Atoltivimab + maftivimab + odesivimab

Section: 6. Anti-infective medicines > 6.7. Medicines for Ebola virus disease

EMLc | ATC codes: Pending

Indication	Ebola virus disease ICD11 code: 1D60.01
INN	Atoltivimab + maftivimab + odesivimab
Medicine type	Biological agent
List type	Core
Formulations	**Parenteral > General injections > IV:** 241.7 mg + 241.7 mg + 241.7 mg in 14.5 mL vial
EML status history	First added in 2023 (TRS 1049)
Sex	All
Age	Also recommended for children
Therapeutic alternatives	The recommendation is for this specific medicine
Patent information	Main patent is active in several jurisdictions. For more information on specific patents and license status for developing countries visit www.MedsPal.org Read more about patents.
Tags	Biological
Wikipedia	Atoltivimab + maftivimab + odesivimab
DrugBank	Atoltivimab, Maftivimab, Odesivimab

Expert Committee recommendation

The Expert Committee accepted that effective treatments for EVD are of public health relevance, particularly in the context of outbreaks. EVD caused by Zaire ebolavirus is a life-threatening disease with a high case-fatality rate for which early diagnosis and initiation of treatment are essential to reduce mortality. The Committee agreed that although limited, the clinical trial evidence for mAb114 and REGN-EB3 demonstrated important reductions in mortality at 28 days, and that evidence from indirect comparisons of the two therapeutics suggested little or no difference in mortality outcomes between them. The Committee also noted that based on the same evidence presented in the application, the 2022 WHO guidelines on therapeutics for EVD include a strong recommendation for treatment with either of these therapeutics, with the choice of which agent to use depending on availability. The Committee noted with concern that access to these therapeutics is challenging, with no current commercial availability and supply only through expanded access or compassionate use protocols. Furthermore, the price of these agents is unknown and no cost–effectiveness studies have been undertaken. Since late 2021, mAb114 and REGN-EB3 have been included in an expression of interest to manufacturers for WHO prequalification, but to date, no products have been prequalified. Additionally, efforts made by WHO to build a stockpile of the two therapeutics, through requests for quotations from the two manufacturers, have not yet been successful. The Committee requested an update on availability for review in 2025. The Committee considered that inclusion of these therapeutics on the Model Lists represents a strong equity and advocacy message, fully aligned with WHO guidelines, which could contribute to broader actions being undertaken to ensure reliable and affordable access to

quality-assured therapeutics for EVD. The Expert Committee therefore recommended the addition of the monoclonal antibodies mAb114 (ansuvimab-sykl) and REGN-EB3 (atoltivimab + maftivimab + odesivimab-ebgn) to the core list of the EML and EMLc, in a new subsection on medicines for EVD, for the treatment of EVD caused by Zaire ebolavirus in patients (adults and children) with confirmed EVD, and in neonates of unconfirmed infection status aged 7 days or younger, born to mothers with confirmed infection.

Background

Anti-Ebola virus disease monoclonal antibodies have not previously been evaluated for inclusion on the Model Lists.

Public health relevance

Ebola virus disease (EVD) is a life-threatening disease caused by Ebola virus (Zaire ebolavirus). During early EVD, patients present with a non-specific febrile illness, followed by gastrointestinal signs and symptoms that frequently lead to hypovolaemia, metabolic acidosis, hypoglycaemia, and multiorgan failure (1). EVD case fatality is high, with a pooled case fatality rate of 60% (95% confidence interval (CI) 47% to 73%) in outbreaks from 2010 to 2020 (2). In recent years, several outbreaks of EVD have occurred in Africa, including the prolonged 2013–2016 outbreak in West Africa, outbreaks in the Democratic Republic of the Congo (2018–2020, 2020, 2021, 2022), and in Guinea (2021) (3).

Benefits

The PALM study was a randomized, multicentre study of four investigational EVD therapeutics undertaken in the Democratic Republic of the Congo (4). All patients received standard care, which consisted of administration of intravenous fluids, daily clinical laboratory testing, correction of hypoglycaemia and electrolyte imbalances, and administration of broad-spectrum antibiotic agents and antimalarial agents as indicated. Patients were assigned in a 1:1:1:1 ratio to receive intravenous administration of the triple monoclonal antibody 2G4, 4G7, 13C6 (ZMapp; the control group), the antiviral remdesivir, the single mAb114, or the triple monoclonal antibody REGN-EB3. Patients of any age, including pregnant women, were eligible if they had a blood specimen positive for Ebola virus by real-time polymerase-chain-reaction (RT-PCR) assay. Neonates < 7 days of unconfirmed EVD status were also eligible if they were born to a mother with documented EVD. Patients were stratified according to baseline PCR cycle threshold values for the virus (≤ 22 versus > 22), with lower cycle threshold values corresponding to higher viral load. The primary endpoint was 28-day mortality. A total of 681 patients were enrolled from 20 November 2018 to 9 August 2019. An interim analysis of data from 499 patients on 9 August 2019 led to the data and safety monitoring board recommending terminating random assignment to ZMapp and remdesivir on the basis of results showing that the REGN-EB3 group crossed an interim boundary for efficacy with respect to a surrogate endpoint for death at 28 days, and an analysis of mortality that showed clear differences between the mAb114 and REGN-EB3 groups and the ZMapp and remdesivir groups. A total of 673 patients were included in the primary analyses. At 28 days, 290 deaths had occurred (in 18.8% and 76.1% of patients with low and high viral loads, respectively). The difference in 28-day mortality of mAb114 compared with ZMapp was –14.6 percentage points (95% confidence interval (CI) −25.2 to −1.7). The difference in 28-day mortality with REGN-EB3 compared with ZMapp was −17.8 percentage points (95% CI −28.9 to −2.9). From an indirect comparison of mAb114 versus standard care, via ZMapp, informed by data from the PALM (4) and PREVAIL (5) studies, there was moderate-certainty evidence that mAb114 reduced mortality (relative risk (RR) 0.42, 95% CI 0.19 to 0.93). In absolute terms, this represents 229 fewer deaths per 1000 patients (95% CI 320 to 28 fewer) using the lowest baseline risk estimate, and 383 fewer deaths per 1000 patients (95% CI 535 to 46 fewer) using the highest baseline risk estimate (6). From an indirect comparison of REGN-EB3 versus standard care, via ZMapp, informed by data from the PALM (4) and PREVAIL (5) studies, there was moderate-certainty evidence that REGN-EB3 reduced mortality (RR 0.40, 95% CI 0.18 to 0.89). In absolute terms, this represents 237 fewer deaths per 1000 patients (95% CI 324 to 43 fewer) using the lowest baseline risk estimate, and 396 fewer deaths per 1000 patients (95% CI 541 to 73 fewer) using the highest baseline risk estimate (6). A direct comparison of REGN-EB3 versus mAb114 informed by data from

the PALM study (4) showed low-certainty evidence of there being little or no difference between the two treatments for mortality outcomes (RR 0.96, 95% CI 0.71 to 1.29). In absolute terms, this represents 7 fewer deaths per 1000 patients (95% CI 48 fewer to 48 more) using the lowest baseline risk estimate, and 11 fewer deaths per 1000 patients (95% CI 80 fewer to 80 more) using the highest baseline risk estimate (6).

Harms

Adverse events that were reported in >10% of patients in the PALM trial from a predefined list of signs and symptoms that occurred during mAb114 and REGN-EB3 infusion are shown in Table 16 (refer TRS 1049). The adverse event profiles in adult and paediatric participants treated with mAb114 or REGN-EB3 were similar. The evaluation of adverse events in participants may have been confounded by the signs and symptoms of the underlying Zaire ebolavirus infection.

Cost / cost effectiveness

The price of the two therapeutics is currently unknown. No cost–effectiveness studies have been undertaken.

WHO guidelines

The 2022 WHO guideline on therapeutics for Ebola virus disease includes a strong recommendation for treatment with either mAb114 or REGN-EB3 for patients with RT-PCR confirmed EVD and for neonates of unconfirmed EVD status, 7 days old or younger, born to mothers with confirmed EVD. The recommendation applies only to EVD caused by Ebola virus (Zaire ebolavirus) (6).

Availability

Both mAb114 (Ridgeback Pharmaceuticals) and REGN-EB3 (Regeneron) have regulatory approval from the United States Food and Drug Administration (7,8). As of 1 October 2022, no commercial product is available. The two therapeutics are currently used under an expanded access/compassionate use protocol. In 2021, given the evidence of efficacy of the two therapeutics, WHO opened an expression of interest to manufacturers of the therapeutics for product evaluation and prequalification (9). As of March 2023, no therapeutics for EVD have been prequalified by WHO. The International Coordinating Group agreed in October 2021 to build a stockpile of the two therapeutics with 5000 treatments. However, no commercial batches are available. WHO procurement issued a Request for Quotations and invited the two manufacturers to make offers. Ridgeback Pharmaceuticals responded that the company does not have the capacity to produce mAb114 commercially and is in the process of agreeing a commercial partner to produce it, and it is estimated to be on the market in 2024/2025. Regeneron has not yet submitted an offer. The United States government’s Biomedical Advanced Research and Development Authority has an agreement with Regeneron to procure REGN-EB3 for the US National Strategic Stockpile.

1. Jacob ST, Crozier I, Fischer WA, 2nd, Hewlett A, Kraft CS, Vega MA, et al. Ebola virus disease. Nat Rev Dis Primers. 2020;6(1):13.
2. Kawuki J, Musa TH, Yu X. Impact of recurrent outbreaks of Ebola virus disease in Africa: a meta-analysis of case fa tality rates. Public Health. 2021;195:89–97.
3. Ebola virus disease – fact sheet [internet]. Geneva: World Health Organization; 2021 (https://www.who.int/news-r oom/fact-sheets/detail/ebola-virus-disease, accessed 6 October 2023).
4. Mulangu S, Dodd LE, Davey RT, Jr, Tshiani Mbaya O, Proschan M, Mukadi D, et al. A randomized, controlled trial of Ebola virus disease therapeutics. N Engl J Med. 2019;381(24):2293–303.
5. Davey RT, Jr, Dodd L, Proschan MA, Neaton J, Neuhaus Nordwall J, Koopmeiners JS, et al. A randomized, controlled trial of ZMapp for Ebola virus infection. N Engl J Med. 2016;375(15):1448–56.
6. Therapeutics for Ebola virus disease. Geneva: World Health Organization; 2022 (https://apps.who.int/iris/handle/1 0665/361697, accessed 6 October 2023).
7. Prescribing Information. EBANGA (ansuvimab-zykl) injection for intravenous use. Silver Spring, MD: United States Food and Drug Administration; revised 12/2020 (https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/76117 2s000lbl.pdf, accessed 6 October 2023).
8. Prescribing Information. INMAZEB (atoltivimab, maftivimab, and odesivimab-ebgn) injection for intravenous use. Silver Spring, MD: United States Food and Drug Administration; revised 10/2020 (https://www.accessdata.fda.gov/dr ugsatfda_docs/label/2020/761169s000lbl.pdf, accessed 6 October 2023).
9. 1st Invitation to manufacturers of therapeutics against Ebola virus disease to submit an Expression of Interest (E OI) for product evaluation to the WHO Prequalification Unit. Geneva: World Health Organization; 2021 (https://extra

net.who.int/pqweb/sites/default/files/documents/EOI_EbolaVirusDisease_V1_Oct2021.pdf, accessed 6 October 2023)
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