Validation of Biomarkers of Intravenously Administered Oncolytic Vaccinia Virus in a Phase I Trial

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Background

Early indicators of viral activity are required to enable the monitoring of viral activity and determination of potential efficacy in the short-term, as an adjunct to traditional long-term monitoring of tumour regression.

In this study, oncolytic vaccinia virus (GL-ONC1) was administered intravenously in a Phase I dose-escalation clinical trial. Observations of viral activity including viral kinetics, gene expression, and antibody response were monitored in serial blood samples. The virus carries transgenes encoding β-glucuronidase, β-galactosidase, and luciferase-GFP proteins.

Results

Fig 1. Viral DNA was detectable in a time- and dose-dependent fashion.

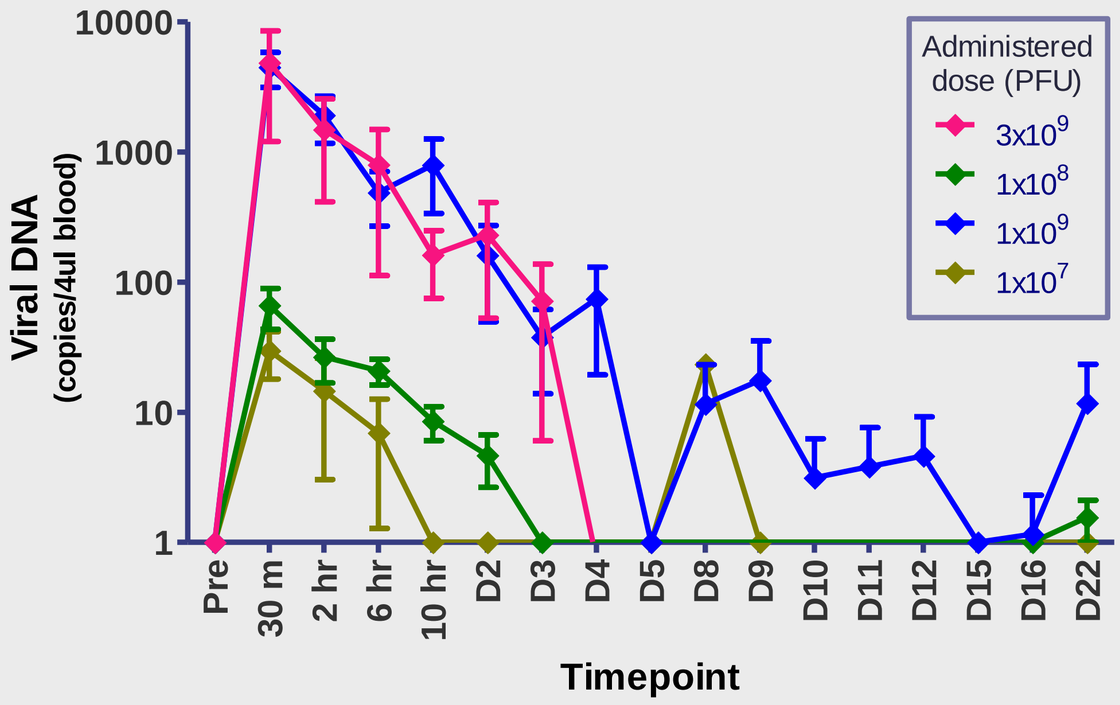


Fig 2. Antibody responses to the virus were slower with doses of $1x10^7$ PFU or lower, but all higher doses caused peak titre within 7 days.

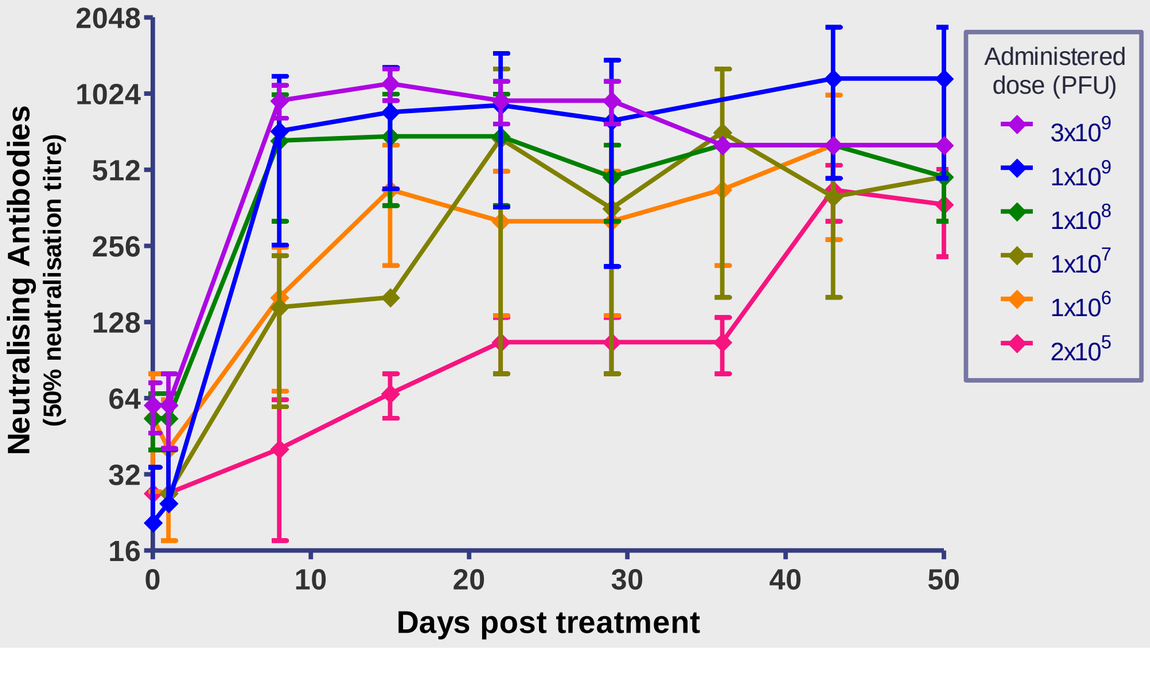


Fig 3. Viral GFP expression enabled non-invasive rapid confirmation of superficial viral infection

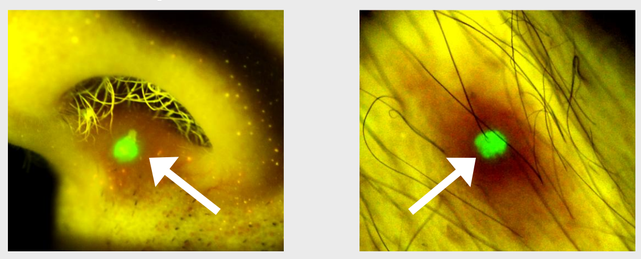


Fig 4. (a) Viral β-glucuronidase was detected at day 7 in patients with confirmed viral shedding. **(b)** C-reactive protein levels peaked at day 2.

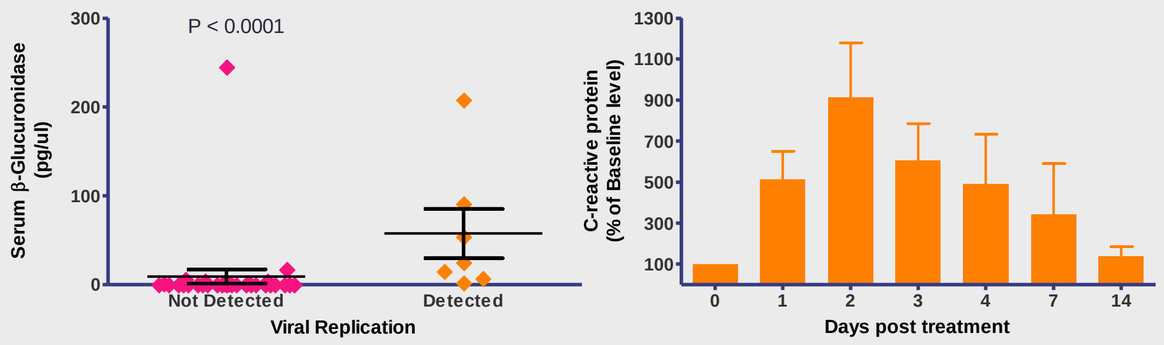
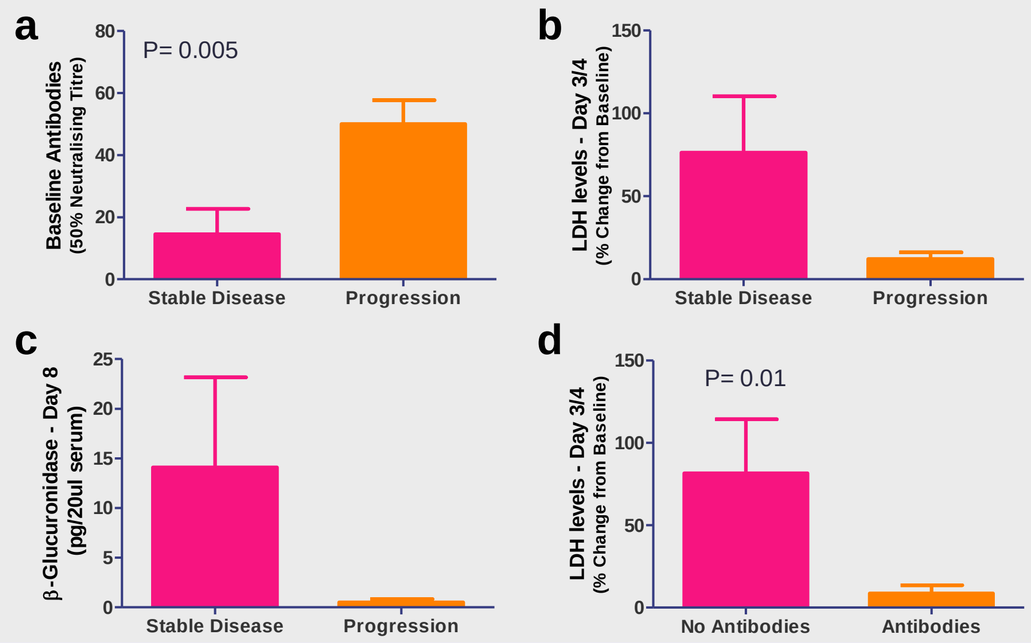


Fig 5. Patients who went on to have stable disease had **(a)** significantly lower antibody titres at the beginning of the study, **(b)** greater lactate dehydrogenase and **(c)** β-glucuronidase levels following treatment. **(d)** LDH response correlated with pre-immune status.



Methods

-Viral DNA was detected by qPCR on DNA of whole blood samples
-Antibodies were detected by serum titration and neutralisation of virus
-GFP was visualised by illumination with blue (395nm) light
-β-glucuronidase was detected by fluorescent enzyme activity assay
-CRP and LDH levels were detected by absorbance assays

Conclusion

Confirmed active infections in patients in this study demonstrated that the biomarkers used were able to detect viral replication. Additionally, pre-immunity to vaccinia virus forecast a poor prognosis.

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