authorities) has been advocated. It is argued that this may entail the creation of an independent global agency, as to develop and implement a coherent strategy for global biopreparedness [71].

Table 1
EMA's support scheme for medicine development and early access

Characteristic	Regulatory tool	Key features	Comments
Presubmission phase	SA	Nonbinding advice on quality, nonclinical and clinical aspects of drug development plan	• Scope for parallel EMA/FDA or EMA/HTA SA in some cases. • Tailored SA pilot launched for new biosimilar products; quality issues restricted to comparability between biosimilar and reference product; advice may also include nonclinical and clinical aspects.
	Protocol assistance	SA pertaining to orphan designated drugs	• Orphan drug: medicine for diagnosis, prevention or treatment of a life-threatening or chronically debilitating condition that is rare or where medicine is unlikely to generate sufficient profit to justify research and development costs. • Incentives apply (e.g. fee reductions).
	PRIME	Priority scheme: support for development of medicines of major interest that target unmet medical need	• Continuous support and early interactions with reviewers; SA at key development milestones involving additional stakeholders such as HTA. • Potential for combination with one or several early access tools at time of MAA.
Early access	Accelerated review	Reduced evaluation time frame	• Rapid assessment of medicines that are of major interest for public health, especially ones that are therapeutic innovations (unmet medical need).
	Conditional MAA	Earlier authorization of medicines for patients with unmet medical needs, on basis of less complete clinical data	• Eligibility includes medicines for seriously debilitating or life-threatening diseases, emergency situations, orphan drugs. • Comprehensive data are expected to be generated after authorization within agreed time frame but risk/benefit ratio is clearly positive at time of approval.
	Compassionate use	Benefits seriously ill patients who cannot be treated satisfactorily or cannot enrol in ongoing clinical trials	• Pertains to unauthorized medicinal products for chronically, seriously debilitating or life-threatening diseases, with no satisfactory treatment authorized in EU; targeted at a group of patients rather than individual; or undergoing centralized MAA or clinical trials

EMA, European Medicines Agency; FDA, US Food and Drug Administration; HTA, health technology assessment bodies; MAA, marketing authorization application; SA, scientific advice.

Conclusions

Although research and clinical development of mAbs has intensified, it remains to be proven if a new dawn is on the horizon for this product class to become commonplace in the fight against an array of infections. Inroads have been made so far, as illustrated by the few licensed mAbs against infectious agents or associated toxins. However, for a broader anti-infective potential to be fully exploited, scientific, regulatory and commercial barriers to development need to be addressed. Amongst other initiatives, an early dialogue with regulatory authorities is encouraged to ensure streamlined development and to enable early access for patients.

Transparency declaration

All authors report no conflicts of interest relevant to this article. The views expressed in this article are the personal views of the authors and ought not be understood or quoted as being made on behalf of or reflecting the position of the European Medicines Agency or one of its committees or working parties.

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