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Recent successes in therapeutics for Ebola virus disease: no time for complacency

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The PALM trial in the Democratic Republic of the Congo identified a statistically significant survival benefit for two monoclonal antibody-based therapeutics in the treatment of acute Ebola virus disease; however, substantial gaps remain in improving the outcomes of acute Ebola virus disease and for the survivors. Ongoing efforts are needed to develop more effective strategies, particularly for individuals with severe disease, for prevention and treatment of viral persistence in immune-privileged sites, for optimisation of post-exposure prophylaxis, and to increase therapeutic breadth. As antibody-based approaches are identified and advanced, promising small-molecule antivirals currently in clinical stage development should continue to be evaluated for filovirus diseases, with consideration of their added value in combination approaches with bundled supportive care, their penetration in tissues of interest, the absence of interaction with glycoprotein-based vaccines, and filoviral breadth.

Introduction

The Pamoja Tulinde Maisha (Swahili for together save lives; PALM) study¹ was a randomised, controlled trial (RCT) of three investigational agents (mAb114,^{2,3} REGN-EB3,^{4,5} and remdesivir⁶) compared with a control group that included ZMapp⁷ for the treatment of patients with Ebola virus disease, caused by Ebola virus (Filoviridae: Ebolavirus).⁸ This trial was part of the emergency response to the ongoing Ebola virus disease outbreak in the Democratic Republic of the Congo (DR Congo) that started in August, 2018,⁹ and has included at least 3463 cases and 2280 deaths (as of May 28, 2020).¹⁰ The overall outbreak case fatality rate (CFR; number of deaths per number of infected patients) has steadily approximated 66%, although this number has consistently included large numbers of community deaths—ie, patients with Ebola virus disease who never arrived at the treatment centres.

On Aug 12, 2019, a year after the outbreak was initially declared, the Institut National de la Recherche Biomédicale (DR Congo), WHO, and the US National Institutes of Health announced that an independent data and safety monitoring board reviewed interim data from the PALM study and recommended early termination of the trial on the basis of observed survival benefit in patients treated with either of the investigational agents mAb114 or REGN-EB3. The Board further recommended that all future patients with Ebola virus disease at the study sites should be randomised in an extension phase to receive either mAb114 or REGN-EB3, while terminating the remdesivir experimental and ZMapp control groups.¹¹ The PALM study results, published in 2019, support a statistically significant survival benefit in patients treated with mAb114 or REGN-EB3, with the greatest benefit seen in patients receiving early therapy or those with higher Ebola virus RT-PCR nucleoprotein gene (NP) cycle threshold (CT) values (an inverse proxy for higher Ebola virus load) at admission.¹

The PALM effort represents a landmark achievement in the development of Ebola virus disease medical countermeasures, with the study team conducting a rigorous, well controlled study in a historically difficult outbreak setting, made even more challenging by armed conflict and instability.¹² For the first time since the discovery of Ebola virus in 1976,^{13–15} clinical outcomes of patients with Ebola virus disease arriving at treatment centres in DR Congo were shown to be improved by particular therapeutic agents beyond the likely (but unproven) benefits of optimised supportive patient care (oSOC) alone. In the PALM study control group, the 28-day CFR in patients treated with oSOC plus ZMapp (a mixture of three monoclonal antibodies [mAbs] preventing Ebola virus particle cell entry)⁷ was 50% (84 of 169), which was statistically similar to the 53% (93 of 175)

Key messages

- The PALM randomised controlled trial in the Democratic Republic of the Congo was the first to identify two effective antibody-based therapeutics for Ebola virus disease, but substantial room to improve outcomes remains.
- Combinations of therapeutics, including mechanistically independent antivirals bundled with a high level of supportive care, might improve outcomes in severely ill patients at highest risk of dying.
- Therapeutic penetration into immune-privileged sites might mitigate public health risk and improve clinical sequelae associated with viral persistence in Ebola virus disease survivors.
- Consideration of post-exposure prophylaxis requires understanding of the potential interactions between glycoprotein-based vaccines and therapeutic strategies.
- Anticipation of future filovirus disease outbreaks requires consideration of therapeutic breadth.

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CFR in the group treated with oSOC plus remdesivir (an RNA-directed RNA polymerase-inhibiting nucleoside).^{16,17} ZMapp was chosen as the control on the basis of positive but inconclusive data from the PREVAIL 2 study.¹⁸ However, the 28-day CFR was significantly reduced to 34% (52 of 155) in patients receiving oSOC plus mAb114 (a single mAb preventing Ebola virus particle cell entry)^{2,3} and to 35% (61 of 174) in those receiving oSOC plus REGN-EB3 (a mixture of three mAbs preventing Ebola virus particle cell entry).^{4,5}

Although the overall reduction to a residual 34–35% CFR with the most effective mAb-based therapeutics represents a remarkable step forward, the PALM results suggest substantial room to improve outcomes in acute Ebola virus disease. Additionally, outside the scope of acute disease, broader questions of the role of therapeutic intervention in the human–filoviral interaction still need to be considered. Regarding the filovirus-specific human therapeutic portfolio, key areas for attention are immediately apparent: (1) more effective strategies for individuals with severe disease at highest risk of death, (2) therapeutic penetration and combination therapy to reduce risk of relapse from immune-privileged sites and prevention or treatment of viral persistence, (3) consideration of the interaction between vaccination and therapeutic strategies for post-exposure prophylaxis, and (4) therapeutic breadth. We argue that further development of small-molecule therapies with broad-spectrum activity and unique penetration of immune-privileged sites should continue to be pursued, both to improve current benchmarks and to complement mAb-based therapeutic intervention.

Room for improvement: severe Ebola virus disease

The cautious note from the PALM RCT is perhaps most apparent in outcome data from patients presenting with the highest risk of death—namely, the 40% of study patients who presented at admission with Ebola virus RT-PCR CT *NP* of 22 or less. Although the survival benefits for mAb114 and REGN-EB3 versus ZMapp (and by inference, remdesivir) were maintained in this subset, the absolute CFRs remained unacceptably high (CFR was 70% with mAb114 and 64% with REGN-EB3) even with the most effective therapeutics. The contribution of viral load to risk of death is likely to be a continuous (ie, non-binary) variable; the frequency of poor outcomes is probably even higher in patients presenting with the highest viral loads. In these highest-risk patients, who often also presented late into illness with severe multiorgan dysfunction or failure, further improvement of outcomes will require considerable effort to improve filovirus-specific therapeutics and supportive care approaches. There is an urgent need to develop more effective, efficient strategies than are currently available, including the provision of monitoring and critical care in resource-constrained settings.

Should we be surprised by the relative lack of efficacy in patients presenting late in the course of the disease? All four investigational agents examined in the PALM RCT were evaluated at the US Army Medical Research Institute of Infectious Diseases and its many partners for efficacy in rhesus monkeys (*Macaca mulatta*) exposed to Ebola virus by the intramuscular route, essentially mimicking a needlestick injury. Detailed characterisations of the timing and progression of the disease in this model have shown that many of the key disease signs observed in human patients can be recapitulated, although at an accelerated pace.¹⁹ Preclinical evaluation of therapeutics has been based on the initiation of treatment at the time of virus exposure or shortly after disease signs were observed. No published studies have described the efficacy of treatments initiated at later timepoints to animals with severe disease. Published landmark studies thus far have described the administration of candidate medical countermeasures only as late as 4–5 days after viral exposure.^{2–5,7,16,17} Preclinical studies might, therefore, overestimate the effects of a given agent in patients with advanced disease.

Extrapolation of therapeutic benefit from non-human primate (NHP) models to human disease is a challenge particularly well illustrated by PALM data that shed light on the dramatically different timing of therapeutic intervention in human Ebola virus disease. Notably, study patients with Ebola virus disease did not seek medical help until an average of 5·5 days after the onset of symptoms, often deep into illness and already with multi-organ dysfunction. An addition of this prolonged symptomatic period (5·5 days) onto even a conservative estimate of the typical human incubation period (6–10 days) suggests that clinical intervention (with medical countermeasures or supportive care) are frequently only applied 11–12 days after the likely Ebola virus exposure. This timeframe is in stark contrast to the preclinical NHP benchmark to receive clinical intervention 4–5 days after viral exposure, routinely referred to as a so-called success.¹ This delay might reflect a limitation in the NHP model in assessing drug efficacy in severe disease. Clearly, effective therapeutic strategies for these highest-risk patients are needed that address not only viral replication but also amelioration of systemic inflammatory response and organ failure.

Strategy: bundled combination therapy for acute Ebola virus disease

The PALM results support an important anchoring role for effective mAb-based strategies, prioritising further development and optimisation of current lead clinical and advanced preclinical candidates. These include improving potency (neutralisation and antibody Fc region effector function), drug delivery, and therapeutic half-life in disease states. Potential synergies from combined administration of an mAb-based product with a mechanistically independent small molecule might improve early outcomes as well as subsequent viral clearance from extravascular

tissue compartments in the recovery phase. mAb-based therapies are proposed to exert their antiviral effects by binding and neutralising virus particles present in circulation, thus inhibiting cell entry, and by sequestering viral products such as sGP, a secreted non-structural Ebola virus glycoprotein.²⁰ However, reports of human Ebola virus disease cases in Africa reveal plasma viral RNA concentrations of 10^4 – 10^8 genome equivalents per mL at the time of patient admission into studies.⁹ With such high titres of circulating virus particles, many cells in multiple organs are probably already infected at treatment initiation, and a substantive effect of mAb treatments in infected cells is unlikely. Because small-molecule antivirals could penetrate cellular membranes to inhibit viral replication, administration in combination with mAbs might protect both infected and uninfected cells. Such a combination might help reduce viral titres, clear the virus from immune-privileged sites, and potentially decrease the likelihood of treatment-escape mutants.^{21–24} Anecdotally, the first newborn survivor of perinatal Ebola virus transmission received experimental ZMapp and remdesivir in western Africa (as defined by the UN Geoscheme) in 2016.²⁵

To date, no published studies have described the efficacy of combination mAb and small-molecule treatment regimens in humans or even NHP models. This absence of research is due in part to difficulties in showing synergy in existing NHP models, as well as proprietary barriers to undertaking combination studies. At a minimum, however, proof-of-concept studies showing the non-interference and safety of combining mAb-based and appropriate small molecules are urgently needed to lend first-do-no-harm confidence to clinicians and researchers at the bedside. In addition to lethality, secondary endpoints of interest in both NHPs and humans include the differential effect of combination therapy on viral decay kinetics, development of treatment-emergent resistance, severity of organ dysfunction, seeding of immune-privileged tissues and viral persistence, and downstream clinical sequelae in Ebola virus disease survivors (as mentioned in the following section).

Equally important, although outside the scope of this Personal View, bundled combination approaches to severely ill patients with Ebola virus disease should include further optimisation of supportive care in the field setting. As appropriate antibiotic therapy is necessary but far from sufficient in patients with sepsis related to bacterial infection, the degree of organ dysfunction at admission in the PALM data suggests that effective filovirus-specific therapeutics cannot be uncoupled from requisite supportive care and will require coordinated development in both fields. Indeed, future combinations in selected patients might also include strategies targeting the host response that might mitigate immunopathology without compromising effective immunity; specific immunomodulation and general optimisation of supportive care could open and extend therapeutic

windows both for mAb-based and small-molecule drugs that otherwise appear less effective.

Room for improvement: viral persistence and clinical sequelae in Ebola virus disease survivors

Surviving acute Ebola virus disease by no means guarantees a healthy outcome. The understanding of Ebola virus disease-associated sequelae continues to develop as more careful attention is paid to increasing numbers of Ebola virus disease survivors who have made near-term,²⁶ medium-term,²⁷ and long-term^{28,29} observational studies feasible, building on case reports³⁰ derived from earlier outbreaks, including the 1995 Ebola virus disease outbreak in Zaire (now DR Congo).^{31–33} Survivors have reported a range of sequelae, colloquially referred to as post-Ebola (virus disease) syndrome,³⁴ which manifest as mild, moderate, or severe complications within a few weeks of discharge and which could last for years.^{26–28}

During acute Ebola virus disease, Ebola virus might seed immune-privileged tissues, including the brain, eyes, and testes,³⁵ leading to viral persistence potentially consequential both for the individual survivor—ie, recrudescence organ-specific inflammatory syndromes (eg, meningoencephalitis, uveitis)—as well as for the public—ie, the risk of person-to-person transmission and reignition of outbreaks. Ebola virus RNA has been detected in the cerebrospinal fluid^{36–38} during acute illness,^{36,39} in the weeks shortly after serum Ebola virus clearance,³⁷ and most notably 9 months after discharge in an Ebola virus disease survivor with severe meningoencephalitis.³⁸ More than 2 months after clearance of viraemia and recovery, persistent viable Ebola virus has been detected in the aqueous humour of a survivor with severe sight-threatening unilateral panuveitis.⁴⁰ Ebola virus and Ebola virus RNA is commonly detected in the semen of male survivors in the first 3–6 months after survival,⁴¹ and long-term semen persistence of Ebola virus RNA has been described repeatedly.^{41–43} Although a rare event, sexual transmission of Ebola virus has been proven or strongly suspected eight times, with the first molecular evidence shown in 2016,⁴⁴ and several events leading to multiple generations of transmission and reignition flare-ups at the tail end of outbreak timelines.^{42,44–48} Ebola virus RNA has been detected in the breastmilk of a female survivor 500 days after acute infection, although long-term viral persistence in this fluid has not been convincingly shown.⁴⁹ Undefined at present is the potential for Ebola virus persistence in immune-privileged tissues to cause remote inflammatory sequelae in survivors (eg, generalised fatigue, arthritis, or myalgia syndromes).

The relatively new understanding of clinical sequelae and viral persistence was substantially informed by survivors of the 2013–16 western Africa Ebola virus disease outbreak. In the current and future outbreaks, the number of people with viral sequelae and persistence will increase.

Nearly all of the more than 1000 survivors exiting treatment centres in DR Congo during the ongoing outbreak have received an experimental therapeutic, either under the PALM RCT or via an emergency compassionate use protocol. This proportion is by stark contrast with the 2013–16 Ebola virus disease outbreak, during which far less than 5% of survivors received an Ebola virus-specific therapeutic. The differential class or specific therapeutic effect on viral persistence or clinical sequelae, if any, are unknown, but it should be pointed out that the organ-specific inflammatory meningoencephalitis³⁸ and uveitis⁴⁰ syndromes associated with Ebola virus persistence were described in very ill Ebola virus disease survivors receiving Ebola virus-specific therapeutics and extraordinary advanced levels of supportive care. Whether historical concern about the relationship between a specific therapeutic class (eg, receipt of convalescent plasma and downstream neurological syndromes in patients with Argentinian haemorrhagic fever)^{50,51} and clinical sequelae or viral persistence is relevant here is an important and outstanding question. Concerns about potential Ebola virus disease relapse or recrudescence in DR Congo⁶ highlight the need to understand the human–filovirus–therapeutic relationships, including best approaches to prevent and treat relapse, viral persistence in immune-privileged sites, and associated organ-specific inflammatory or more generalised sequelae.

Strategy: targeting immune-privileged sites in acute Ebola virus disease and survivors

Therapeutics that can access immune-privileged sites at clinically meaningful concentrations are likely to be required to completely clear Ebola virus infection whether during acute Ebola virus disease or after survivors exit treatment centres. Antibodies tend to be limited to the circulatory system. By contrast, nucleoside analogues are designed as prodrugs that foster their distribution to immune-privileged sites through cellular uptake and metabolism into directly acting antiviral drugs targeting intracellular viral replication and transcription.¹⁷ In accordance, studies with remdesivir have shown robust penetration in the brain, eyes, and testes in crab-eating macaques (*Macaca fascicularis*) after a single intravenous dose.¹⁶ Treatment of the recrudescence meningoencephalitis described above with remdesivir and high-dose corticosteroids was followed by clinical recovery and Ebola virus RNA concentration decline and eventual clearance.³⁸ Although a single case is insufficient to find out whether the antiviral altered the clinical course of the disease, the recovery is illustrative of a potential utility of small-molecule therapeutics and the need for further study. A randomised, placebo-controlled clinical trial was initiated in Liberia and Guinea to evaluate Ebola virus RNA clearance from semen by remdesivir;⁵² although results are pending, similar questions are at hand regarding Ebola virus disease survivors in the current and future outbreaks.

Room for improvement: post-exposure prophylaxis in high-risk contacts

Although experimental therapeutics and vaccines have been used occasionally in DR Congo for post-exposure prophylaxis (PEP) after high-risk health-care worker exposures to Ebola virus, increasing attention has focused on the potential use of Ebola virus-specific therapeutics for PEP in non-health-care workers—ie, in the highest risk contacts of newly identified Ebola virus disease cases. Decision-making around this question has been confounded by the fact that these contacts routinely now receive a recombinant vesicular stomatitis Indiana virus vaccine expressing Ebola virus glycoprotein (VSVΔG-ZEBOV-GP; Ervebo; Merck, New Jersey, USA)⁵³ (approved by the US Food and Drug Administration [FDA] and European Medicines Agency) as part of an outbreak-wide ring vaccination strategy, some of whom are essentially receiving the vaccine as PEP. Potential bidirectional interaction between the vaccine (and developing immune responses) and specific therapeutics is unknown. This concern applies especially to mAb-based therapeutics targeting the Ebola virus glycoprotein, which is expressed by rVSVΔG-ZEBOV-GP and Ebola virus. Indeed, uncertainty about any interaction has so far precluded the use of mAb-based therapeutics as PEP in vaccinated high-risk close contacts. However, as long as there is no interaction with the rVSVΔG vaccine vector, effective antivirals might avoid potential interaction around the glycoprotein axis. Indeed, remdesivir is not active against this vector¹⁷ and could plausibly be considered as PEP in just-vaccinated high-risk contacts before the development of active vaccine-induced immunity. Although the vaccine is reported to provide high levels of protection from Ebola virus 10 days or more after vaccination, infection rates match those of unvaccinated control participants at less than 10 days after vaccination.⁵³ Post-exposure antiviral prophylaxis offered by a small molecule might provide immediate protection from clinical disease by reducing the severity or preventing emergence, in addition to augmenting protection provided by vaccination.

Room for improvement: therapeutic breadth

It is important to note that the three mAb treatments tested in the PALM RCT have a narrow therapeutic spectrum and are ineffective against ebolaviruses other than Ebola virus (eg, Bundibugyo, Sudan, and Taï Forest viruses) and the closely related lethal Marburg viruses. By contrast with these mAb treatments, remdesivir has broader-spectrum in vitro activity against the Sudan virus and Marburg virus that cause filovirus disease, as well as paramyxovirids (eg, Hendra virus, Nipah virus, and human parainfluenza virus), pneumovirids (eg, human respiratory syncytial virus), mammarenaviruses (eg, Lassa virus), several flaviviruses,⁵⁴ betacoronaviruses, including severe acute respiratory syndrome-related coronavirus and Middle East respiratory syndrome-related coronavirus,⁵⁵

and deltacoronaviruses.⁵⁶ In vivo, remdesivir protected grivets from Nipah virus disease and death.⁵⁷

It is crucially important to point out that remdesivir is far from unique in its broad-spectrum antiviral activity—several small-molecule antivirals share these properties. Although there are many examples to enumerate, notable compounds include FDA-approved hepatitis drugs, such as ribavirin, with some clinical activity against Lassa fever and Crimean–Congo haemorrhagic fever among others;⁵⁸ and sofosbuvir with activity against dengue⁵⁹ and yellow fever⁶⁰ viruses. Those in clinical development include favipiravir⁶¹ and galidesivir, both with activity against multiple haemorrhagic fever viruses.⁶² In addition to directly acting antivirals, indirect and host-directed therapeutics should also be considered for potential broad-spectrum activity and reduced potential for the development of viral resistance.^{63,64}

Room for improvement: enhanced understanding of antiviral pharmacology

Given existing evidence, small-molecule antivirals might have use as a component of combination therapy for acute Ebola virus disease, in the treatment of post-Ebola virus disease sequelae, and potentially as PEP. However, a greater understanding of the pharmacology of antiviral drugs to treat Ebola virus disease, including remdesivir, is necessary. Pharmacokinetic evaluation of remdesivir has not yet been done in the rhesus monkey model of Ebola virus disease or in Ebola virus-infected humans. In light of substantial hepatic and renal impairment in Ebola virus disease, such analyses could identify alterations in the formation or clearance of the active remdesivir triphosphate form of the drug. This alteration, in turn, might require an in-depth reanalysis of dose and dose schedule that might improve survival in patients treated for Ebola virus disease. Alternatively, novel nucleoside analogues could be developed that have the desired pharmacokinetic properties while maintaining efficacy. The same imperative exists to better understand the pharmacology of other antiviral approaches.

Finally, special consideration should be given to the potential use of weaponised Ebola virus in the form of small-particle aerosols. Crab-eating macaques exposed to Ebola virions via aerosol develop systemic viraemia and die within a similar timeframe to animals exposed by the intramuscular route. Protection against aerosol exposure in this model has not been shown for mAb-based approaches. Remdesivir treatment provided statistically significant survival benefit to animals 4 days after Ebola virus aerosol exposure,⁶⁵ suggesting that small molecules could be pursued as general anti-bioweapon regimens when it could be expected that the virus used for an attack is tailored to escape mAbs in common use. The site of action of small-molecule therapeutics might offer a broader spectrum of antiviral activity^{16,54,56,57,66} and a lower likelihood of escape mutant evolution.

Conclusions

What seemed almost unachievable even 5 years ago—the license of an effective therapeutic for Ebola virus disease—is now within reach given the encouraging results from the PALM trial. However, considerable additional work is needed to optimise Ebola virus disease treatment regimens for existing and future threats. The potential therapeutic breadth, tissue penetration, and absence of interaction with vaccines underscore the importance of continued development of small molecules to define therapeutic roles, along with improvements in supportive care in resource-limited settings.

The 2018–20 outbreak of Ebola virus disease in eastern DR Congo is ongoing, with recent new cases emerging in Nord Kivu just days before the projected end of the outbreak. An independent outbreak of Ebola virus disease was declared on June 1, 2020, in northwest DR Congo in which four of six patients have died. Coincident filoviral outbreaks (potentially colliding with severe acute respiratory syndrome coronavirus 2 and the world's largest measles outbreak) are sobering reminders of the need to improve disease outcomes. There is no time for complacency in the post-PALM landscape.

Contributors

We participate in the US Army Medical Research Institute of Infectious Diseases Filovirus Animal Model Working Group. PLI, CDK, TKW, JHK, KAM, and DLS conceived and co-wrote the manuscript. XZ, RGP, SRR, ACS, FN, AJD, EEZ, MS-L, and IC revised and edited the manuscript. All authors reviewed and approved the manuscript.

Declaration of interests

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