that is intolerant of, or resistant to treatment with standard antivirals. This "salvage therapy" situation may range from asymptomatic infection with lower viral loads to severe end-organ disease and/or extreme viral loads, in those with various degrees of immunosuppression. Only limited data are available from small open label nonrandomized studies, giving the impression of mixed outcomes dependent on risk factors yet to be quantified.

Avery and colleagues (2010) reported a series of six cases of maribavir salvage therapy at 400 mg twice daily involving lung, heart, kidney, intestinal, and stem cell transplant recipients. A total of four of the six had documented ganciclovir-resistant viral infection, and five patients had symptomatic CMV disease, including pneumonitis, enteritis, or retinitis (Avery *et al.*, 2010). Starting viral loads ranged from 7,200 to 1.8 million copies/ml (median 34,600). Treatment duration was 15–376 days (median 207). Four of the patients cleared their plasma CMV DNA within 6 weeks of therapy. The stem cell recipient with pneumonia died at 15 days, despite clearing viral DNA, but disease was stable or resolved in three others. The patient with the highest starting viral load became the first case of genotypic and phenotypic maribavir resistance (Strasfeld *et al.*, 2010) but eventually achieved plasma viral DNA suppression with reduced immunosuppression. Anecdotally, the patient with the most rapid and sustained viral load response was concomitantly receiving sirolimus, which synergizes with maribavir *in vitro* (Chou *et al.*, 2006). Dose adjustment was required for sirolimus as predicted (Pescovitz *et al.*, 2009). No dose-limiting adverse effects were attributed to maribavir.

An open-label program for maribavir salvage therapy in Europe has resulted in some preliminary outcome data being made public. In 12 solid organ (mainly kidney) or stem cell recipients in France, mostly treated with 400 mg twice daily, the viral load response to therapy was considered good in 6 cases and delayed or poor in the rest (Alain *et al.*, 2013). Interpretation of outcome was complicated by the concomitant use of foscarnet in several cases. A more recent update on 22 solid organ and 13 stem cell transplant recipients receiving salvage therapy at 800–1600 mg/day for at least 3 weeks reported a 60% response rate, as defined by a drop in viral load at 3 weeks of > 2 log or to undetectable (Alain *et al.*, 2015). There were 5 resulting cases of genotypic maribavir resistance (14% of the 35 subjects). No clear predictors of treatment failure were reported.

A phase II trial of maribavir salvage therapy in stem cell and solid organ transplant recipients randomized subjects to twice daily doses of 400, 800, and 1200 mg (clinicaltrials.gov identifier NCT01611974, active 2012–2014). Entry criteria included plasma viral DNA > 1000 copies/ml. Therapy in combination with other CMV antivirals was not permitted. Those with severe gastrointestinal disease or expected survival < 6 weeks were excluded. Pending publication of results, it was announced by the sponsor (Shire, 2015) that "approximately two-thirds of patients across the maribavir treatment groups achieved an undetectable plasma CMV DNA (viral load) within 6 weeks." Preliminary data have been posted at clinicaltrials.gov. A new phase III trial of twice daily 400 mg doses as salvage therapy in transplant recipients was initiated at the end of 2016 (clinicaltrials.gov identifier NCT02931539).

7b. EBV infection

The observed *in vitro* antiviral activity of maribavir on EBV replication has not been assessed clinically.

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