Recurring Problems and Mitigation Strategies in the Development of Monoclonal Antibodies Against AMR Pathogens: A Report from the COMBINE Expert Workshop

Linda Marchioro*[1,2], Rakel Arrazuria*[1], Benjamin Hofner[1,2], Bernhard Kerscher[1], Lena E. Friberg[3], Isabelle Bekeredjian-Ding[1,4]

[1] Division of Microbiology, Paul-Ehrlich-Institut, Langen, Germany. [2] Section Biostatistics, Paul-Ehrlich-Institut, Langen, Germany. [3] Department of Pharmacy, Pharmacokinetics and Pharmacodynamics, Uppsala University, Uppsala, Sweden. [4] Institute of Medical Microbiology, Immunology and Parasitology, University Hospital Bonn, Bonn, Germany. * Contributed equally to the work.

Motivation for the workshop

One of the aims of the COMBINE project, part of the IMI AMR Accelerator, is to identify and overcome bottlenecks in the development of medicines against antimicrobial resistant (AMR) infections. The Paul-Ehrlich-Institut, on behalf of COMBINE, hosted a virtual expert workshop to discuss recurring problems and mitigation strategies in the development of monoclonal antibodies (mAbs) against AMR infections (8th and 9th of June, 2022). Twenty-three experts from industry, academia, public health and regulatory bodies shared their opinions.

Summary of expert opinions and discussions

Preclinical development

Different approaches to develop mAbs against AMR bacteria may target the bacteria directly, or target the virulence factors to preserve the immune response to clear the infection.

IgM mAb development targeting bacterial polysaccharides is a promising approach for lung infections, as it allows to decrease the required mAb dose.

Robust ***in vivo* models** are necessary to demonstrate clear therapeutic or prophylactic mAb activity before progressing to the clinical stage.

Inhaled delivery route for bacterial lung infections has a good safety profile and can improve dose delivery efficiency.

Translation

Recurring **challenges** refer to modelling PK exposure at the site of action, different PK in healthy volunteers vs. patients, and different immunogenicity in animals vs. humans.

Potential **solutions** include the application of physiologically-based pharmacokinetic (PBPK) models and the incorporation of inflammation levels, tissue distribution, bacterial growth or other clinically relevant markers.

PBPK models could be improved by including more systematic information, especially in the case of inflammation.

Clinical development

There are key differences in the clinical testing of mAbs to **treat or prevent** AMR infections (e.g. endpoints).

Pragmatic and adaptive **trial designs** may be a way forward, but have their own caveats.

More **sensitive endpoints**, e.g. hierarchical composite endpoints, may mitigate power issues, but need to be clinically interpretable.

Population enrichment strategies have facilitated the conduct of previous trials. The success of the strategy depended on the availability of **rapid diagnostic** tools. How population enrichment would impact indication is controverse and needs further discussions between developers, regulators and practitioners.

Stratification of randomisation at country vs. site level should be reflected carefully, as it impacted the data generation and interpretation in previous trials.

Harmonisation, centralisation and optimisation of the clinical trial infrastructure, e.g. via clinical trial networks, would help to overcome operational challenges and speed up clinical testing.

Further issues: (a) Addressing multiple virulence factors (in a single antibody or in a mAb cocktail) may backfire, particularly in elderly or critically ill populations. (b) Timing of mAb administration during infection is key (the earlier, the better). (c) PK studies should include vulnerable populations to optimise dosing and timing of administration.

Conclusions

The workshop provided an open discussion forum to identify challenges and propose mitigation strategies for future development of mAbs against AMR infections. Recurring issues in drug development, preclinical and clinical testing as well as translation were discussed. A report of the workshop will be published in a peer-reviewed journal. We thank all the experts and workshop participants for their contributions.

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Correspondence: IMI-COMBINE@pei.de

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