Editorial

A pioneering countermeasure against measles virus

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Submitted Jan 23, 2015. Accepted for publication Feb 06, 2015.
doi: 10.3978/j.issn.2305-5839.2015.02.29
View this article at: http://dx.doi.org/10.3978/j.issn.2305-5839.2015.02.29

Measles virus (MeV) is a morbillivirus from the paramyxoviridae family that causes a highly contagious respiratory disease that generally afflicts young children. MeV infection generally occurs in unvaccinated children and can lead to fever, nasal discharge, a cough, and a distinctive rash all over the body. In addition, approximately one in ten children also gets an ear infection, and 1 in 20 may develop pneumonia. Further, a person with measles is contagious 4 days before the symptoms are apparent, and MeV infection can be fatal or cause neurological complications.

In the last decade, MeV was well on its way to elimination, at least regionally through effective vaccination. MeV has no known non-human reservoir which means that eradication is attainable goal. In 2000, MeV was considered eliminated in the United States; however unvaccinated individuals are still at risk from imported cases of measles. Globally, measles cases fell 73% from 853,480 in 2000 to a historic low of 226,722 in 2012 (1,2). Unfortunately, the subsequent years saw significant increases in MeV cases worldwide, currently MeV outbreaks are raging in parts of the United States, and sadly MeV deaths are not decreasing. Measles cases in the United States reached a 20-year high in 2014 with 644 cases reported in 27 states (89% of which were linked to 23 outbreaks) (3,4). Earlier in 2014, a large MeV outbreak occurred in a largely unvaccinated Amish community in Ohio that resulted in 380 cases, while most recently, 59 measles cases were linked to an amusement park in California over the winter holiday period (5). Like in the Ohio outbreak, 82% of those infected in the California outbreak have not been vaccinated.

Although proven safe and effective, recent years have seen a reduction in MeV vaccine uptake caused by unfounded and perceived side effects such autism purported to be linked to thimerosal which is a mercury-containing organic compound used in vaccine to help prevent contamination with harmful microbes. Interestingly, most childhood vaccines including the measles, mumps, and rubella vaccine (MMR), do not and did not ever contain thimerosal or any preservative. Unfortunately, the number of unvaccinated children has instigated a worldwide problem. Some parents choose to not to have their children immunized for personal or religious reasons, while others are unaware or unable to get MeV vaccination for their children before they arrive in countries that vaccinate for MeV. For example, of the unvaccinated residents of the United States that got measles in 2014, 85% declined vaccination due to the aforementioned religious, philosophical, or personal objections, 6% missed opportunities for vaccination, and 5% were too young to receive vaccination (6). Since MeV is one of the most contagious human pathogens with an R_0 (basic reproduction number) =12-18 (meaning that 12 to 18 new cases can come from a single infection), at least 95% of the population will need to be immune (herd immunity) to prevent an outbreak (7). Apparently, some parents rely on herd immunity to protect their children and refuse to vaccinate. It is clear that this does work effectively and anti-viral drugs targeting MeV may be an option to protect those infected with MeV from getting ill, as well as prevent them from spreading the virus to others. It is still not clear if parents who refuse to vaccinate will accept the use of a novel drug, but to be clear, the drug is only a countermeasure to prevent disease and death, and not a replacement for vaccination.

There were no antiviral drugs to date available for treating MeV infection. Ribavirin, a broad spectrum

antiviral drug currently prescribed for chronic hepatitis C, showed limited efficacy against MeV and had side-effects at efficacious doses that out-weighed any benefit. Only a handful of experimental compounds has been investigated for their specific-activity against MeV, and most targeted MeV RNA-dependent RNA polymerase (RdRp) (8). The encouraging findings from Krumm *et al*. from the Plemper group come at a time when health officials are scrambling to control the MeV outbreaks (9). The Plemper group recently reported a novel anti-morbillivirus drug, ERDRP-0519, which showed a level of efficacy *in vitro* against MeV and the closely related canine distemper virus (CDV). ERDRP-0519 is an orally bioavailable small molecule inhibitor of morbillivirus RdRP. The drug was built upon an earlier generation lead candidate, AS-136a, which was shown by the same group to be highly potent against MeV, but with low oral bioavailability and poor water solubility (10,11). The Plemper group evaluated ERDRP-0519 efficacy *in vivo* in ferrets, a natural host of CDV. CDV causes a related measles-like disease and is typically 100% lethal in ferrets. ERDRP-0519 was administered orally (50 mg/kg) twice daily, either prophylactically (beginning 24 h before infection and continuing for 15.5 days) or therapeutically, starting 3 days post-exposure at the onset of viremia (day 3 pi) in ferrets. Although prophylactic treatment reduced viral load, delayed lymphopenia and prolonged survival by 2 weeks, all animals eventually died. However, ferrets that received the novel drug after intranasal exposure to CDV survived the lethal challenge, showed no clinical signs of disease, and mounted an immune response that protected them against experimental reinfection with CDV. However, ERDP-0519 pharmacokinetics and efficacy for MeV infection in human has yet to be established. Ferrets were used to model drug safety and efficacy because there is no good animal model for testing MeV infection. Furthermore, the Plemper group also evaluated CDV drug resistance. The group identified two hotspots for mutations in the viral L protein (the catalytically active subunit of RdRP) that confer resistance to ERDP-0519. Interestingly, these hotspots are within similar location as those mutations in MeV resistant to an earlier generation RdRP inhibitor (11). However, drug-resistant resistant viruses will likely be clinically insignificant, as no significant gain in fitness or increased in pathogenicity was apparent with ERDP-0519 resistant CDV.

This study showed that the small-molecule viral polymerase inhibitors can bolster immunity against viral infections, and the authors believe that administration of ERDRP-0519 at the onset of viremia could allow time for the host to elicit an efficacious antiviral response. However, when given prophylactically, low level of viremia at early time of infection was perhaps insufficient to induce adequate immune stimulation. This may explain the inability of prophylactic treatment to prevent collapse of immune response despite reduction in virus titer and lymphopenia, resulted in prolonged survival but not rescue from death. Thus, the timing of drug treatment will be crucial. Nevertheless, perhaps drug compounds that work in this way could aid the eradication of MeV by controlling sporadic outbreaks in people or subpopulations with low level of vaccination coverage.

Acknowledgements

Disclosure: The authors declare no conflict of interest.

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Cite this article as: Perwitasari O, Tripp RA. A pioneering countermeasure against measles virus. Ann Transl Med 2015;3(S1):S15. doi: 10.3978/j.issn.2305-5839.2015.02.29

