Thesis for the Degree of Doctor of Medicine,
University of Adelaide

Treatment of HIV infection with didanosine and foscarnet

Submitted by

Graeme John Moyle

Chelsea and Westminster Hospital
369 Fulham Road London SW10 9NH UK

October 1995

TABLE OF CONTENTS

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SUBMITTED BY GRAEME JOHN MOYLE

THESIS ABSTRACT

Treatment options for the management of HIV disease are increasing with a range of new antiretovirals as well as drugs for the treatment of and prophylaxis against opportunistic dieases becoming available. This thesis will cover clinical data relating to trials with two antiretroviral agents, didanosine (ddI) and foscarnet, conducted at St Stephen's clinic, London, discussing aspects of their therapetic efficacy, effect on survival, clinical and laboratory tolerability.

Didanosine (ddI) is an orally available purine based nucleoside analogue which, after intracellular triphosphorylation to ddATP, is a potent inhibitor of HIV *in vitro*. Data from phase 2 trials with ddI showed evidence of beneficial effects on surrogate markers such as CD4 cell counts and P24, with the principal dose-limiting toxicity being identified as peripheral neuropathy. This thesis presents data from a phase 3 open-label noncomparative single centre study of ddI in zidovudine-intolerant HIV infected persons with symptomatic disease and provides evidence that ddI is well tolerated in this patient group. Comparison of survival data with an historical database of zidovudine-treated patients suggests that ddI provides at least the same survival as that which would have been provided by continued zidovudine and superior to receiving no further antiretroviral therapy. These conclusions are supported by data from subsequent randomised blinded prospective trials of ddI.

The pyrophosphate analogue Foscarnet (phosphonoformate) is an antiviral agent with *in vitro* activity against both Herpes family viruses and HIV. In clinical practice it has utility as an anti-cytomegalovirus (anti-CMV) agent and in persons with acyclovir-resistant herpes virus. Wider use of Foscarnet has been precluded by the need for intravenous administration and toxicities which include renal dysfunction, disturbance of calcium and magnesium levels and penile ulceration. Data presented in this thesis show that in a randomised open-label comparative study, Foscarnet provides similar efficacy to the estsblished anti-CMV agent ganciclovir both as an initial treatment for CMV retinitis and as a maintainance therapy to prevent further recurrence. Additionally, although Foscarnet was not noted to provide a survival advantage over ganciclovir in this patient group, foscarnet patients were more likely to be able to continue zidovudine, hence gain the survival advantage provided by this therapy. Foscarnet was noted to have a distinctly different toxicity profile to ganciclovir providing the possibilities of both sequencing and combining these agents.