ST-246 was used as part of the treatment regimen for several clinical cases of orthopoxvirus infection. ST 246 was used for the treatment of a child with eczema vaccinatum.[112] The patient, a 28-month-old male child with a history of eczema and failure to thrive, was exposed to virus through direct contact with a vaccinee. He presented to the emergency room with high fever and severe eczema. Vesicular skin scrapings and viral culture supernatant from vesicles on the child's skin were obtained and determined by PCR to be positive non-variola orthopox virus. The child's condition continued to worsen despite initial treatment with vaccinia immune globulin intravenous (VIG i.v.) and he exhibited progressive metabolic then respiratory acidosis, hypoalbuminemia, hypothermia and hypotension. ST-246 was administered orally *via* a naso-gastric tube. The subject also received one dose of CDV and repeated doses of VIG IV. Clinical signs of the child's improvement were observed within 1 week of the antiviral intervention (ST 246, CDV and VIG IV).

A second case was reported in a 20-year-old male who received the smallpox vaccine and was subsequently diagnosed with acute myeloid leukemia ~12 days after vaccination.[113] Chemotherapy was initiated to treat the leukemia, which caused a severe impairment of immune function, resulting in progressive vaccinia 6–7 weeks after vaccination. He received topical imiquimod (5%) at the vaccination site and VIG IV was administered intermittently throughout the course of treatment. ST-246 was administered at 400 mg once per day for 15 days and increased to 800 mg for 5 days and then 1200 mg for ~2 months. CMX001 was administered at 200 mg ~3.5 weeks after diagnosis or progressive vaccinia and 100 mg every week for 5 weeks. An increase in lymphocyte count correlated with improvement of symptoms and the patient was declared virus free and treatment was discontinued 9 weeks after diagnosis.

4.5 Conclusion

Although smallpox is no longer a disease that affects humans, OPVs continue to circulate in the environment, causing sporadic disease outbreaks in isolated populations. The continued threat of terrorism, coupled with reports of smallpox bioweapons experimentation, provides impetus for the development of new therapeutics that will complement our existing vaccine stocks. Developing two antivirals that work by different mechanisms will increase the genetic barrier to resistance and may be required to prevent disease caused by engineered viruses. Reports in the literature describe the construction of recombinant vaccinia and ectromelia viruses expressing IL-4 that are highly virulent, causing lethal infection in mice that were previously vaccinated against OPV infection.[114] Fortunately, the combined effects of CMX001 and ST-246, which have been shown to be synergistic, could protect mice from lethal infection with these viruses.[115,116] As smallpox fades from our memories, complacency becomes our enemy, making it essential that we continue our efforts to prevent the re-emergence of this devastating disease.