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Current Pharmacological Approaches to the Therapy of Varicella Zoster Virus Infections

A Guide to Treatment

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Abstract

Varicella zoster virus (VZV), a member of the herpesvirus family, is responsible for both primary (varicella, chickenpox) as well as reactivation (zoster, shingles) infections. In immunocompetent patients, the course of varicella is generally benign. For varicella zoster, post-herpetic neuralgia is the most common complication. In immunocompromised patients (particularly those with AIDS), transplant recipients and cancer patients, VZV infections can be life-threatening. For these patients and also for immunocompetent patients at risk such as pregnant women or premature infants, the current treatment of choice is based on either intravenous or oral aciclovir (acyclovir).

The low oral bioavailability of aciclovir, as well as the emergence of drug-resistant virus strains, have stimulated efforts towards the development of new

compounds for the treatment of individuals with VZV infections. Among these new compounds, penciclovir, its oral prodrug form famciclovir and the oral prodrug form of aciclovir (valaciclovir), rank among the most promising. As with aciclovir itself, all of these drugs are dependent on the virus-encoded thymidine kinase (TK) for their intracellular activation (phosphorylation), and, upon conversion to their triphosphate form, they act as inhibitors/alternative substrate of the viral DNA polymerase. Therefore, cross-resistance to these drugs may be expected for those virus mutants that are TK-deficient and thus resistant to aciclovir. Other classes of nucleoside analogues dependent for their phosphorylation on the viral TK that have been pursued for the treatment of VZV infections include sorivudine, brivudine, fialuridine, fiacitabine and netivudine. Among oxetanocins, which are partially dependent on viral TK, lobucavir is now under clinical evaluation. Foscarnet, which does not require any previous metabolism to interact with the viral DNA polymerase, is used in the clinic when TK-deficient VZV mutants emerge during aciclovir treatment. TK-deficient mutants are also sensitive to the acyclic nucleoside phosphonates (i.e. [s]-1-[3-hydroxy-2-phosphonylmethoxypropyl]cytosine; HPMPC); these agents do not depend on the virus-encoded TK for their phosphorylation but depend on cellular enzymes for conversion to their diphosphoryl derivatives which then inhibit viral DNA synthesis.

Vaccination for VZV has now come of age. It is recommended for healthy children, patients with leukaemia, and patients receiving immunosuppressive therapy or those with chronic diseases. The protection induced by the vaccine seems, to some extent, to include zoster and associated neuralgia. Passive immuniatin based on specific immunoglobulins does not effectively prevent VZV infection and is therefore restricted to high risk individuals (i.e. immunocompromised children and pregnant women).

1. Clinical Presentation of Varicella Zoster Virus (VZV) Disease

Varicella zoster virus (VZV) is a member of the herpesvirus family. It is responsible for a primary disease (varicella or chickenpox) as well as recurrent disease (zoster or shingles) following reactivation of the virus in one or more dorsal root ganglia. Mostly, the rash due to varicella infections is a typical feature of the disease and the course of the illness is generally benign, with a low grade fever persisting as long as new lesions continue to appear. The most marked symptom of these infections is pruritus which can last throughout the different stages of the disease. The most frequent complication of varicella infections in the normal host is bacterial superinfection of the skin lesions.[1-4]

Varicella pneumonia is the most common serious complication in adults. It is rarely seen in children. The incidence of varicella pneumonia has varied in different studies from 4.5 up to 50%.[5-7] Symptoms are often more severe than the physical examination would suggest and 70% of cases of varicella pneumonia have occurred within the first 3 days of illness. Mortality has ranged from 10 to 40%[6,8] and fatal cases have been mostly associated with widespread haematogenous dissemination. Fatalities have also occurred due to one single organ failure.[9] Pregnant women are at greater risk of VZV pneumonia than other adults.[7,10-13] More atypical presentations, such as rhabdomyolysis, have also been associated with acute varicella infection.[14]

The congenital varicella syndrome was thought to occur after maternal VZV infection only in the first trimester of pregnancy, but current information indicates that the period of risk appears to extend to the first half of pregnancy.[15] If infections

occur later in pregnancy, malformations are less extensive, sometimes involving only peripheral scars.

About 1 to 5% of pregnancies exposed early in the gestation to VZV will lead to a congenital varicella syndrome.[13,16,17] The clinical features of the syndrome include scarring of the skin, hypoplasia of the limbs, muscular atrophy, rudimentary digits, cortical atrophy, psychomotoric retardation, chorioretinitis, microcephaly and cataracts. Defects involving the brain and the eye are similar to those seen in congenital infections caused by the rubella virus and cytomegalovirus (CMV) but the other features are quite different. Scars of the skin, usually cicatricial lesions in a dermatomal distribution are a unique feature of the varicella syndrome and indicate that VZV is dermatotropic, even *in utero*.

While similar fetal abnormalities may follow maternal herpes zoster infection, the congenital syndrome attributable to herpes zoster is exceedingly rare.[18,19] Therefore, it seems that the fetus is in much greater danger following primary than recurrent maternal infection, as is also the case for herpes simplex virus (HSV) or CMV infections. Neonatal varicella is seen in infants without sufficient maternal antibodies who have been contaminated just before or soon after birth. The disease is often widely disseminated with pneumonitis and visceral involvement,[20] and the fatality rate can exceed 30%.[21]

As a neurotropic virus, VZV has also caused encephalitis, most often in children; this is the second most frequent indication for hospitalisations due to varicella infections, after secondary infections.[22] Other neurological complications include Reye's syndrome, transient neurological signs, aseptic meningitis, transverse myelitis, polyneuritis and Guillain-Barré syndrome. The severity of VZV infections in cancer patients, particularly those with haematopoietic or reticuloendothelial malignancies undergoing cytotoxic and/or radiation therapy, is now well demonstrated.[1,2,23-25]

Herpes zoster is common in bone marrow transplant (BMT) patients. The median time of occurrence is 4 to 5 months after transplantation, with almost all cases occurring in the first year. An overall mortality rate of 5 to 10% has been observed among patients not receiving antiviral treatment, death being the result of progressive disease dissemination with pneumonia. The mortality rate is nearly 30% in patients presenting with disseminated rash without dermatomal localisation.[26,27] In adult patients undergoing autologous BMT for Hodgkin's disease, prior history of varicella is often associated with the development of herpes zoster in the first 150 days after transplantation.[28]

VZV infections in patients with HIV may be more prolonged or severe, and their clinical presentation is often unusual. Multidermatomal involvement and hyperkeratotic skin lesions seem to occur specifically in immunocompromised patients. Coalescence of single lesions, haemorrhagic bullae, extensive ulceration with epidermal necrosis and black eschars have also been observed. Isolation of the virus from these lesions has proved difficult.[29-34] VZV infections are also a frequent cause of morbidity and hospitalisation for HIV-1–infected children.[35]

Herpes zoster occurs in individuals previously infected with VZV. After initial infection, VZV establishes and maintains latency within the dorsal root ganglia until a stimulus leads to its reactivation. Immune senescence, characterised by the decline in T cells specific for certain microbial antigens with age, is mostly responsible for the increased incidence of zoster in persons over 45 years of age.[36] The complications of herpes zoster are essentially neurological, and postherpetic neuralgia is the greatest cause of acute and chronic morbidity associated with herpes zoster, particularly in the elderly. Other neurological complications include motor neuropathy, particularly in patients with zoster ophthalmicus.[37] Symptomatic meningoencephalitis and myelitis are rare, despite pleocytosis in about 40% of the cerebrospinal fluid (CSF) samples tested. Nevertheless, in some series of encephalitis without Guillain-Barré syndrome, elevated CSF lymphocyte counts and protein levels were observed in all cases.[38]

VZV is almost never recovered from the CNS during the acute phase, which tends to support an immunologic pathogenesis.[39-41] CNS diseases attributed to VZV in immunocompromised patients can appear without skin rash.[42-48] Recently, several authors reported zoster myelitis in both HIV-infected[49-51] and nonimmunocompromised[51] patients. In patients with AIDS, VZV is often associated with acute retinal necrosis, a disease with severe prognosis.[52,53]

2. Prevention of VZV Infections

Prevention of varicella infections is mostly reserved for immunocompromised patients and is based on both passive and active immunisation. Patients at risk of contracting severe forms of varicella (who are therefore candidates for a prophylactic action) include patients with leukaemia or Hodgkin's disease or other diseases of the lymphoreticular system, patients with cancer treated with immunosuppressive drugs and BMT patients, irrespective of their own or the donor's serological VZV status. Also, patients with diseases requiring high doses of systemic corticosteroids for a long period, children of mothers who contracted varicella during pregnancy or premature infants of mothers without a history of varicella have to be considered as being at greater risk for the development of a severe varicella infection.

2.1 Passive Immunisation

Passive immunisation is based on the use of human immunoglobulin preparations with high titres of antibody to VZV which are obtained from patients recovering from varicella zoster infections. Specific VZV immune globulins should be given preferably not longer than 96 hours after contact with either varicella or herpes zoster. Nevertheless, most of the studies concluded that specific immune globulins do not effectively prevent VZV infection.[54] Even in patients at risk, where the rationale of administering specific immune globulins was not so much to prevent infection but to mitigate the severity of the disease, no clear-cut data have been obtained.[55,56] The use of VZV-specific immune globulins has been restricted to high risk individuals, including immunocompromised children and pregnant women, who have had close exposure to an individual with varicella or herpes zoster.[57-59]

2.2 Active Immunisation

A live-attenuated varicella vaccine has been obtained starting from the reference strain Oka.[59-61] Predisposition for the development of severe varicella is due to impairment of the cell-mediated immune response to VZV, rather than to a defect in humoral immunity.[62,63] The vaccine is highly protective in healthy children, and those that are not fully protected show evidence of partial immunity.[64] Seroconversion in healthy children after 1 dose of vaccine has been about 95% and persistence of antibodies has been observed in >90% for at least 2 years.[64,65] Some data have suggested that antibody- and cell-mediated immune responses to VZV develop in parallel after immunisation.[66]

The more robust the antibody response after VZV vaccination, the more likely an individual is to have complete protection from disease in subsequent years. The antibody titres measured 6 weeks after vaccination could be used as a surrogate marker for protection from natural disease.[67] Most breakthrough infections seem to occur in the first few years after vaccination. No virus has ever been grown from these lesions and it has been recently demonstrated that there was no transmission of the live-attenuated vaccine strains to immunocompromised children after immunisation of their sibling.[68]

The varicella vaccine is highly protective in children with leukaemia, although a minority of children only achieve partial immunity. The seroconversion rate was >90% when the children received a 2-dose vaccination regimen.[69] Thus, the efficacy of the vaccine in children with leukaemia who seroconverted has been similar to that in healthy children. In children with leukaemia, the incidence of adverse effects in the first 6 weeks after immunisation was significantly higher than in healthy children. About 1 month after vaccination,

50% of children have developed rashes and fever, and some of them had to be treated with oral or intravenous aciclovir. It was possible to isolate the viral vaccine strain from the skin lesions.[70-71] After vaccination, patients with leukaemia acquired a long term immunity. In addition, the attack rate of clinical varicella among vaccinees who had again become seronegative and who had household exposures was only 30%, compared with 80 to 90% that could be expected in varicella-susceptible patients.[70]

It has been shown that zoster is less common after vaccination with the varicella vaccine than after natural infection.[66-72] It has also been demonstrated that immunisation of elderly people with the varicella vaccine causes a durable cell-mediated immune response to VZV.[73-75] Also, statistically significant increases in varicella antibody titres were observed after immunisation with high doses of live-attenuated or heat-inactivated vaccine in healthy seropositive adults.[76]

After VZV infection of the skin, the virus migrates along the nerves to the posterior ganglia, where it persists in a latent form. However, a haematogenous migration of the virus to the ganglia cannot be completely ruled out. VZV has been recovered from the blood of patients with natural varicella, but not from healthy vaccine recipients. Thus, the question arises whether the VZV vaccine strain can cause latent infection. Children with leukaemia do have a higher incidence of zoster than those in a healthy matched population. Therefore, vaccinated children with leukaemia have been followed closely for zoster and compared with children with leukaemia who have had natural varicella. From this surveillance study it appeared that the incidence of zoster was significantly lower in vaccinees than in children with leukaemia with past natural varicella.[72,77] The lower incidence of varicella zoster in the vaccinees could be explained by the fact that the vaccine strain is attenuated. Most likely, the virus may have no access to the sensory ganglia if the skin is not infected.[78]

This was confirmed by follow-up studies of children with leukaemia where zoster developed far more frequently in those who had had rash after immunisation than those without rash.[63] A study of vaccination in the elderly showed that the immune response was similar and sustained when that group was compared with 35- to 40-year-old individuals. Age had little effect on the response to the vaccine, but larger doses were associated with longer duration of enhanced immunity. Only 3 out of the 200 patients that were vaccinated developed zoster in the subsequent 4 years.[79,80]

In summary, the target groups for vaccination are healthy children older than 12 months, patients with acute leukaemia (total lymphocyte counts >1200/μl), patients receiving immunosuppressive therapy who have lymphocyte counts >1200/μl, patients who have to undergo a solid organ transplantation, patients with chronic diseases and people in close contact with immunocompromised patients. The actual recommendations for the administration of the varicella vaccine are as follows:
(a) one dose for healthy children between 12 and 18 months of age without a history of VZV infection;
(b) one dose for children between 18 months and 13 years of age that have not been vaccinated yet and do not have a history of VZV infection and;
(c) two doses with an interval of 4 to 8 weeks for healthy teenagers and adults that have not been vaccinated yet and do not have a history of VZV infection.[81,82]

2.3 Prevention with Antiviral Drugs

In a recent study, aciclovir given orally (40 mg/kg/day in 4 divided doses) for 5 days to healthy children susceptible to varicella was shown to prevent or modify the clinical course of varicella.[83] Persistence of protective immunity after post-exposure prophylaxis of varicella with oral aciclovir in the family setting was recently demonstrated.[84]

3. Treatment of VZV Infections

The appearance of new drugs with better bioavailability has considerably changed the landscape of VZV chemotherapy[85-88] (table I).

Table I. Recommended dosages of currently available drugs in the treatment of varicella zoster virus (VZV) in patients with normal renal function

Drug	Formulation	Indication	Patient group	Dose	Dosage interval	Treatment duration (days)
Aciclovir (acyclovir)[89]	Oral tablets, capsules and suspension	Treatment of varicella (chicken pox)	Adults Children	800mg 20 mg/kg (≤800mg)	5 times daily qid	7 5
		Treatment of herpes zoster (shingles)	Adults	800mg	5 times daily	7
		Management of severely immunocompromised patients	Adults and children (>2 years)	800mg	qid	≥ 6mo
	Intravenous solution for infusion	Treatment of VZV infections	Adults Children (3 mo-12y)	5 (10[a]) mg/kg 250 (500[a])/mg/m^2	every 8h every 8h	≥ 5 ≥ 5
Valaciclovir[90]	Oral tablets	Treatment of herpes zoster	Adults	1000mg	tid	7
Famciclovir[91]	Oral tablets	Treatment of herpes zoster	Adults	250mg or 500mg	tid	7

a In immunocompromised patients.

mo = months; **qid** = four times daily; **tid** = three times daily; **y** = years.

3.1 Current Status of Varicella Chemotherapy

3.1.1 Immunocompetent Patients

In patients with normal immune status, varicella infections are usually benign and symptomatic treatment most often suffices. This includes closely cropping finger and toe nails, a cleansing bath to prevent secondary bacterial infections and treatment of pruritus and pyrexia. Several clinical studies have been conducted recently to define the clinical place of aciclovir in the treatment of varicella.[92-95] Two studies performed in children from 2 to 12 years of age concluded that oral aciclovir 20 mg/kg 4 times per day for 5 days accelerated cessation of lesion formation, decreased the total number of new lesions formed and lowered the need for antipruritic and analgesic treatment when aciclovir treatment was initiated within 24 hours of disease onset.[92,93] Another study, comparing oral aciclovir with placebo in adults with varicella, confirmed these results.[93] Similar conclusions were obtained in adolescents[94] and adults[95] to whom intravenous aciclovir was administered.

Since uncontrolled studies had shown some efficacy of oral aciclovir in adult varicella infection,[96] a randomised, placebo-controlled trial, using oral aciclovir 800mg 5 times daily for 7 days, was undertaken.[6] This study ascertained that early therapy within 24 hours with aciclovir decreased the time of cutaneous healing (whatever parameter was used), shortened the duration of fever and diminished symptoms. Starting aciclovir treatment within 24 hours after onset of symptoms was of no value in uncomplicated cases of adult varicella.

The use of oral aciclovir in normal and atopic children with varicella infections has been reviewed elsewhere,[97] and recommendations for the use of oral aciclovir have also been published.[98] In addition, intravenous aciclovir may improve the outcome of varicella pneumonia in adults, including pregnant women.[10-12] Aciclovir therapy did not alter the acquisition of long term immunity to VZV.[92] To date, no clinical trials have been conducted with valaciclovir and famciclovir, the prodrugs of aciclovir and penciclovir, respectively, for the treatment of varicella infections in nonimmunocompromised patients. Recently, another nucleoside analogue, sorivudine (B-Vara-U, brovavir, BV-Ara-U, BVAU), which is known to be the most potent inhibitor of VZV *in vitro*, was compared

with placebo for the treatment of varicella infections in immunocompetent adults.[99] Given orally once a day at 10 or 40mg, sorivudine shortened the mean time to crusting and cessation of new lesion formation.[100]

3.1.2 Immunocompromised Patients

Because of the recognised complications of varicella infections in the immunocompromised host, several experimental antiviral drugs have been tried in limited clinical trials. Cytarabine (cytosine arabinoside; Ara-C) and idoxuridine have proven too toxic for systemic use in patients with VZV infections.[101,102] In addition to aciclovir,[89,103] interferon-α and vidarabine also lead to an improvement of varicella and herpes zoster symptoms. Interferon-α (IFNα) has been used to treat varicella infections in a group of children with cancer.[104,105] Intramuscular IFNα 0.4 to 3.5×10^5 IU/kg/day for 5 days significantly reduced the duration of lesion formation and visceral dissemination.

The first drug that proved successful in the chemotherapy of varicella in immunocompromised hosts was vidarabine. In a study where vidarabine at 10 mg/kg/day was compared with placebo, patients receiving vidarabine ceased to form new lesions and fever in these patients abated more rapidly than in patients receiving placebo. The incidence of life-threatening complications was significantly lower in the treated group than in the placebo group, and when therapy was initiated within 72 hours of the disease onset, outcome was beneficially influenced.[106] When aciclovir was used in a similar study, therapy had no effect on cutaneous healing or fever. However, administration of aciclovir did counteract the development of pneumonitis.[107] Improvement in the outcome of varicella in immunocompromised children treated with aciclovir was confirmed in another study.[108] Oral aciclovir 800mg 5 times daily for 7 days proved to be efficacious in 25 immunocompromised children with varicella infections. In only 2 children was oral aciclovir required to be changed to the intravenous formulation. All children recovered from their VZV infection.[109]

3.2 Current Status of Herpes Zoster Chemotherapy

3.2.1 Immunocompetent Patients

Intravenous aciclovir in healthy patients with herpes zoster accelerates the rate of cutaneous healing and reduces the severity of acute neuritis, but has no effects on postherpetic neuralgia.[110-112] Oral administration of aciclovir has accelerated the rate of cutaneous healing and reduced the severity of acute neuritis.[113,114] If the therapy was initiated within 48 hours after disease onset, clinical benefits were more evident, particularly in herpes zoster ophthalmicus where the incidence of uveitis and keratitis were reduced as compared with the placebo group.[115] In another study, a topical ophthalmic aciclovir preparation was compared with topical corticosteroids, and fewer relapses of ocular inflammation were noted in the aciclovir group.[116] In a randomised study, oral aciclovir reduced peripheral sensory axonopathy due to ganglion damage and prevented the possibility of spread to anterior roots and spinal motorneurons, thus reducing the incidence of segmental motor neuritis.[117]

The major problem with herpes zoster is the development of postherpetic neuralgia.[118] Systemic corticosteroids have been widely used for prevention of postherpetic neuralgia.[119,120] The rationale for their use has been to limit inflammation and subsequent scarring in the dorsal root ganglia, factors that might be responsible for postherpetic neuralgia. However, a controlled study of aciclovir with or without prednisolone in patients with zoster failed to show any benefit.[121] Two recent studies indicated that the addition of corticosteroids to aciclovir accelerated resolution of acute pain but had no effect on long term pain.[122,123] However, in 1 of these studies addition of corticosteroids to aciclovir improved quality of life.[123]

The effect of aciclovir on postherpetic neuralgia is rather limited, as has been shown in several studies.[124,125] A meta-analysis from 5 trials of oral aciclovir (800mg per day within 72 hours of rash onset) for the treatment of herpes zoster showed that aciclovir may reduce the incidence of residual

pain at 6 months by 46% in immunocompetent adults.[126] Valaciclovir, the prodrug of aciclovir, has been compared with placebo in adult patients with herpes zoster. Valaciclovir 1000mg 3 times daily for 7 days was significantly more effective than placebo in terminating new lesion formation.[90] In a large study in immunocompetent adults, in comparison with aciclovir, valaciclovir 1000mg 3 times daily for 7 days accelerated the resolution of pain while cutaneous manifestations resolved at similar rates in both groups.[127] Valaciclovir not only proved to be more efficient than aciclovir in promoting healing of lesions, but was also more effective than aciclovir in shortening the duration of postherpetic neuralgia.[128]

In a double-blind randomised study, intravenous penciclovir or aciclovir 5 mg/kg 3 times daily for 5 days each, had comparable efficacy in the treatment of immunocompetent patients with herpes zoster.[129]

In a prospective double-blind study enrolling 419 patients, famciclovir 500 or 750mg 3 times daily for 7 days, compared with placebo, was effective, well tolerated and decreased the duration of postherpetic neuralgia.[130] The beneficial effect of famciclovir on postherpetic neuralgia was further confirmed by Huse and colleagues.[131] In a randomised, multicentre trial, famciclovir 250, 500 and 750mg 3 times daily was as effective as aciclovir 800mg 5 times daily in healing cutaneous zoster lesions. Time to loss of acute pain was similar in all famciclovir and aciclovir groups. All 3 regimens of famciclovir were associated with a more rapid resolution of zoster-associated pain than in those receiving aciclovir.[132] The safety data analysis of 13 completed clinical studies has demonstrated that famciclovir has a safety profile similar to that of placebo.[133]

3.2.2 Immunocompromised Patients

Interferon IFNα, vidarabine and aciclovir have been shown to be useful in patients at high risk for the development of life-threatening infection due to herpes zoster. IFNα given to patients with herpes zoster and an underlying malignancy resulted in a decrease in vesicle formation and a lowered frequency of cutaneous dissemination.[134] Patients treated with IFNα also had a significant decrease in postherpetic neuralgia. Vidarabine was shown to be active against herpes zoster if therapy was begun within 72 hours of onset: vidarabine prevented progression of lesion formation within the dermatome and allowed gradual regression of the lesions in the area involved.[135-137] Vidarabine therapy also resulted in a significant decrease in visceral complications (encephalitis, hepatitis and uveitis) as compared with the placebo group.[136] Like IFNα, vidarabine clearly reduced the duration of the chronic pain associated with zoster.[39] This was obtained when vidarabine 10 mg/kg/day over 12 hours for 7 days was administered. Aciclovir, like vidarabine and IFNα, favourably influenced the duration of new lesion formation and virus shedding, lesion healing time and rate of dissemination of lesions to skin and viscera.

Intravenous, but not oral, aciclovir therapy has resulted in plasma concentrations that exceed the concentration required to reduce viral replication by 50% (IC_{50}) for VZV.[138] The oral bioavailability of aciclovir is relatively low (≤20%). After repeated oral doses of aciclovir 200 or 800mg, mean steady state peak plasma concentrations of 0.6 and 1.6 mg/L have been reported, respectively, while after intravenous administration of doses of 5 or 10 mg/kg, peak plasma aciclovir concentrations reached 10 and 20 mg/L, respectively. The terminal half-life of aciclovir in plasma is 2 to 3 hours in adults with normal renal function.[103]

Aciclovir was first demonstrated to be active against herpes zoster in a placebo-controlled trial,[139] where it reduced the frequency of cutaneous dissemination and visceral complications. In those studies where the efficacy of aciclovir and vidarabine were compared in the treatment of herpes zoster in immunocompromised patients,[140,141] aciclovir proved clearly advantageous over vidarabine in terms of cutaneous healing or disease progression. In addition, those patients receiving aciclovir were discharged from hospital more promptly.[142]

Brivudine (BVDU, bromovinyldeoxyuridine) and sorivudine have also been the subject of lim-

ited clinical trials and have proven to be efficacious in the treatment of zoster infections in immunocompromised patients.[143,144] Brivudine has been used successfully in the treatment of progressive outer retinal necrosis.[143] Also, oral brivudine has proven to be as efficacious as, if not more so than, intravenous aciclovir in the treatment of immunocompromised patients.[144]

Oral brivudine 7.5 mg/kg/day administered for 5 days to patients with underlying malignancy and severe herpes zoster has stopped disease progression within 1 day after initiation of treatment.[145] Similar results were obtained in children with cancer (receiving brivudine orally at 15 mg/kg/day for 5 days)[146] and in immunocompetent adults with herpes zoster.[147,148] As a rule, all patients recovered rapidly from their VZV infection, and in no case was treatment required to be prolonged for more than 5 days. In addition, none of the brivudine-treated patients showed any evidence of drug toxicity in bone marrow, liver, kidney or any other organ. Sorivudine was found clinically efficacious in both immunocompetent[149] and immunocompromised patients,[150,151] who received oral sorivudine 10 or 50 mg/kg 3 times a day. Recently, in a comparative study of sorivudine and aciclovir in the treatment of dermatomal herpes zoster in HIV patients, sorivudine was as effective as aciclovir when the time to the resolution of zoster-associated pain, the frequency of dissemination and the frequency of zoster recurrence were recorded. Administration of sorivudine resulted in accelerated cutaneous healing compared to aciclovir.[152]

A serious drug interaction between sorivudine and fluorouracil has been identified. Bromovinyluracil, a metabolite of sorivudine made mainly by bacteria in the gut, is an inhibitor of dihydropyrimidine dehydrogenase, an enzyme required for the metabolism of pyrimidines and pyrimidine derivatives such as fluorouracil.[153] In Japan, death occurred in patients receiving fluorouracil concomitantly with sorivudine. These deaths were attributed to fluorouracil myelotoxicity, resulting from the inhibitory effect of sorivudine (via bromovinyluracil) on fluorouracil degradation.[154] Accordingly, it is unlikely that sorivudine will be developed further for commercial use.

3.3. Resistance

Recently, several case reports have appeared on the emergence, following long term aciclovir therapy, of aciclovir-resistant VZV strains in patients with AIDS.[46,155-158] That Cole and Balfour Jr[159] could not detect aciclovir-resistant VZV strains in immunocompromised patients after treatment with aciclovir is probably due to the short period (10 days) during which these patients were treated with the drug.

Mutations at the level of the VZV thymidine kinase (TK) are responsible for development of VZV resistance to those drugs that depend on the viral TK for their phosphorylation.[46,160-163] It was demonstrated that aciclovir-resistant VZV is 3- to 20-fold more sensitive to arabinosyl nucleoside analogues than the parent virus.[164] Talarico et al.[165] as well as Boivin et al.[166] analysed the TK gene from aciclovir-resistant VZV strains isolated from AIDS patients. They found a non-sense mutation introducing a terminator codon, thus resulting in the expression of a truncated protein. Previously, a TK deletion was described that was 873 nucleotides long, located in the coding region of the TK gene in a VZV strain isolated from the CSF of an AIDS patient with meningoradiculoneuritis.[46] The mutated TK protein was 51 amino acids long and comprised the 13 aminoterminal amino acids linked to the 38 carboxyterminal amino acids of the wild type protein. Most of the ATP-binding site and the entire nucleoside binding site (proposed by Talarico et al.[165]) were missing in this truncated protein which, consequently, was completely inactive.[46]

There is only little evidence for resistance due to mutations located at the level of the VZV DNA polymerase although suggestive evidence for such alterations stems from the increased IC_{50} of the virus for foscarnet.[155] Five cases of aciclovir-resistant VZV infections treated with foscarnet have been reported,[167] where the clinical responses were not predicted by the *in vitro* drug

susceptibility; healing was observed despite resistance to foscarnet and clinical failure was observed despite susceptibility to foscarnet. This discrepancy could at least be partially explained by variations in the pharmacokinetics of foscarnet, particularly the plasma drug concentrations.[168]

This is also true with regard to foscarnet concentrations within the CSF. In 2 studies, the concentrations of foscarnet in the CSF of patients with AIDS were recorded. According to Raffi et al.,[169] foscarnet penetrates well into the CSF and even better into inflammatory CSF, while Hengge et al.[170] found no correlation between the concentrations of foscarnet in the CSF and the integrity of the blood-brain barrier. In both studies, foscarnet concentrations in the CSF were sufficient to recommend the use of the drug for the treatment of herpesviral encephalitis in AIDS patients. *In vitro* foscarnet resistance was shown to correlate with absence of clinical response in an AIDS patient with multidermatomal zoster.[171]

4. Different Drugs Active Against VZV and Their Molecular Targets

4.1 Thymidine Kinase (TK) Phosphorylation, Targeted at Viral DNA Polymerase

Most of the compounds that have been pursued for the treatment of VZV infections are nucleoside analogues requiring phosphorylation by the viral TK. The reference molecule for all these compounds is aciclovir.[89,103,172] Aciclovir is converted by the virus-encoded TK to its monophosphate which is then converted to the di- and triphosphate forms by cellular enzymes, resulting in a 40- to 100-fold increase in aciclovir-triphosphate (aciclovir-triphosphate) in infected cells, as compared to uninfected cells. Aciclovir-TP inhibits viral DNA synthesis by competing with deoxyguanosine triphosphate as substrate for the viral DNA polymerase.[173,174] Aciclovir-TP acts as a chain terminator.[175,176] However, since the oral bioavailability of aciclovir is relatively low and variable (between 15 and 30%),[177] prodrugs of aciclovir have been developed.

The L-valyl ester valaciclovir (VACV) is the prodrug of aciclovir. VACV is well absorbed and quickly converted to aciclovir, thus increasing the bioavailability of aciclovir by 3- to 5-fold. The increased bioavailability of aciclovir from VACV may be explained by absorption of the prodrug via a stereospecific transporter followed by its rapid and efficient conversion to aciclovir, presumably via a VACV hydrolase.[178] VACV may be expected to exhibit a similar safety profile as aciclovir itself.

Aciclovir has been reported to have little if any toxicity. The renal dysfunction reported in some cases in patients treated with large doses of aciclovir[179,180] is usually reversible and could be avoided by infusing aciclovir slowly in association with good hydration. Oral aciclovir has not been associated with renal dysfunction.[181] Intravenous administration of aciclovir has been associated with some disturbances at the CNS level.[182,183]

Recently, another guanosine analogue, penciclovir, was found to exhibit in cell culture potent activity against both reference strains and clinical isolates of HSV and Epstein-Barr virus.[91,184,185] Penciclovir is highly selective against herpesviruses, because it is phosphorylated, and hence activated, only in herpesvirus-infected cells.[186] The viral TK seems to play a key role in the activation of the molecule, since penciclovir is not active against mutant HSV strains that are deficient in the expression of their TK.[184] In VZV-infected cells, the rate of formation of penciclovir-TP increases as the infection proceeds, but this rate is about 10-fold less than in cells infected with either HSV-1 or HSV-2. However, the intracellular concentration of penciclovir-TP was at least 30-fold higher than that of aciclovir-TP under the same conditions.[187]

Penciclovir-TP is a less powerful inhibitor of HSV-1 DNA polymerase and VZV DNA polymerase than aciclovir-TP [inhibition constant (Ki) value 100-fold greater for penciclovir-TP than for aciclovir-TP]. Thus, the high concentrations of penciclovir-TP compensate for its diminished affinity for the DNA polymerase, which means that

in standard plaque reduction assays aciclovir and penciclovir afford similar antiviral activity.

Penciclovir-TP is a competitive inhibitor of HSV-1 and HSV-2 DNA polymerase with respect to the natural substrate deoxyguanosine triphosphate (dGTP). In conditions where aciclovir-TP is clearly acting as a chain terminator, penciclovir-TP does allow limited DNA chain elongation.[185] In addition, penciclovir-TP is a poorer substrate for incorporation into DNA than aciclovir-TP. Penciclovir has been shown to be active against DNA polymerase-based virus mutants resistant to aciclovir, suggesting that the interaction at the level of the enzyme is different for the triphosphates of aciclovir and penciclovir.[185] Also, penciclovir-TP has a longer intracellular half-life than aciclovir-TP. The half-life of penciclovir-TP in cells infected with HSV-1, HSV-2 or VZV was 10, 20 or 7.2 hours, respectively; for aciclovir-TP the half-life was 0.7 and 1.0 hour in HSV–1- or HSV–2-infected cells, respectively. In VZV-infected cells, the aciclovir-TP concentrations were under the detection limit.[186,187]

Penciclovir is poorly absorbed when given orally to rodents and humans, and even in mice oral absorption of penciclovir is less than for aciclovir.[188] Therefore, various derivatives (particularly esters) of penciclovir have been synthesised in attempts to increase its oral bioavailability. Famciclovir, the diacetyl ester of 6-deoxy-penciclovir, has emerged as the best candidate.[189] After oral administration in rats, famciclovir is rapidly absorbed, and taking the sum of all the metabolites the time needed to reach the maximum concentration in blood is about 15 to 20 minutes. Similar results were obtained in human volunteers.[190] Further studies are needed to assess the comparative usefulness of famciclovir (or penciclovir) relative to that of aciclovir[191,192] or valaciclovir.

Among the nucleoside analogues that have been pursued (albeit on a limited scale) for the treatment of VZV infections, the most potent inhibitors of *in vitro* VZV replication that have ever been described are brivudine and sorivudine.

Sorivudine and brivudine inhibit *in vitro* VZV replication at an IC_{50} of approximately 0.001 mg/L, while for aciclovir in similar experimental conditions the IC_{50} is about 4 mg/L. Sorivudine-resistant VZV strains selected *in vitro* were shown to have a decreased viral TK activity.[193]

The selective antiviral action of brivudine and sorivudine depends primarily on their phosphorylation by the virus-induced TK. Upon further conversion of the 5'-mono- or diphosphates of the pyrimidine 2'-deoxynucleoside analogues by cellular kinases to the corresponding 5'-triphosphates, the latter may inhibit the DNA polymerase reaction by direct competition with the natural substrate deoxythymidine triphosphate (dTT).[194]

Incorporation of brivudine into DNA does not cause premature termination of chain elongation, suggesting that brivudine is incorporated *via* internucleotide linkage. The incorporation of brivudine into viral DNA leads to a single-strand DNA breakage. When incorporated into synthetic DNA, brivudine reduces the DNA template activity for RNA synthesis. Thus, incorporation of brivudine into DNA may result in both selective degradation of the DNA as well as inadequate mRNA transcription. In contrast with aciclovir, both brivudine and sorivudine have good oral bioavailability. Pharmacokinetic analysis for sorivudine revealed that the elimination half-life has varied from 5 to about 8 hours, with a statistically significant greater half-life in the elderly as compared with young volunteers. Serial measurements of trough serum concentrations showed that sorivudine does not accumulate upon repeated administration. In addition, the trough concentration at 24 hours after a single oral dose was still above the IC_{50}, suggesting that a once-daily dosage regimen may be appropriate for the treatment of VZV infections.

Fluorinated nucleoside analogues (e.g. fialuridine) have also proved effective against a number of herpesviruses including CMV, HSV and VZV. Fiacitabine has shown good activity *in vitro* against VZV in 3 different cell lines.[195] *In vivo*, in the simian varicella virus model using African green monkeys fialuridine was less potent (when

given orally) than its 5-methylated counterpart 1-(2′-deoxy-l-fluoro β-l-arabinofuranosyl-5-methyuracil (FMAU).[196] The activity of fialuridine was similar to that of brivudine.[197] In immunosuppressed patients with herpes zoster, fiacitabine was considered superior in efficacy to vidarabine.[198]

Of the 5-alkynyl-substituted pyrimidine analogues, 2'-deoxy-5-ethynyluridine proved active against VZV but also too toxic to the host (MRC-5) cells, while netivudine (882C) proved to be a selective inhibitor of VZV replication with an IC_{50} ranging from 0.17 to 1.07 mg/L.[199] No activity could be detected against other herpesviruses. Netivudine is dependent on the VZV-encoded TK for its antiviral activity. The compound is phosphorylated to the mono- and diphosphate form by the viral enzyme. The triphosphate of netivudine inhibits the VZV DNA polymerase. The compound retains activity against some TK-altered substrate aciclovir-resistant clinical isolates of VZV and it is also active against laboratory-selected DNA polymerase-based VZV mutants.[200]

Pharmacokinetic studies with netivudine in humans showed a relatively long half-life (12 to 14 h) in the plasma. Drug concentrations in the plasma stayed well above the IC_{50} for at least 24 hours after a single 50mg oral dose.[201] The oral bioavailability of a 200mg dose of netivudine was 21.1% in the young and 24.6% in the elderly. Higher plasma concentrations in the elderly are explained by reduced renal clearance and a trend to higher bioavailability.[202] Initial clinical studies in elderly patients with localised herpes zoster also suggested a therapeutic benefit with respect to rash healing and pain,[203] but further development of the compound has been suspended by findings of toxicity after long term administration of netivudine to rodents.

Other classes of nucleoside analogues depending for their phosphorylation on the viral TK have been synthesised. Methoxypurine arabinoside (Ara-M) has been described as a selective and potent inhibitor of VZV *in vitro*[204] and shows efficacy similar to that of aciclovir in hairless guinea pigs.[205] From a series of seven 6-alkoxypurine arabinosides, methoxypurine arabinoside was the most efficient substrate for the VZV-encoded TK as well as the most potent anti-VZV agent. *In vitro*, methoxypurine arabinoside was almost 10-fold more active against VZV replication than aciclovir. The antiviral spectrum of the 6-alkylaminopurine nucleosides appeared to be limited to VZV, the 6-methylaminopurine and the 6-dimethylaminopurine derivatives being the most potent VZV inhibitors from this group. These compounds are not detectably phosphorylated by either adenosine kinase or 2'-deoxycytidine kinase. Instead, there was a clear correlation between their *in vitro* antiviral potency and their substrate affinity for the VZV-encoded TK.[206]

Oxetanocins (OXT) may be regarded as cyclobutyl nucleoside analogues in which the carbocyclic carbon has been replaced by an oxygen. OXT-adenine, OXT-guanine and OXT-2-aminoadenine proved active against TK-expressing and TK-deficient strains of VZV.[207] The guanosine derivative lobucavir is now under clinical evaluation for the treatment of both VZV and HBV infections. A-73209 (1[2'R,3'R,4'5]-3',4'-bis-(hydroxymethyl)2'-oxetanyl-5-methyl uracil) belongs to the oxetanocin family. A-73209 is 100-fold more potent than aciclovir against TK-positive strains of VZV. Activity against TK-deficient VZV strains is much lower than against TK-positive VZV strains. A-73209 has been reported to cross the blood-brain barrier following oral administration.[208]

4.2 Viral Thymidylate Synthase

VZV encodes a thymidylate synthase (TS) that catalyses the conversion of deoxyuridylate (dUMP) to thymidylate (dTMP). Although it has been shown that brivudine, upon its conversion to brivudine monophosphate by the viral TK, can inhibit the virus-induced TS,[209] this by no means proves that the mode of its anti-VZV action is due to inhibition of the VZV-encoded TS. In fact, recent results have suggested that the VZV-encoded TS is not essential for viral replication in cell culture.[210] Other antiherpes compounds such as sorivudine,

aciclovir, ganciclovir or vidarabine do not inhibit TS activity in VZV-infected cells.[209]

4.3 Viral Ribonucleotide Reductase

HSV encodes a specific ribonucleotide reductase. This enzyme is responsible for the reduction of the ribonucleotides to the corresponding deoxyribonucleotides and can be considered as a target for antiviral chemotherapy. Recently, a ribonucleotide reductase was partially purified from cells infected with VZV. A-1110U [2-acetylpyridine-5-[(dimethyl-amino)thiocarbonyl]thiocarbonohydr azone], which is a potent inhibitor of the ribonucleotide reductase induced by HSV and VZV, was shown to potentiate the activity of aciclovir *in vitro*.[211] The 2-acetylpyridine 5-[(2-chloroanilino)thiocarbonyl]thiocarbonohydrazone (348U87) was shown to inhibit both VZV and HSV ribonucleotide reductase, and inactivate the viral ribonucleotide reductase faster than A-1110U. In addition, 348U87 has a more favourable toxicological profile than A-1110U.[212]

4.4 Drugs Not Dependent on Viral TK Phosphorylation Targeted at Viral DNA Polymerase

Vidarabine has been extensively investigated in clinical trials as described above. It is no longer the drug of choice for the treatment of VZV infections, mainly because of its relatively low activity, rapid degradation (by deamination) and poor aqueous solubility which necessitates the infusion of large amounts of liquid.

Foscarnet has been used clinically against VZV infections, particularly when resistant viruses appeared under aciclovir treatment, mainly in AIDS patients. The main disadvantage of foscarnet is that it can only be given as an intravenous infusion because of its poor bioavailability. No metabolites of foscarnet have been detected. Sequestration into bone may be responsible for the long terminal phase half-life (88 hours) while the first and the second elimination half-lives are 0.5 to 1.4 hours and 3.3 to 6.8 hours, respectively.[213] The most frequent dose-limiting adverse effect of foscarnet therapy is a 2- to 3-fold increase in serum creatinine level in about 45% of the patients. This is due to acute tubular necrosis which tends to be reversible upon foscarnet withdrawal. Reversible hypercalcaemia and hyperphosphataemia occur in over 66% of foscarnet recipients, although symptomatic hypercalcaemia has been also observed. Foscarnet also leads to anaemia in 20 to 50% of patients treated, and penile ulceration has been observed.[213]

We have previously described a new class of compounds, namely acyclic nucleoside phosphonates,[214-222] which contain a phosphorus-carbon linkage that resists hydrolysis by cellular esterases. These compounds fall into two categories: phosphonylmethoxyethyl (PME) derivatives, [i.e. 9-(2-phosphonylmethoxy-ethyl)adenine; adefovir (PMEA)[217] and 9-(2-phosphonylmethoxyethyl)diaminopurine; PMEDAP],[223] that are active against both retro- and herpesviruses, and 3-hydroxy-2-phosphonylmethoxypropyl (HPMP) derivatives, [i.e. (S)-9-(3-hydroxy-2-phosphonylmethoxypropyl)adenine; HPMPA],[213,214,217]) which are active against a broad range of DNA viruses including herpesviruses (HSV, VZV, CMV, Epstein-Barr) but also poxviruses (vaccinia virus), iridoviruses (African swine fever virus), hepadnaviruses (hepatitis B virus) and adenoviruses. The prototype compound HPMPA can be regarded as the hybridisation of two previously described antiviral entities, the (S)-9-(2,3-dihydroxypropyl)adenine (DHPA), which has a broad spectrum antiviral activity against several RNA and DNA viruses, and foscarnet, which is active against herpes-, hepadna- and retroviruses.

Owing to the presence of the phosphonate group, the PME and HPMP derivatives do not need to be phosphorylated by the virus-encoded TK which explains why they are active against TK-deficient strains of HSV and VZV[46,215,224] and DNA viruses like CMV that do not encode for such viral TK.[216,225] In the case of HPMPA, the active derivative is HPMPA diphosphate (HPMPApp) which acts at the DNA polymerase level as a competitive inhibitor with respect to the natural substrate deoxyATP.[226,227] HPMPApp can also be

incorporated internally into the DNA chain. HPMPC is assumed to act in a similar fashion as HPMPA.[228] In addition to HPMPC monophosphate (HPMPCp) and HPMPC diphosphate (HPMPCpp), the HPMPCp-choline adduct has been isolated as a major metabolite of HPMPC, with a very long intracellular half-life (48 hours). HPMPCp-choline could act as an intracellular reservoir from which the drug is slowly released.[227,228] The phosphonate derivatives also show a long-lasting antiviral response *in vivo*,[229,230] which seems to be related to their long half-life.

5. Conclusions

Vaccination for VZV has now come of age and since the protection induced by the vaccine seems, to some extent, to include zoster and the herewith associated neuralgia, one might consider VZV vaccination in children. Vaccination of immunocompromised children, particularly those with malignancies, should be recommended because of the high morbidity of VZV infection in such patients.

Two new antiviral drugs derived from aciclovir or penciclovir, respectively, have emerged during the last few years. They are characterised by an improved oral bioavailability. The first is valaciclovir, the L-valyl ester of aciclovir, which retains the same activity and safety profile as the mother compound. The second is famciclovir, the oral derivative of penciclovir. Both compounds are active against HSV and VZV, and famciclovir has also been pursued for the treatment of hepatitis B. In addition to valaciclovir and famciclovir, brivudine and sorivudine have proved efficacious in the treatment of VZV infections, and brivudine is currently the subject of a large clinical trial for the treatment of herpes zoster in immunocompetent individuals.

The possible emergence of drug-resistant VZV strains should be taken into account when using new antiviral drugs. For those drug-resistant viruses that emerge under the pressure of aciclovir and related drugs, foscarnet remains an appropriate alternative. Nevertheless, foscarnet-resistant strains as well as patients progressing despite sensitivity of the virus to the drugs have both been described. Therefore, acyclic nucleoside phosphonate analogues, particularly cidofovir, may acquire an important place in the armamentarium of anti-VZV drugs. An adequate strategy to prevent emergence of virus-drug resistance may be based on the alternating use of the appropriate anti-VZV drugs, particularly in patients with AIDS who need long term prophylaxis for relapsing VZV disease.

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