Maribavir: A Novel Antiviral Agent with Activity Against Cytomegalovirus

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OBJECTIVE: To review the pharmacology, pharmacokinetics, efficacy, and safety of maribavir, a novel antiviral agent in the benzimidazole drug class.

DATA SOURCES: Articles were identified through searches of MEDLINE (January 1998–July 2008). Abstracts from recent scientific meetings and the manufacturer were also included.

STUDY SELECTION AND DATA EXTRACTION: All English-language in vitro and in vivo studies and abstracts evaluating maribavir were reviewed and considered for inclusion. All human studies were included.

DATA SYNTHESIS: Maribavir has significant activity against both human cytomegalovirus (CMV) and Epstein-Barr virus, but not other herpesviruses. Unlike ganciclovir, which needs to be phosphorylated by UL 97 kinase to become an active inhibitor of DNA polymerase, maribavir directly inhibits UL 97 kinase. UL 97 kinase is an early viral gene product involved in viral DNA elongation, DNA packaging, and egress or shedding of capsids from viral nuclei. Maribavir has also been found to be effective against ganciclovir-resistant CMV strains. Maribavir differs from current CMV antiviral agents in its adverse event profile. Maribavir is not associated with nephrotoxicity or hematologic toxicities, but has been associated with taste disturbances. In February 2007, maribavir was granted Food and Drug Administration orphan drug status for prevention of CMV viremia and diseases in at-risk populations. Maribavir Phase 2 trials in stem-cell transplant recipients have been completed, and there are ongoing Phase 3 trials in stem-cell and organ transplant recipients.

CONCLUSIONS: Maribavir may be an option for treatment of ganciclovir-resistant CMV infections. Its bioavailability is greater than that of oral ganciclovir, but less than that of valganciclovir. No differences in pharmacokinetics were seen in renally impaired patients, although dialysis-dependent patients were not evaluated. Maribavir is not associated with hematologic toxicities; however, the high prevalence of taste disturbances may limit its tolerability.

KEY WORDS: cytomegalovirus, Epstein-Barr virus, HIV, maribavir, solid organ transplantation, stem-cell transplantation.

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Cytomegalovirus (CMV), a member of the Herpesviridae virus family, is the most common posttransplant opportunistic infection and a leading viral cause of morbidity and mortality among stem-cell and organ transplant recipients.[1,2] Subclinical CMV infection is common in immunocompetent individuals; worldwide prevalence rates range from 40% to 100%, with frequency increasing in an age-dependent manner.[1] CMV commonly remains latent after primary infection and may reactivate when a patient's immunity is weakened. The incidence of CMV disease after kidney, heart, or liver transplant is around 25% but increases to 50% with pancreas or kidney–pancreas transplantation, and is even greater after heart–lung transplantation.[3]

CMV infection has also been associated with secondary effects in organ transplant recipients, including acute and chronic rejection, superinfections (particularly those due to fungi), and posttransplant lymphoproliferative disorders.[4-6] Moreover, CMV disease has been shown to be an independent risk factor for patient and graft survival.[6] As a result of the potentially devastating effects of CMV disease in these populations, current therapeutic modalities are focused on prevention strategies encompassing prospective viral monitoring and/or antiviral agents.[4,7,8] Moreover, when CMV disease occurs, despite successful treatment, infection recurs in one-third of solid organ transplant recipients.[3]

Currently available antiviral therapies for CMV prevention and treatment, as well as their CMV-related indications, mechanisms of action, advantages, and disadvantages, are summarized in Table 1.[6,9-27] Some of the major limitations of current CMV therapies include limited bioavailability, hematologic and nephrotoxic adverse

Author information provided at the end of the text.

Table 1. Comparison of Antiviral Agents for CMV Prevention or Treatment

Reference	FDA-Approved Indication	Mechanism of Action	Advantages	Disadvantages
Valganciclovir Asberg (2007)[9] Limaye (2000)[10] Product information (2006)[11] Paya (2004)[12] Cochrane (2006)[13] Czock (2002)[14]	prophylaxis CMV infection in high-risk kidney, heart, or kidney/pancreas transplant pts. treatment CMV retinitis in pts. with AIDS	inhibits DNA polymerase	good bioavailability (60%), oral administration, once-daily dosing, equivalent efficacy to intravenous ganciclovir for treatment of CMV in certain transplant populations, dosing guidelines for renal insufficiency excluding dialysis	hematologic toxicities, efficacy may be reduced in liver transplant and has not been established in lung transplant, no dosing guidelines for hepatic impairment, not able to use in dialysis-dependent pts., no data on geriatric or pediatric populations, gastrointestinal adverse effects, resistance to some CMV strains, no generic product available
Ganciclovir Limaye (2000)[10] Product information (2006)[15] Pescovitz (1998)[16]	prophylaxis CMV infection in transplant recipients at risk of CMV disease treatment CMV retinitis in immunocompromised pts., including pts. with AIDS	inhibits DNA polymerase	available as generic product, available as intravenous and oral dosage forms, dosing guidelines for renal impairment and dialysis-dependent pts., data available for pediatric populations	gastrointestinal adverse effects, hematologic toxicities, bioavailability range 5–31%, high pill burden, resistance to some CMV strains, no data on geriatric populations, no data on hepatic impairment
Acyclovir Product information (2005)[17] Flechner (1998)[18] Fletcher (1988)[19]	not approved for CMV prophylaxis or treatment	inhibits DNA polymerase	early randomized controlled trials demonstrated some efficacy in preventing CMV in kidney and liver transplant recipients, available as generic product, dosing guidelines for renal impairment and dialysis-dependent pts., data for pediatric pts. >2 y old and geriatric populations	low bioavailability (6–10%), no dosing guidelines for hepatic impairment, not as efficacious as valganciclovir or ganciclovir for preventing CMV, not effective as CMV treatment
Valacyclovir Product information (2007)[20] Lowance (1999)[21]	not approved for CMV prophylaxis or treatment	inhibits DNA polymerase	showed efficacy in a placebo-controlled trial at preventing CMV in kidney transplant recipients, improved bioavailability over acyclovir (~55%), dosing guidelines for hepatic and renal impairment including dialysis, data on geriatric populations	efficacy has not been well studied in other types of transplants, not as efficacious as valganciclovir or ganciclovir for preventing CMV, not effective as CMV treatment, no data on pediatric populations, not available as generic product
Cidofovir Preiksaitis (2005)[6] Product information (2000)[22]	treatment CMV retinitis in pts. with AIDS	inhibits DNA polymerase	used off-label for pts. with ganciclovir-resistant CMV disease or pts. intolerant to the hematologic toxicities of ganciclovir	rarely used as prophylaxis due to nephrotoxicity, available as intravenous formulation, hematologic adverse effects, no data on pediatric or geriatric populations, dosing not established for pts. with hepatic or renal impairment or dialysis, not available as generic product
Foscarnet sodium Product information (2006)[23] Mattes (2004)[24]	treatment CMV retinitis in pts. with AIDS	inhibits DNA polymerase	used off-label for pts. with ganciclovir-resistant CMV disease or pts. intolerant to hematologic toxicities of ganciclovir, available as generic product, dosing guidelines for renal impairment	rarely used as prophylaxis, nephrotoxicity, available only as intravenous formulation, hematologic adverse effects, electrolyte imbalance effects, may enhance the QTc-interval–prolonging effects of other drugs, no dosing guidelines for hepatic impairment, should not be administered to dialysis pts., limited data on geriatric and no data on pediatric populations
CMV hyperimmune globulin Snydman (1993)[25] Glowacki (1994)[26]	prevention of CMV disease in pts. undergoing kidney, lung, liver, or heart transplants at risk for primary CMV disease (eg, seropositive donor to seronegative recipient)	attempts to provide passive immunity	may help to prevent CMV and treat CMV infection in conjunction with antiviral therapy	results variable, cost, risk of renal insufficiency, no dosing guidelines for hepatic or renal insufficiency or dialysis, no data on pediatric or geriatric populations, intravenous administration necessary, no generic product available
Leflunomide John (2005)[27]	not FDA-approved for CMV prophylaxis or treatment	protein kinase and pyrimidine synthesis inhibitor	may be treatment option for ganciclovir-resistant disease, available as an oral agent (80% bioavailability), available as generic product, dosing guidelines for renal insufficiency and dialysis (not recommended in hepatic insufficiency)	has not been evaluated for CMV prophylaxis, requires concentration monitoring that is not widely available, hematologic toxicity, hepatotoxic, limited data on pediatric and no data on geriatric populations

CMV = cytomegalovirus; FDA = Food and Drug Administration.

events, and lack of efficacy against resistant CMV strains. A comprehensive review of current CMV therapies is outside the scope of this article; the reader is referred to other works for a more in-depth review of the clinical trials and prophylactic and treatment recommendations comparing these antiviral agents.[4,6,9,28]

A critical need exists in transplantation for development of novel antiviral agents with activity against CMV that have limited nephrotoxic and hematologic adverse effects and good bioavailability. Maribavir is one such drug and is currently undergoing Phase 3 clinical investigation for the prevention of CMV in transplant recipients and HIV-infected patients. The purpose of this article is to review the pharmacology, pharmacokinetics, efficacy, and safety data of maribavir.

History of Maribavir

Maribavir was originally developed by GlaxoSmithKline. The company performed several Phase 1 and 2 studies in the US and European Union in 2000–2001 for treatment of congenital CMV infection and CMV retinitis in HIV-infected patients. However, development was discontinued in February 2001 due to perceived lack of clinical need for maribavir.[29] The patents covering maribavir held by GlaxoSmithKline expire in 2015. Maribavir was subsequently licensed to ViroPharma in August 2003. At that time, ViroPharma acquired exclusive worldwide rights (excluding Japan) to develop maribavir for prevention and treatment of CMV infections related to all transplantation, congenital transmission, and HIV-infected individuals. In February 2006, maribavir was granted Food and Drug Administration fast track status; in February 2007, it was granted orphan drug status for prevention of CMV viremia and diseases in at-risk populations.[30]

Chemistry

The chemical name of maribavir is 1-β-L-ribofuranosyl-2-isopropylamino-5,6-dichlorobenzimidazole.[31] Evaluation of maribavir analogs revealed that cyclic and branched alkylamino groups at the 2-position of the benzimidazole moiety are necessary for its activity against CMV.[29] Maribavir is a benzimidazole riboside with an unnatural L-sugar moiety that allows for significant improvement in its biostability and a mechanism of action unique from currently available antiviral drugs.[31] The parent compound of maribavir is β-D-ribofuranoside-2-bromo-5,6-dichloro-1H-benzimidazole (BDCRB). Unlike maribavir, this compound contains a D-sugar and is active against CMV by a different mechanism of action. BDCRB inhibits CMV DNA maturation and processing into genome-length segments, while maribavir inhibits UL 97 kinase. Unfortunately, pharmacokinetic studies in rats and monkeys showed that rapid breakdown of BDCRB during first-pass metabolism liberated the inactive and significantly more toxic aglycone (2-bromo-5,6-dichloro-benzimidazole). Hence, maribavir (the unnatural L-sugar moiety) was synthesized to improve biologic stability.

Data Sources

A non–date-restricted MEDLINE search was conducted for English-language articles using the terms maribavir, 1263W94, VP41263, benzimidavir, and benzimidazole. Data were available from January 1998 to July 2008. Selection focused on human pharmacology, pharmacokinetics, and in vitro and in vivo efficacy or toxicity data when human data were not available. Data from abstracts obtained from recent scientific meetings and the manufacturer were also reviewed.

Pharmacology

Maribavir is a member of the benzimidazole drug class.[29,30] Benzimidazoles possess an antiviral mechanism of action different from those of currently available antiviral agents for CMV. Maribavir directly inhibits UL 97 kinase, an early viral gene product involved in viral DNA elongation, DNA packaging, and egress or shedding of capsids from viral nuclei.[2,31,32] In contrast, ganciclovir needs to be phosphorylated by UL 97 kinase to become an active inhibitor of DNA polymerase (UL 54).[33] UL 97 kinase mutations in certain CMV strains have been associated with ganciclovir resistance.[10] Interestingly, maribavir has also been found to be effective against ganciclovir-resistant CMV strains, suggesting a distinctly different mechanism of action than ganciclovir.[34] In vitro analysis demonstrated that maribavir has a higher level of activity than ganciclovir against the human CMV strain AD169, as evidenced by greater effects of maribavir on DNA hybridization (approximately 4-fold lower than ganciclovir), plaque reduction (50% inhibitory concentrations 0.12–0.56 μM for maribavir vs 0.80–7.00 μM for ganciclovir), and yield reduction (~5-fold more active than ganciclovir).[31]

Mutations of UL 97 that impart resistance to maribavir have been identified in vitro, but they are at different locations than the mutations associated with ganciclovir resistance.[35] No maribavir-resistant CMV strains have been detected in clinical trials, although the follow-up period is not long (longest follow-up for completed trials is 5 months).[36] Cross-resistance between maribavir and ganciclovir, cidofovir, or foscarnet has not been detected and would not be anticipated based on their differing mechanisms of action.[34] Maribavir's antiviral activity against select human herpesviruses has been evaluated in an in vitro analysis by various techniques, including cytopathic effect assay,

plaque reduction assay, immunofluorescence assay, enzyme-linked immunosorbent assay, in situ DNA hybridization, and fluorescence-activated cell sorter flow cytometry. Maribavir demonstrated significant in vitro antiviral activity against human CMV and Epstein-Barr virus (EBV), but not against herpes simplex virus (HSV)-1, HSV-2, varicella zoster virus, human herpes virus (HHV)-6, or HHV-8.[37] Clinical trials are necessary to further evaluate maribavir's activity against CMV and EBV in vivo.

Pharmacokinetics

HUMAN DATA

Phase 1 and 2 studies are summarized in Table 2.[38-44] Phase 1 studies have shown that maribavir pharmacokinetics are similar between healthy and HIV-infected patients as well as in patients with renal dysfunction.[38-42,44] Maribavir is rapidly absorbed after oral administration, with at least 30–40% absorption. The pharmacokinetics of maribavir were linear as maximum concentration and area under the curve (AUC) increased nearly proportionately to the dose. This was also demonstrated in a Phase 2 study in stem cell transplant recipients where the highest administered dose was associated with the highest exposure amount.[43] Maribavir is highly protein bound (98%), and the extent of protein binding remains constant over a range of doses. Unbound maribavir plasma concentrations are thought to be responsible for its antiviral activity.

Maribavir is rapidly eliminated independent of dose and minimal concentrations are detected in the urine (3%). In vitro experiments conducted by Glaxo Wellcome have shown that maribavir's metabolite 4469W94 (also known as VP 44469) is primarily formed by CYP3A4; therefore, maribavir could interact with other medications that interfere with or are metabolized by CYP3A4. This system is responsible for approximately 35% of maribavir's clearance.[41] It is also thought that nonrenal pathways of VP 44469 elimination must exist to prevent the exponential increase in the metabolite's AUC in patients with decreasing renal function.[40] Studies of maribavir pharmacokinetics in patients with hepatic dysfunction have not yet been reported; however, there is an ongoing Phase 3 trial evaluating maribavir use in liver transplant recipients.[45]

Pharmacodynamics

Results from Phase 1 and 2 studies are summarized in Table 2.[38-44] In a Phase 1 study examining CMV in the semen of HIV-infected patients, maribavir administered for 28 days demonstrated in vivo activity at all dosage regimens tested.[39] Semen CMV titers were measured by plaque assay and semen and serum viral loads were measured by DNA polymerase chain reaction (PCR). Quantitative reductions in semen and the differences in cohorts were less pronounced than were the results for titers. The authors thought an explanation for this may be that synthesis of DNA continues to a degree in the presence of maribavir, but that intact viable virus is not produced. They also noted that quantitative reduction in viral DNA may lag behind plaque reduction. No resistance was identified in isolates obtained at day 28, but the authors noted that to assess the risk of developing resistance, it would be necessary to determine the inhibitory concentrations of the isolates after patients received maribavir for at least 90 days.

Another Phase 1 study evaluating maribavir in patients with AIDS and CMV retinitis has been published only in abstract form to date.[44] Plasma was collected over 24 hours and a single vitreous humor sample was collected between 1 and 8 hours after the final dose. Samples were measured by mass spectrometry for maribavir concentrations and blood was collected for CMV quantification by PCR. Three patients with detectable viral loads were found to have decreases in viral loads with maribavir. The authors also noted that maribavir possessed a good vitreous humor concentration, making it a promising candidate for further study as oral treatment against CMV disease.

The results of a Phase 2 study evaluating the use of maribavir for CMV prophylaxis in allogeneic stem cell transplant recipients have recently been reported (Table 2).[43] The primary endpoint was the incidence and time to onset of CMV infection or disease. CMV infection was defined as a positive pp65 antigenemia assay (≥1 positive cell per 100,000 leukocytes) or positive plasma CMV DNA by PCR (≥1000 DNA copies/mL). CMV disease was defined by previously published criteria. Secondary endpoints included the incidence of CMV disease alone and the use of antiviral therapy for CMV infection treatment. The authors noted that although a wide range of maribavir doses (300–2400 mg/day) have been evaluated in Phase 1 trials, relatively low doses were selected for this study with a goal of identifying a regimen that would provide good tolerability yet retain potent antiviral activity. CMV surveillance by weekly CMV pp65 antigenemia and PCR was performed, and if CMV was detected, maribavir was stopped and preemptive CMV therapy was started. The 4 groups were similar in terms of age, underlying disease, donor type, stem-cell source, conditioning regimen, and time of initiation of study drug after transplantation. However, there were more men than women in each study group, except for the maribavir 400-mg twice-daily group. Most stem cell donors in each group were CMV-seropositive, except in the placebo group, which had more CMV-seronegative donors (61% vs 39%).

Compared with placebo, maribavir-treated patients had less infection based on pp65 antigenemia, although this was not significant, and less plasma CMV DNA, which was significant. There were no significant differences in the incidence of CMV disease between the maribavir

Table 2. Phase 1 and 2 Maribavir Clinical Trials

Reference	Design	Pts. (n) and Treatment Groups	Results
Wang (2003)[38]	2 Phase 1, multicenter, double-blind, randomized, placebo-controlled, single-dose escalation studies	Trial 1 12 randomized healthy men: 10 received maribavir 50,100, 200, 400, 800, and 1600 mg 2 received placebo Trial 2 16 randomized HIV-infected men: 12 received maribavir 100, 400, 800, and 1600 mg 4 received placebo	C_{max} 1–3 h after dosing across all dose levels but as late as 5–6 h in some pts. after higher dose administration at least 30–40% of single dose absorbed in HIV trial, high-fat meal delayed t_{max} by about 2 h and decreased C_{max} and AUC by 30% maribavir associated with high protein binding (98%), remained constant over dose range (200–1600 mg) principal *N*-dealkylated inactive metabolite, 4469W4, detected in plasma within 30 min of dosing and 1.5–2 times longer $t_{1/2}$ than maribavir undergoes further metabolism to glucoronide conjugate rapid elimination (mean plasma $t_{1/2}$ 3–5 h independent of dose) <2% maribavir eliminated unchanged in urine, metabolite accounted for 30–40%
Lalezari (2002)[39]	Phase 1, multicenter, multiple-dose, randomized, parallel-dose, dose escalation study performed over 28 days	62 HIV-infected men with asymptomatic CMV shedding in semen randomized to maribavir: 100 mg twice daily (n = 11) 200 mg twice daily (n = 12) 400 mg 3 times daily (n = 10) 600 mg twice daily (n = 7) 900 mg twice daily (n = 12) 1200 mg twice daily (n = 10) placebo (n = 16)	CMV serum titer (mean ± SD) decrease at day 28 200- and 400-mg groups: 3.7 ± 0.96 $\log_{10}$ PFU/mL 100-mg group: 2.9 ± 0.79 $\log_{10}$ PFU/mL 600-mg group: 3.3 ± 1.32 $\log_{10}$ PFU/mL no. and % of pts. in each group with ≥2 $\log_{10}$ unit reductions from baseline in semen CMV titers at day 28 100-mg group: 6 of 7 (86%) 200-mg group: 5 of 5 (100%) 400-mg group: 6 of 6 (100%) 600-mg group: 5 of 6 (83%) only 1 pt. (600 mg twice daily) had quantifiable CMV in blood at baseline (4.81 $\log_{10}$ copies/mL); viral load decreased to below the limit of detection by PCR at day 28
Swan (2007)[40]	Phase 1, multicenter, open-label, single-dose pharmacokinetic study	31 pts. with varying renal function received one 400-mg dose of maribavir renal impairment (determined using Cockcroft-Gault equation) mild Cl_{cr} 50–80 mL/min (n = 5) moderate Cl_{cr} 30–49 mL/min (n = 5) severe Cl_{cr} < 30 mL/min (n = 9) normal Cl_{cr} > 80 mL/min (n = 12)	renal impairment associated with a 2-fold increase in AUC values for the *N*-dealkylated inactive metabolite of maribavir, VP 44469 no significant pharmacokinetic differences between pts. with normal renal function or any degree of impairment based on total and unbound maribavir plasma concentrations
Goldwater (2008)[41]	Phase 1, open-label, single-center, random-sequence, 2-way crossover study of ketoconazole and maribavir	20 pts. total (10 healthy men and women) treatment 1: maribavir 400 mg once followed by 1-wk washout treatment 2: ketoconazole 400 mg once followed by maribavir 400 mg once	ketoconazole moderately reduced the clearance of both maribavir and VP 44469 maribavir C_{max} increased by 10% (95% CI 1 to 19) and mean AUC_{0-t} increased by 46% (95% CI 38 to 55) CYP3A4 responsible for ~35% of maribavir clearance
Ma (2006)[42]	Phase 1, randomized, double-blind, placebo-controlled 11-day study of effects of maribavir on liver enzyme activity	20 healthy adults maribavir (n = 16) 400 mg twice daily for 10 days vs placebo (n = 4) for 10 days each pt. also received a drug cocktail containing 5 drugs (caffeine, warfarin plus vitamin K, omeprazole, dextro-methorphan, midazolam) for 4 days prior to maribavir initiation and 7 days after therapy completion	maribavir did not affect CYP1A2, 2C9, or 3A; NAT-2; or XO activities, but did inhibit or decrease CYP2C19 and 2D6 activity rapid absorption C_{max} 1 h postdose, with C_{max} similar after first and last dose mean $t_{1/2}$ on day 1 was 3.7 ± 0.9 h

AUC = area under the curve; C_{max} = maximum concentration; Cl_{cr} = creatinine clearance; CMV = cytomegalovirus; NAT-2 = *N*-acetyltransferase-2; PCR = polymerase chain reaction; $t_{1/2}$ = half-life; t_{max} = time to C_{max}; XO = xanthine oxidase.

(continued on page 1452)

Table 2. Phase 1 and 2 Maribavir Clinical Trials (continued)

Reference	Design	Pts. (n) and Treatment Groups	Results
Winston (2008)[43]	Phase 2, multicenter, randomized, double-blind, placebo-controlled, dose-ranging study over 12 wk	after stem cell transplant, 111 pts. were randomized to: maribavir 100 mg twice daily (n = 27, median 57 days) maribavir 400 mg once daily (n = 27, median 57 days) maribavir 400 mg twice daily (n = 26, median 29 days) placebo (n = 28, median 34 days)	within the first 100 days posttransplant: incidence of CMV infection by CMV pp65 antigenemia for respective maribavir group (15%, p = 0.046; 19%, p = 0.116; 15%, p = 0.053) vs placebo (39%) incidence of CMV infection by plasma CMV DNA for respective maribavir group (7%, p = 0.001; 11%, p = 0.007; 19%, p = 0.038) vs placebo (46%) preemptive antiviral therapy used significantly less often in each of the respective maribavir groups (15%, p = 0.001; 30%, p = 0.051; 15%, p = 0.002) vs placebo (57%) no patient in any maribavir group developed CMV disease vs 3 (11%) pts. in the placebo group (p = NS), and no additional cases of late CMV disease occurred after 100 days
Hendrix (2000)[44] (abstract)	Phase 1, open-label 1-wk study to evaluate ocular penetration in CMV retinitis	8 pts. with AIDS and CMV retinitis randomized: 800 mg 3 times daily for 7 days (n = 4) 1200 mg twice daily for 7 days (n = 4)	7 pts. completed the study 3 pts. had detectable CMV viral loads at baseline that decreased by 1.9, 0.26, and ≥1.1 $\log_{10}$ CMV copies/mL by day 8 vitreous humor maribavir concentrations were >50% inhibitory concentration against CMV

CMV = cytomegalovirus.

groups and the placebo group. Among the maribavir groups, approximately half of all CMV infections (pp65 antigenemia in 7 pts. and CMV DNA PCR in 5 pts.) occurred while the patient was taking maribavir, while the other half occurred after drug discontinuation. The authors also noted that there were no significant differences in maribavir plasma concentrations between patients who developed CMV infection and those who did not. Patient subsets based on the randomization stratification of transplant type, myeloablative (70% of all enrolled patients) versus nonmyeloablative, found the incidence of CMV infection or disease to be numerically lower in each maribavir group compared with placebo (data not reported). Twenty-one percent of patients who received placebo died, compared with 14%, 11%, and 12% of maribavir patients, respectively; no deaths were attributed to the study drug.[43]

Adverse Effects

Adverse events are summarized in Table 3.[38-43] The most commonly reported adverse effect across all trial populations in both Phase 1 and 2 trials was taste disturbance. Taste disturbances are most often described as a metallic or bitter taste, and the onset, intensity, and frequency appear to be dose related. In 2 of the Phase 1 studies in healthy volunteers or patients with renal impairment, the onset of taste disturbance was generally within one hour after dosing, with variable duration (3 min–25 h).[40,41] In the Phase 2 placebo-controlled study comparing 3 dosing regimens of maribavir (100 mg twice daily, 400 mg once daily, 400 mg twice daily) in stem cell transplant recipients, the median onset times to taste disturbance were 22 days, 6 days, and 3 days after maribavir initiation, respectively, but varied greatly among patients in each dose group.[43] In this trial, taste distur-

Table 3. Summary of Adverse Effects[38-43,a]

Adverse Effect	Overall Incidence, n (%)
Taste disturbance	162 (42.9)
Headache	36 (9.5)
Nausea	25 (6.6)
Diarrhea	18 (4.8)
Rash	15 (4.0)
Pruritus	13 (3.4)
Tiredness/drowsiness/fatigue	10 (2.6)
Vomiting	8 (2.1)
Fever	4 (1.1)
Dizziness	3 (0.8)
Abdominal pain	3 (0.8)
Herpes simplex of lips	2 (0.5)
Sore throat	2 (0.5)

[a]Incidence and severity of adverse effects not reported by Hendrix et al.[44]

bance was the only adverse event for which the observed incidence rates were statistically higher compared with placebo ($p = 0.025$); 6 (7%) patients discontinued maribavir due to this adverse effect. On the basis of the onset and duration of taste disturbance, this adverse effect is thought to be due to secretion of maribavir into the salivary glands after systemic absorption rather than the local taste of the product itself or the substance upon ingestion.[38]

In the Phase 1 study that compared maribavir with placebo for 28 days in HIV-infected males, after approximately 7–12 days of therapy, 5 maribavir-treated patients prematurely discontinued the drug due to a diffuse maculopapular rash of moderate intensity.[39] Two patients were receiving 200 mg 3 times a day, and one each received 600, 900, and 1200 mg twice daily. Four (80%) patients had a history of allergic reaction to other drugs. After maribavir discontinuation, the rash resolved within 1–4 days without sequelae in all patients. The effects of antiretrovirals or antiinfectives as CYP3A4 inducers or inhibitors on maribavir were not assessed. Interestingly, this adverse effect was not observed in the Phase 2 trial in stem cell transplant recipients.[43]

There was no significant increase in adverse events in patients with varying degrees of renal impairment.[40] Overall, there were no changes in vital signs, electrocardiograms, or clinical laboratory parameters (including neutrophil and platelet counts or use of hematopoietic growth factors in stem cell transplant recipients), serious adverse events, or patient deaths associated with maribavir in Phase 1 or 2 trials.

Drug Interactions

Maribavir was not found to affect the CYP1A2, CYP2C9, CYP3A4, *N*-acetyltransferase-2, or xanthine oxidase activities.[42] Maribavir did inhibit or decrease CYP2C19 and CYP2D6 activity; the clinical significance of this is unknown. However, patients receiving maribavir and drugs metabolized by CYP2C19 (eg, proton pump inhibitors, diazepam, warfarin, clopidogrel, nelfinavir) or CYP2D6 (eg, carvedilol, metoprolol, haloperidol, selective serotonin–reuptake inhibitors, venlafaxine, metoclopramide, oxycodone, tramadol) may require additional therapeutic monitoring. The reader is referred to a more in-depth resource on drugs metabolized by or that interact with CYP2C19 and CYP2D6.[46]

An open-label trial assessed the effects of ketoconazole on maribavir pharmacokinetics in 20 healthy adults.[41] Despite near-complete inhibition of CYP3A4 metabolism with concomitant ketoconazole, there was only a moderate change in maribavir pharmacokinetics. The authors noted that these findings suggest that maribavir is eliminated via multiple metabolic pathways and suggested that no dose adjustment is necessary when maribavir is coadministered with CYP3A4 inhibitors or substrates.

The anti-CMV effect of maribavir when used in combination with other antiviral agents has been assessed via a modified fractional inhibitory concentration to measure the strength and statistical significance of drug interactions.[47] Defining interactions with antiretrovirals will be particularly relevant, since maribavir may be used in HIV-infected patients. Anti-HIV agents were generally not affected by the addition of maribavir, with 4 exceptions. Zidovudine, amprenavir, and indinavir produced some potentiation of maribavir's anti-CMV effects. Abacavir's modest anti-CMV activity was enhanced when combined with maribavir. This study also showed that acyclovir, ganciclovir, and foscarnet had additive effects when combined with maribavir, while cidofovir displayed synergistic effects.

In contrast, a separate in vitro study reported that maribavir had an indeterminate effect on foscarnet and cidofovir and had an antagonistic effect on ganciclovir. This antagonism is thought to be due to maribavir inhibiting UL 97 kinase and preventing ganciclovir's phosphorylation by this enzyme.[48] Theoretically, since maribavir inhibits UL 97, ganciclovir and maribavir could be antagonistic in vivo. The clinical significance of these interactions is unknown.

Pediatric and Geriatric Considerations

Data on maribavir in pediatric and geriatric patient populations have not been reported. Efficacy and safety data are required before maribavir can be recommended for routine use in these populations.

Study Limitations

The human studies discussed here have several limitations. Sample sizes were limited and no data were obtained on pediatric or geriatric populations. While Phase 3 trials will provide data in larger sample sizes, patient selection will still be limited by strict inclusion and exclusion criteria. Although maribavir has been assessed in patients with impaired renal function, it has not yet been evaluated in those requiring any type of dialysis. Therefore, dosing recommendations for this population are unavailable. Similarly, no published data or dosing recommendations are available for patients with impaired hepatic function.

Although human trials are ongoing to assess maribavir's effect on CMV activity, no human trials have been published to date assessing the drug's in vitro activity against EBV. Moreover, none of the clinical trials to date provide long-term data on use of maribavir. This is a particular concern regarding development of resistance. Additionally, although drug interaction studies were performed, the effects of newer antiretrovirals and antiinfective agents as CYP3A4 inducers or inhibitors on maribavir have not been assessed. Maribavir did inhibit or decrease CYP2C19 and

CYP2D6 activity; whether there is any clinical significance to that action is unknown. It is also unclear from the present conflicting study results whether ganciclovir and maribavir are antagonistic in vivo. Studies in larger populations with longer follow-up periods are necessary to address these important clinical issues.

Therapeutic Implications

Phase 1 and 2 studies conducted to date have demonstrated that maribavir has a remarkably different toxicity profile compared with the existing agents approved to prevent CMV infections in immunocompromised patients. While one advantage of maribavir is the absence of hematologic toxicities, the high prevalence of taste disturbances may limit tolerability. The impact of this will be further elucidated by Phase 3 studies.

Currently, 2 Phase 3 clinical trials evaluating the safety and efficacy of maribavir are recruiting participants.[45,49] One study will assess the safety and efficacy of maribavir for prevention of CMV disease in allogeneic stem cell recipients, and the second will compare maribavir with oral ganciclovir for CMV prophylaxis in liver transplant recipients. These clinical trials are expected to be completed in the fall of 2008 and 2009, respectively.

Since maribavir is active only against CMV and EBV, its use for prophylaxis may require the addition of acyclovir. Despite this, the pill burden and frequency of administration are less than with oral ganciclovir. The impact of this on patient adherence and tolerability is not known.

A concern with oral ganciclovir prophylaxis has been that its low bioavailability (5–31%), resulting in lower systemic exposure, could promote the emergence of viral resistance. Human data have demonstrated that maribavir has greater bioavailability than ganciclovir (30–40%), but lower bioavailability than valganciclovir (60%). Nevertheless, it may be a viable option for patient populations such as liver transplant recipients who, in some cases, receive intravenous ganciclovir as prophylaxis in place of oral ganciclovir or valganciclovir.

It is also plausible that, since maribavir has demonstrated in vitro activity against ganciclovir-resistant CMV, it may eventually be found to be valuable in treating patients with CMV disease caused by these strains. Whether future development of maribavir-resistant strains may result as a consequence of its use for prophylaxis is unknown, but if it does occur, it could limit the potential value of this drug in CMV treatment in the years to come.

As maribavir is not yet marketed, its cost is unknown. When the cost is determined, one factor to consider in comparing it with the cost of intravenous ganciclovir is that maribavir does not require intravenous administration, with the attendant healthcare resources and risk of line infections.

The therapeutic use of maribavir is anticipated to be for the prevention of CMV in transplant recipients, and it may also be useful in the treatment of ganciclovir-resistant strains of CMV infection. Due to maribavir's ability to achieve high drug concentrations in the vitreous humor, it may also represent an oral option for patients with CMV retinitis.[44] However, research will be necessary to compare these options in large, prospective, randomized clinical trials. Currently, there are no other benzimidazoles in clinical trials. GW275175X, a GlaxoSmithKline compound, is a benzimidazole that has the same mechanism of action as the parent compound BDCRB, but is less protein bound and has a longer plasma half-life compared with the other candidates in this drug class.[50] Although GW275175X completed a Phase 1 single-dose escalating trial, its development was halted in favor of maribavir.[2]

Dosage and Administration

In Phase 1 and 2 trials published to date, maribavir has been administered as an oral agent over a varying range of doses (100–1600 mg) 1, 2, or 3 times a day. Since maribavir is extensively protein bound, antiviral activity may correlate closely with the unbound maribavir plasma concentrations.[38] To date, there are no published dosing recommendations for maribavir use in hepatically impaired patients; however, a Phase 3 trial evaluating maribavir as CMV prophylaxis in liver transplant recipients is underway. A Phase 1 study of patients with mild-to-severe renal impairment has shown that the pharmacokinetics of maribavir are not altered during renal impairment. However, there are no published dosing recommendations on maribavir in patients undergoing any type of dialysis.

Although it is not known which pharmacokinetic parameter or plasma concentration of maribavir is essential in determining efficacy, results from the Phase 2 trial in stem cell transplant recipients found that maribavir dosages of 100 mg twice daily and 400 mg once daily provided similar trough plasma concentrations.[43] At the higher dosage of 400 mg twice daily, the authors noted that higher maximum concentration and AUC values were achieved, but the increased exposure was not associated with improved efficacy and caused more frequent adverse events. Therefore, the authors suggested that future trials for CMV prophylaxis consider using maribavir doses of 100 mg twice daily or 400 mg once daily.

Summary

Maribavir is a novel oral antiviral agent with in vitro activity against both CMV and EBV and an adverse event profile different from that of current antivirals for CMV prevention and treatment. Maribavir may offer slight im-

provement in adverse effects over existing therapies. The bioavailability of maribavir appears to be less than valganciclovir but greater than oral ganciclovir. Since maribavir has demonstrated in vitro activity against ganciclovir-resistant CMV, it may be found in clinical trials to be valuable in this setting. One advantage is the absence of hematologic toxicities, but the high prevalence of taste disturbances may limit tolerability. The impact of this is being further elucidated by ongoing Phase 3 studies, as well as its efficacy in vivo against CMV and EBV. A critical need exists in transplantation for an antiviral agent with good oral bioavailability and limited nephrotoxic, hematologic, and hepatotoxic adverse events. Future maribavir research should focus on dosing recommendations in dialysis patients and patients with impaired hepatic function; long-term efficacy, drug resistance, and safety outcomes; and further define drug interactions.

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Maribavir: Un Nuevo Agente Antiviral con Actividad Contra el Citomegalovirus

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Ann Pharmacother 2008;42:1447-57.

EXTRACTO

OBJETIVO: Revisar la farmacología, la farmacocinética, la eficacia, y la seguridad del maribavir, un nuevo agente antiviral.

FUENTES DE INFORMACIÓN: Se identificaron artículos mediante búsquedas en MEDLINE (enero 1998–abril 2008). Los extractos de reuniones científicas recientes y del fabricante también se incluyeron.

SELECCIÓN DE FUENTES DE INFORMACIÓN Y MÉTODO DE EXTRACCIÓN DE INFORMACIÓN: Todos los estudios in vitro e in vivo y los extractos en inglés fueron revisados y considerados para inclusión. Se incluyeron todos los estudios en humanos.

SÍNTESIS: El maribavir es un agente antiviral de una clase de drogas conocida como bencimidazolas. Éste posee actividad significativa contra el citomegalovirus (CMV) de humanos y el virus de Epstein-Barr, pero no contra otros virus del herpes. A diferencia del ganciclovir, el cual necesita fosforilación por la cinasa UL 97 para convertirse en un inhibidor activo de la polimerasa del ADN, el maribavir directamente inhibe la cinasa del UL 97. La cinasa del UL 97 es un producto temprano de un gen viral que participa en la elongación del ADN viral, el empaque del ADN y salida o desprendimiento de cápsidos del núcleo viral. Además, se ha encontrado que el maribavir es efectivo contra cepas del CMV resistentes al ganciclovir. El maribavir difiere de los agentes antivirales contra el CMV en cuanto al perfil de acontecimientos adversos. El maribavir no está relacionado con nefrotoxicidad ni toxicidad hematológica, pero se ha relacionado con disturbios del gusto. En febrero de 2007, la FDA otorgó condición de droga huérfana al maribavir en la prevención de viremia y enfermedades causadas por CMV en poblaciones a riesgo. Se han completado estudios de fase 2 de maribavir en recipientes de trasplante de células madre, y se están llevando a cabo estudios de fase 3 en recipientes de trasplante de células madre y órganos.

CONCLUSIONES: El maribavir puede ser una opción para el tratamiento de infecciones causadas por CMV resistentes al ganciclovir. Su biodisponibilidad es mayor que la del ganciclovir oral, pero menor que la del valganciclovir. No se observaron diferencias en cuanto a la farmacocinética en pacientes con impedimento renal, aunque no se evaluaron pacientes dependientes de diálisis. El maribavir no está relacionado con toxicidades hematológicas; sin embargo, la alta incidencia de disturbios del gusto pudieran limitar su tolerabilidad.

Traducido por Rafaela Mena

Le Maribavir: Un Nouvel Agent Antiviral avec une Activité Contre le Cyto-Mégalo-Virus

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Ann Pharmacother 2008;42:1447-57.

RÉSUMÉ

OBJECTIF: Analyser le profil pharmacologique, la pharmacocinétique, les essais cliniques, l'effet clinique, et la tolérance du maribavir, un nouvel agent antiviral.

REVUE DE LITTÉRATURE: Des articles ont été identifiés via des recherches bibliographiques MEDLINE (janvier 1998–avril 2008). Des informations provenant d'extraits de congrès scientifiques et de données du fabricant ont également été recueillies.

SÉLECTION DES ÉTUDES ET SÉLECTION DE L'INFORMATION: Toutes les études in vitro et in vivo et tous les résumés évaluant le maribavir ont été analysés et considérés pour leur inclusion dans l'étude.

RÉSUMÉ: Le maribavir est un agent antiviral appartenant à la classe des benzimidazolés. Il possède une activité pharmacologique significative contre à la fois le cyto-mégalo-virus humain (CMV) et le virus d'Epstein-Barr, mais pas contre les autres virus de l'herpès. À la différence du ganciclovir qui nécessite une phosphorylation par la protéine kinase virale pUL97 pour devenir un inhibiteur actif de l'ADN polymérase, le maribavir inhibe directement la pUL97. La kinase pUL97 est le produit génique viral précoce impliqué dans l'élongation virale de l'ADN, dans l'encapsidation de l'ADN et dans l'élimination des capsides virales des noyaux viraux. Le maribavir a également été efficace contre les souches de CMV résistantes au ganciclovir. Il diffère des antiviraux CMV actuels dans son profil d'effets secondaires et n'est lié à aucune néphrotoxicité ou toxicité hématologique. Cependant, il a été associé à des troubles du goût. En février 2007, la FDA a attribué au maribavir le statut de médicament Orphelin pour le traitement préventif

de la virémie CMV et des maladies chez les populations à risque. Les essais cliniques de phase 2 chez les receveurs de greffes de cellules souches ont été complétés et des essais cliniques de phase 3 sont en cours.

CONCLUSIONS: Un agent viral présentant une bonne biodisponibilité orale avec des effets secondaires néphrotoxiques, hématologiques, et hépatotoxiques limités est un besoin crucial qui existe dans les transplantations d'organes. Le maribavir est un nouvel agent antiviral avec une activité contre à la fois le CMV et l'Epstein-Barr. Il présente un profil d'effets secondaires qui diffère des antiviraux actuels pour la prévention et le traitement du CMV. Aussi, il est actuellement en phase 3 chez les receveurs de greffes d'organes.

Traduit par Thierry Youmbi