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Prophylaxis against Herpesvirus Infections in Transplant Recipients

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Contents

Abstract

Herpesvirus infections are important after stem cell and organ transplant. During the last decades several antiviral agents have been introduced with efficacy against herpesviruses. These agents are the nucleoside analogues aciclovir, valaciclovir, famciclovir, and ganciclovir; the nucleotide analogue cidofovir; and the pyrophosphate analogue foscarnet. Several studies have been performed with antiviral agents with the aim to reduce morbidity and mortality associated with herpesvirus infections in transplant recipients. Aciclovir and valaciclovir have been examined in randomised, controlled trials in both solid organ and stem cell transplant patients, and were shown to be very effective for the prevention of herpes simplex virus (HSV) and varicella-zoster virus infections. In addition, these drugs were shown to reduce cytomegalovirus (CMV) infection and improve survival in allogenic stem cell transplant patients and to reduce CMV infection, CMV disease (aciclovir and valaciclovir), and acute rejection (valaciclovir) in renal transplant patients. Ganciclovir is very effective for the prevention of CMV infection and disease in both stem cell and solid organ transplant recipients. It can also be used in preemptive strategies in which the aim is to prevent CMV disease in patients who have ongoing CMV infection documented by antigenae-

mia or detection of CMV DNA. The latter strategy has the advantage of reducing the exposure to the drug and thereby the risk for toxicity. Foscarnet has also been shown to be effective as preemptive therapy for CMV in allogenic stem cell transplant patients and as therapy for aciclovir-resistant HSV infections. Finally cidofovir is an interesting agent with broad spectrum antiherpesvirus efficacy. However, because of the drug's toxicity profile, further studies are needed.

Herpesvirus infections are important complications after solid organ and stem cell transplantation. Herpes simplex virus (HSV), varicella-zoster virus (VZV), cytomegalovirus (CMV), and Epstein-Barr virus (EBV) have all been associated with morbidity and mortality in transplant recipients. The roles as pathogens of the recently discovered members of the human herpesvirus family types 6, 7 and 8 (Kaposi's sarcoma herpesvirus) are being investigated. The first preventive measure that proved effective against CMV in transplant recipients was immunoglobulin (not reviewed in this paper). However, during the last 2 decades major advances have been achieved regarding the prevention of herpesvirus infections and disease by antiviral drugs and these are reviewed in this paper.

Currently available drugs with anti-herpesvirus efficacy are aciclovir and the prodrug valaciclovir, penciclovir with the prodrug famciclovir, ganciclovir, cidofovir, and foscarnet. All available drugs, except for foscarnet, require phosphorylation by viral or cellular enzymes to become activated. Of these agents, aciclovir, valaciclovir, ganciclovir and foscarnet have been used in controlled trials for the prevention of herpesvirus disease in transplant recipients. Famciclovir has been used extensively in non-immunocompromised hosts and cidofovir has been used as therapy of CMV retinitis in patients with HIV infection. Since a very large number of studies have been performed with aciclovir and ganciclovir, this review only includes randomised, controlled studies with these agents.

1. Aciclovir and Valaciclovir

The first antiviral drug that was used in large, prospective, randomised trials in transplant patients was aciclovir. Valaciclovir is the valin-ester of aciclovir and is converted to aciclovir in the gut mucosa. Since the active substance is the same, the 2 drugs are covered together in this review. Aciclovir is first phosphorylated to monophosphate by a viral enzyme (thymidine kinase in HSV and VZV and the gene product of UL97 in CMV). The second and third phosphorylations are performed by cellular kinases. The aciclovir triphosphate is then incorporated in viral DNA and acts as an obligate chain terminator.

1.1 Herpes Simplex

HSV disease is common after solid organ and stem cell transplantation. Before the introduction of aciclovir, HSV disease occurred in 70 to 80% of seropositive blood and marrow transplantation recipients. HSV disease is also important in lung and heart/lung transplant patients, whereas it is of less importance in other solid organ transplant recipients.

Several randomised, controlled trials of aciclovir prophylaxis in stem cell transplant (SCT) recipients have been published. The main points that came out of these trials were:

- Aciclovir 5 mg/kg (250 mg/m^2) given intravenously every 8 to 12 hours during the early neutropenic period after allogenic SCT almost entirely eliminated HSV disease.[1-3]
- When aciclovir was given orally instead of intravenously during the early neutropenic phase, breakthroughs of HSV disease were seen, usually caused by poor compliance with oral medication.[4-6]
- HSV disease was common when prophylaxis was discontinued early after transplantation,[1,2,6,7] whereas prolonged therapy was highly effective in reducing clinically important HSV disease.[3,8]

The results of these trials were translated into a

treatment strategy that has remained unchanged for more than a decade in most allogenic SCT centres.

In contrast to the situation in allogenic SCT recipients, only few trials have been performed in solid organ transplant recipients. Two randomised, controlled trials showed high efficacy of aciclovir for the prevention of HSV disease in renal transplant patients.[9,10] Two studies comparing aciclovir-treated groups with untreated historical control groups have been published. Carrier et al.[11] performed a study in heart transplant recipients and Paya et al.[12] in liver transplant patients. Both studies showed less HSV disease in patients receiving aciclovir. In addition, studies with high dose aciclovir with the aim of preventing CMV have been performed in organ transplant patients. No controlled trial of valaciclovir as prophylaxis against HSV has been published in transplant recipients. However, the study by Lowance et al.[13] (reviewed in section 1.3.2) showed that high dose valaciclovir (for CMV prevention) effectively prevented HSV reactivation in renal transplant recipients.

Treatment of HSV disease in immunocompromised patients can select for resistant strains. Although aciclovir has now been in extensive use for more than 15 years, there has only been a moderate increase in the detection rate of aciclovir-resistant strains.[14-16] It has been suggested that prophylaxis is less likely to select for resistant strains than repeated short treatment courses.[17] Foscarnet is the drug of choice for aciclovir-resistant strains.[18] However, there is no indication for HSV-prophylaxis with foscarnet in transplant recipients.

1.2 Varicella-Zoster

Primary VZV infection (varicella) is a very severe complication to both SCT and organ transplant patients. Because of the epidemiological pattern of infection, the risk is highest in children. The recommended prophylactic options are varicella vaccine and varicella zoster immunoglobulin. There are no published data regarding antiviral chemoprophylaxis after exposure to VZV.

Reactivated VZV infections (herpes zoster; shingles) are common after both autologous and allogenic SCT, and can occur in solid organ transplant recipients. In contrast to HSV, which reactivates rapidly with disease occurring during the first few weeks after transplantation, the peak risk of herpes zoster is between 3 and 6 months after transplantation. Thus, the duration of antiviral prophylaxis must be long to prevent reactivated VZV disease. Two randomised, controlled studies have been performed comparing 6 months of prophylactic aciclovir with placebo.[3,19] Both studies showed that aciclovir was effective in reducing the risk for herpes zoster during the 6 months of therapy, but 12 months after transplantation there was no longer any difference. Thus, there is no obvious advantage of aciclovir as prophylaxis against reactivated VZV disease in allogenic SCT recipients although it could be argued that it might be beneficial to postpone the reactivation to a time when the patients are less immunosuppressed and therefore less likely to develop severe complications. However, this assumption has not been proven.

Valaciclovir has not been studied for VZV prophylaxis, but there were no cases of VZV disease in the valaciclovir arm in the study by Lowance et al.,[13] when valaciclovir was given as CMV prophylaxis.

1.3 Cytomegalovirus (CMV)

Aciclovir has only limited activity against CMV when tested *in vitro* and it was debated for a long period whether it could be phosphorylated into active triphosphate in CMV-infected cells. However, it has now been shown that a CMV enzyme UL97 is capable of the first critical phosphorylation step to monophosphate.[20,21] The first publication indicating an activity of aciclovir against CMV in allogenic SCT patients was by Gluckman et al.[5] In this study, a low dose of aciclovir 200mg 4 times daily was shown to reduce the risk for CMV disease. This observation has never been confirmed. Because of the poor *in vitro* activity of aciclovir, other studies investigated the efficacy of higher dosages. Meyers et al.[22] compared the risk for CMV disease in 2 patient cohorts stratified by HSV serologic status. Patients who were HSV seropos-

Table I. Randomised trials of the use of aciclovir (ACV) as prophylaxis for cytomegalovirus (CMV).

Reference	Design	Aciclovir dosage (mg/day)	Patient population	Number of patients	Results
Balfour et al.[25]	Randomised, double-blind, placebo-controlled	800-3200	Renal transplant patients	104	ACV reduced CMV disease. Best effect in D+/R–
Rostaing et al.[26]	Randomised ACV *vs* ACV + CMV Ig	3200	Renal transplant (D+/R–) patients	28	No difference in viraemia or CMV disease
Kletzmayr et al.[27]	Randomised open study	800-3200 for 12 weeks	Renal transplant (D+/R–) patients	32	No difference in CMV disease
Gavalda et al.[28]	Randomised, open study	2000 for 16 weeks	Liver transplant (R+) patients	73	ACV reduced CMV disease

D+ = donor positive; **Ig** = immunoglobulin; **R–** = recipient negative.

itive were given aciclovir 500 mg/m^2 3 times daily from 5 days before to 30 days after allogenic SCT, while patients who were HSV seronegative received no therapy. The results of this study were that aciclovir reduced the risks for CMV infection, CMV disease, and improved survival compared with no therapy. However, the study by Meyers et al.[22] was not a randomised, controlled study and it could be argued that some selection bias might have influenced the results. Therefore, a large randomised, controlled study was performed by Prentice et al.[23,24] This study had 3 arms:

- Aciclovir 500 mg/m^2 3 times daily from 5 days before to 30 days after allogenic SCT followed by oral aciclovir 800mg 4 times daily for 6 months.
- Aciclovir 500 mg/m^2 3 times daily from 5 days before to 30 days after allogenic SCT followed by placebo.
- Aciclovir 200 to 400mg 4 times daily for 1 month followed by placebo.

The study showed that CMV viraemia was delayed and survival improved in the arm receiving intravenous followed by oral aciclovir while the risk for CMV disease was the same compared with the low dose aciclovir/placebo arm. Thus, these 2 studies clearly showed that high dose aciclovir has some effectiveness as prevention of CMV infection and has an effect on survival in allogenic SCT recipients.

1.3.1 Solid Organ Transplant

Aciclovir as prophylaxis against CMV has been tested in several controlled trials in organ transplant patients. The studies comparing aciclovir with ganciclovir are reviewed in section 3.

One problem with most randomised studies comparing aciclovir with either placebo or immunoglobulin is the low number of patients. A summary of the results of these studies is presented in table I and shows an effect of aciclovir in reducing CMV disease in organ transplant recipients.

1.3.2 Valaciclovir as CMV Prophylaxis

Based on the results with aciclovir, valaciclovir has been studied as CMV prophylaxis both in solid organ and allogenic SCT recipients. Lowance et al.[13] compared valaciclovir 2000mg 4 times daily with placebo in a randomised controlled trial in renal transplant patients. 616 patients were included in the study approximately two-thirds R+ and one-third D+/R. Similarly to previously published results with aciclovir, valaciclovir reduced the risk for CMV disease in high risk D+/R patients (3 *vs* 45% at 90 days after transplantation). The risk was also lower in R+ patients (0 *vs* 6%). The most interesting finding, however, was that the risk for acute rejection was significantly reduced (26 *vs* 52%) in the D+/R group supporting previous findings that CMV has a role in the pathogenesis of acute rejection.

Recently, a randomised, controlled study has been performed comparing intravenous aciclovir followed by valaciclovir with intravenous aciclovir followed by oral aciclovir. The study has only been reported in abstract form, but the results show an additional reduction of CMV infection and virae-

mia, reduction of the need for pre-emptive therapy, but no difference in survival in patients treated with valaciclovir compared with aciclovir.[29] The results of these studies imply that aciclovir can be safely used as an anti-CMV agent but that aciclovir prophylaxis must be combined with a strategy of pre-emptive therapy based on antigenaemia or polymerase chain reaction (PCR) [see section 3.1].[30]

1.4 Epstein-Barr

EBV is important as the cause of lymphoproliferative disease (PTLD) in SCT and organ transplant patients. Aciclovir has some efficacy against EBV *in vitro* and in patients with infectious mononucleosis.[31-33] No controlled study has been performed with the aim to prevent EBV PTLD. However, a few uncontrolled studies have suggested some effect with high dose aciclovir with or without a combination with pre-emptively given ganciclovir for the reduction of risk for EBV PTLD.[34-36]

2. Penciclovir and Famciclovir

Penciclovir is a nucleoside analogue that is effective against HSV and VZV. It is not absorbed and can therefore only be given intravenously. Famciclovir is a prodrug of penciclovir and can be given orally. Considering the results in immune competent individuals, it is likely that penciclovir and famciclovir would also be effective against HSV and VZV in transplant patients. However, no study with penciclovir or famciclovir as prophylaxis against HSV and VZV has been published in this setting.

3. Ganciclovir

Ganciclovir is a nucleoside analogue that *in vitro* is effective against CMV, HSV, VZV, EBV and human herpes virus type 6. However, controlled trials have only been performed with ganciclovir given for prevention of CMV. Ganciclovir can be given both intravenously and orally. In transplant patients, 2 different strategies for CMV prevention can be used either prevention of infection (prophylaxis) or prevention of disease after CMV infection has been detected (pre-emptive therapy).

3.1 Stem Cell Transplant Recipients

Ganciclovir's main adverse effect is bone marrow suppression. Therefore, ganciclovir cannot be given to SCT patients during the immediate post-transplant phase when the patients are aplastic because of the preparatory regimen, but must be started after marrow engraftment has occurred. Two randomised, placebo-controlled trials have been performed in SCT patients.[37,38] The designs of the studies were slightly different but the results of the 2 studies were similar with ganciclovir reducing CMV infection in both. In the study by Goodrich et al.,[37] ganciclovir reduced the risk for CMV disease, while in the study by Winston et al.[38] there was a trend in favour of ganciclovir. Neither study showed any difference in mortality, and in both studies, ganciclovir induced neutropenia. Thus, ganciclovir given at engraftment is an effective strategy for the prevention of CMV infection during the time the prophylaxis is given.

When ganciclovir is given at engraftment and continued for several weeks, a particular problem in SCT patients is the increased risk for CMV disease because of poor CMV-specific immune reconstitution.[39] An alternative strategy is therefore not to give ganciclovir until a CMV infection is detected, i.e. pre-emptive therapy. This strategy has been tested in randomised controlled trials. Goodrich et al.[40] studied the effect of ganciclovir given after detection of CMV by rapid virus isolation from any site and showed that ganciclovir reduced the risk for CMV disease both during ganciclovir therapy and after discontinuation of the drug. Schmidt et al.[41] compared ganciclovir with no therapy when CMV was detected from bronchoalveolar lavage and showed a reduction in the rate of CMV pneumonia. During the last decade, new more rapid diagnostic tests for CMV such as antigenaemia and PCR have been introduced. Einsele et al.[42] showed in a randomised study that pre-emptive therapy based on CMV diagnosed by PCR

was more effective than when based on rapid isolation.

Today both strategies are widely used in SCT patients. Boeckh et al.[43] compared pre-emptive therapy with ganciclovir prophylaxis started at engraftment. This study showed that the risk for CMV disease at 100 days was significantly lower in the ganciclovir at engraftment group, whereas there was no difference at 180 days because of an increased risk for late CMV disease in the group treated at engraftment. An advantage with pre-emptive therapy is that fewer patients are exposed to the toxic adverse effects of ganciclovir, in particular, the bone marrow suppression. Salzberger et al.[44] showed that neutropenia ($<1.0 \times 10^9$/L) developed in 41% of patients receiving ganciclovir at engraftment and that ganciclovir-induced neutropenia was an independent risk factor for mortality.

Oral ganciclovir has only been studied in SCT patients in a small phase I/II trial.[45] Gastrointestinal adverse effects requiring drug discontinuation were common. However, the antiviral efficacy must be assessed in a randomised controlled trial.

3.2 Solid Organ Transplant Recipients

Several studies have been performed with ganciclovir in solid organ transplant patients. Table II shows a summary of studies in which ganciclovir has been given as prophylaxis against CMV infection.

The studies have different designs comparing ganciclovir with either placebo or high dose aciclovir. Most placebo-controlled studies showed that ganciclovir reduced the risk for both CMV infection and disease. Ganciclovir also reduced the risk for CMV infection and disease compared with aciclovir in most studies. This was also the case in a study of oral ganciclovir.[47]

In a randomised trial, Hertz et al.[54] compared daily versus prophylactic ganciclovir given 3 days per week in heart and heart-lung transplant recipients. This study showed a slight survival difference in the daily ganciclovir arm. However, there was no difference in the risks for CMV infection or disease between the 2 study arms.

Singh et al.[55] compared high dose aciclovir with pre-emptive ganciclovir therapy based on surveillance cultures in liver transplant patients. Pre-emptive ganciclovir reduced the risk for CMV disease to 4% compared with 29% in the aciclovir group ($p < 0.05$).

4. Foscarnet

Foscarnet is a pyrophosphate analogue that has been available for more than 15 years. Although it has a broad antiviral activity against most herpesviruses, it has been used as a prophylactic agent only against CMV in SCT recipients.

4.1 Prevention of Infection

Only 1 very small randomised, controlled study has been performed with foscarnet in SCT patients.[56] This study was interrupted prematurely because of CMV disease in the foscarnet arm. There have also been 2 uncontrolled dose-finding studies performed.[57,58] Although both studies showed a low risk for CMV reactivation, no conclusions regarding efficacy can be drawn because of the uncontrolled nature of these studies.

4.2 Prevention of Disease

In a small randomised study (39 patients), Moretti et al.[59] compared ganciclovir and foscarnet as pre-emptive therapy in SCT patients. There was no difference in the risk for CMV disease, although there was a tendency for foscarnet to be more effective in clearing the CMV antigenaemia ($p = 0.06$). Recently, a larger randomised study that included 213 patients was performed by the Infectious Diseases Working Party of the European Group for Blood and Marrow Transplantation (EBMT). This study was presented only in abstract form at the 39th Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC) in 1999. There was no difference in the risk for CMV disease and the drugs were equally effective in controlling CMV infection.

No study with foscarnet has been performed in solid organ transplant recipients.

Table II. Randomised trials of ganciclovir (GCV) prophylaxis in solid organ transplant patients

Reference	Design	Dosage	Patient population	No. of patients	Results
Flechner et al.[46]	Randomised, ACV *vs* oral GCV	ACV 3200 mg/day GCV 3000 mg/day	High risk renal transplant patients	101	GCV reduced both CMV infection and disease compared with ACV in D+/R– and D+/R+ No difference in D–/R+
Green et al.[36]	Randomised study comparing IV GCV for 14 days followed by ACV for 50 weeks *vs* IV GCV for 14 days	GCV 10 mg/kg/day ACV 3200 mg/day	Liver transplanted children	48	No added effect of ACV to GCV
Gane et al.[47]	Randomised, placebo-controlled study of oral GCV	GCV 3000 mg/day	Liver transplant patients	304	Oral GCV reduced CMV infection and disease
Winston et al.[48]	Randomised, ACV *vs* IV GCV	ACV 30 mg/kg/day IV followed by 3200 mg/day orally. GCV 6 mg/kg IV 5 days/week	Liver transplant patients	250	GCV reduced CMV infection and disease compared with ACV
Macdonald et al.[49]	Randomised, placebo-controlled study	GCV 5 mg/kg IV × 3 weekly	Heart transplant patients	56	GCV reduced CMV disease in D+/R– patients. No effect in D?/R+ patients
Martin et al.[50]	Randomised study comparing oral ACV *vs* IV GCV followed by oral ACV	ACV 3200 mg/day GCV 10 mg/day	Liver transplant patients	143	GCV followed by ACV reduced the risk for CMV infection and CMV disease compared with ACV
Duncan et al.[51]	Randomised study comparing IV GCV *vs* oral ACV followed induction with IV GCV	GCV 5 mg/kg/day 5 days/week ACV 3200 mg/day	Lung transplant patients	25	Early reduction of CMV disease and obliterative bronchiolitis in the GCV group; no difference after 24 months
Dunn et al.[52]	Randomised study comparing ACV given for 12 weeks *vs* GCV for 7 days together with immune globulin	GCV 10 mg/kg/day ACV 3200 mg/day orally or 1600 mg/day IV	Liver or renal transplant patients	311	ACV reduced CMV disease compared with GCV
Merigan et al.[53]	Randomised, placebo-controlled study of IV GCV	GCV 10 mg/kg IV for 14 days followed by 6 mg/kg 5 days/week for 14 days	Heart transplant patients	112	GCV reduced CMV disease in R+ patients. No effect in R– patients

ACV = aciclovir; **CMV** = cytomegalovirus; **D+** = donor positive; **R–** = recipient negative.

5. Cidofovir

Cidofovir is a nucleotide analogue with a broad antiviral spectrum including most herpesviruses and adenovirus. Although its pharmacokinetic profile that allows once weekly administration is attractive, no study of cidofovir as a prophylactic agent has been performed in transplant patients. The main reason for the lack of studies is the toxicity profile with a reported 25% risk for nephrotoxicity in patients with HIV infection treated for CMV retinitis.[60-62]

Recently, the Infectious Diseases Working Party of the EBMT presented data regarding the pre-emptive use of cidofovir against CMV. The results showed a 66% success rate when cidofovir was given as a second-line pre-emptive therapy after failure of either ganciclovir or foscarnet.[63] Approximately 20% of the patients developed some signs of renal toxicity indicating that this drug should be used with caution in allogenic SCT patients, in particular patients receiving therapy with other nephrotoxic agents.

6. Conclusions

Several antiviral drugs are available today for the prevention of herpesvirus infections and disease in transplant patients. Aciclovir and valaciclovir are indicated for the prevention of HSV and VZV infections. These drugs can also be considered for the prevention of CMV infection and disease in transplant patients. However, in patients at high risk for CMV disease such as allogenic SCT patients, the prophylactic use of aciclovir and valaciclovir should be combined with the strategy of pre-emptive therapy with either ganciclovir or foscarnet. Ganciclovir can be used either for the prevention of CMV infection (prophylaxis) or for the prevention of CMV disease (pre-emptive therapy). Foscarnet can be used as pre-emptive therapy for CMV in particular in allogenic SCT patients. Despite these advances achieved with the introduction of antiviral agents against herpesviruses during the last decades, there is a need for additional antiviral agents that can be given orally with a low risk for toxicity.

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