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Maribavir: Antiviral Agent Overview for Treatment of Cytomegalovirus

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ABSTRACT:
Infections with the cytomegalovirus (CMV) are a frequent complication in solid organ transplant (SOT) and hematopoietic stem cell transplant (HSCT) recipients, increasing morbidity and death. Although currently available treatment approaches have lowered infection burdens, their use is constrained by side effects such as nephrotoxicity and/or myelosuppression, as well as the emergence of resistance. It is critical to expand our present arsenal against CMV infection. Here, we look at maribavir, an emerging medicine, and its safety and efficacy in the prevention and treatment of CMV infections, including resistant/refractory illness.
Keywords: Maribavir, Cytomegalovirus, efficacy, safety.

I.INTRODUCTION

Cytomegalovirus (CMV) infections are one of the most common infections after solid organ transplantation (SOT) and hematopoietic stem cell transplantation (HSCT). Optimal prevention and treatment lead to better overall outcomes. CMV infection can cause a variety of symptoms, ranging from asymptomatic CMV DNAemia (detectable CMV DNA in plasma, serum, or whole blood) to CMV syndrome, which includes fevers, malaise, leukopenia, thrombocytopenia, and hepatitis, to more severe end organ disease, including colitis, retinitis, and pneumonitis. In 2003, ViroPharma obtained a licence from GlaxoSmithKline for the prevention and treatment of human cytomegalovirus (HCMV) illness in hematopoietic stem cell/bone marrow transplant patients. Maribavir suppresses HCMV replication by inhibiting the UL97 or pUL97 protein kinase enzyme, which is expressed by the virus. Maribavir showed potential in Phase II clinical studies and was given fast track designation, however in a Phase III trial, it failed to satisfy study goals. However, the Phase III trial's dosage may have been too low to be effective.

Maribavir prophylaxis showed good antiviral effect in a Phase II research, as indicated by a statistically significant reduction in the rate of CMV reactivation in patients of hematopoietic stem cell/bone marrow transplantation. The number of participants who required pre-emptive anti-CMV medication was statistically significantly lower with maribavir compared to placebo in an intent-to-treat analysis of the first 100 days following the transplant.

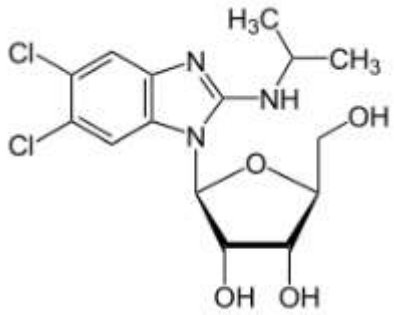

Fig 1: Structure Of Mirabavir.

ViroPharma conducted a Phase III clinical tests to investigate the prophylactic use of CMV vaccine in allogeneic stem cell transplant recipients.. The Phase III study failed to meet its goal, with no meaningful difference between maribavir and a placebo in reducing the rate at which CMV DNA levels were found in patients, according to ViroPharma. In a Phase III, multicenter, open-label, active-controlled trial, the safety and efficacy of maribavir were compared to a treatment assigned cidofovir, valganciclovir, ganciclovir, or foscarnet are some of the antivirals used to treat cytomegalovirus, according to a study researcher.. In this study For up to eight weeks, 352 transplant patients with cytomegalovirus infections who won't respond (with or without resistance) to

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treatment were randomly randomised to receive maribavir or treatment assigned by a researcher. At the end of the eighth week of the study, the researchers evaluated the two groups' plasma cytomegalovirus DNA concentration levels, with effectiveness defined as a level below what is quantifiable. Sixty-six percent of the 235 people who received maribavir had cytomegalovirus DNA levels below what was detectable, compared to only 24 percent of the 117 participants who received an investigator-assigned medication.

Agent	Route of Administration	Route of Elimination	Indication for CMV	Major toxicities
Maribavir	Oral	Hepatix	Treatment of resistant/refractory disease	Taste disturbance and gastrointestinal
Ganciclovir	Intravenous	Renal	Treatment and Prophylaxis	Myelosuppression and nephrotoxicity
Valganciclovir	Oral	Renal	Treatment and Prophylaxis	Myelosuppression and nephrotoxicity
Foscarnet	Intravenous	Renal	Treatment	Nephrotoxicity, myelosuppression, GI and electrolyte wasting
Cidofovir	Intravenous	Renal	Treatment	Nephrotoxicity, myelosuppression, alopecia and asthenia
Lecermovir	Oral, Intravenous	Hepatic	Prophylaxis in HSCT recipients	GI and peripheral edema

II.MECHANISM OF ACTION:

Maribavir, unlike classic CMV antivirals, exerts its antiviral activity through a different target, making it useful in the treatment of CMV infections that have shown resistant to normal therapy. Ganciclovir and valganciclovir should not be given together because they both require activation via CMV pUL97 to have an antiviral effect. When combined with maribavir, an inhibitor with same enzyme, their antiviral efficacy is considerably reduced.

Benzimidazoles were the first CMV terminase inhibitors in clinical trials, and they were seen as a promising option because they didn't interfere with target the core terminase complexes of proteins UL51, UL56, and UL89, which are all necessary for viral replication, with host-cellular DNA replication. Early clinical development of benzimidazoles such as 2-Bromo-5,6-dichloro-1-d-ribofuranosyl-1H-benzimidazole (BDCRB) was tragically discontinued due to adverse in vivo metabolism. Maribavir is a new benzimidazole I-riboside molecule that, while structurally similar to BDCRB, has a different mode of action. Maribavir inhibits CMV UL97 protein kinase without acting as an enzymatic substrate. kinase, which slows DNA synthesis and prevents viral particles from leaving infected cells by nuclear egress. UL97 phosphorylates viral and host cellular proteins, however it is not required for CMV DNA polymerase UL54 or the core terminase complex proteins pUL51, pUL56, and pUL89 to replicate in tissue culture. This has been observed in mutant viruses that have lost the UL97 gene yet are still able to replicate. The whole function of UL97 and its role in replication, as well as how maribavir affects viral replication inhibition, is still unknown.

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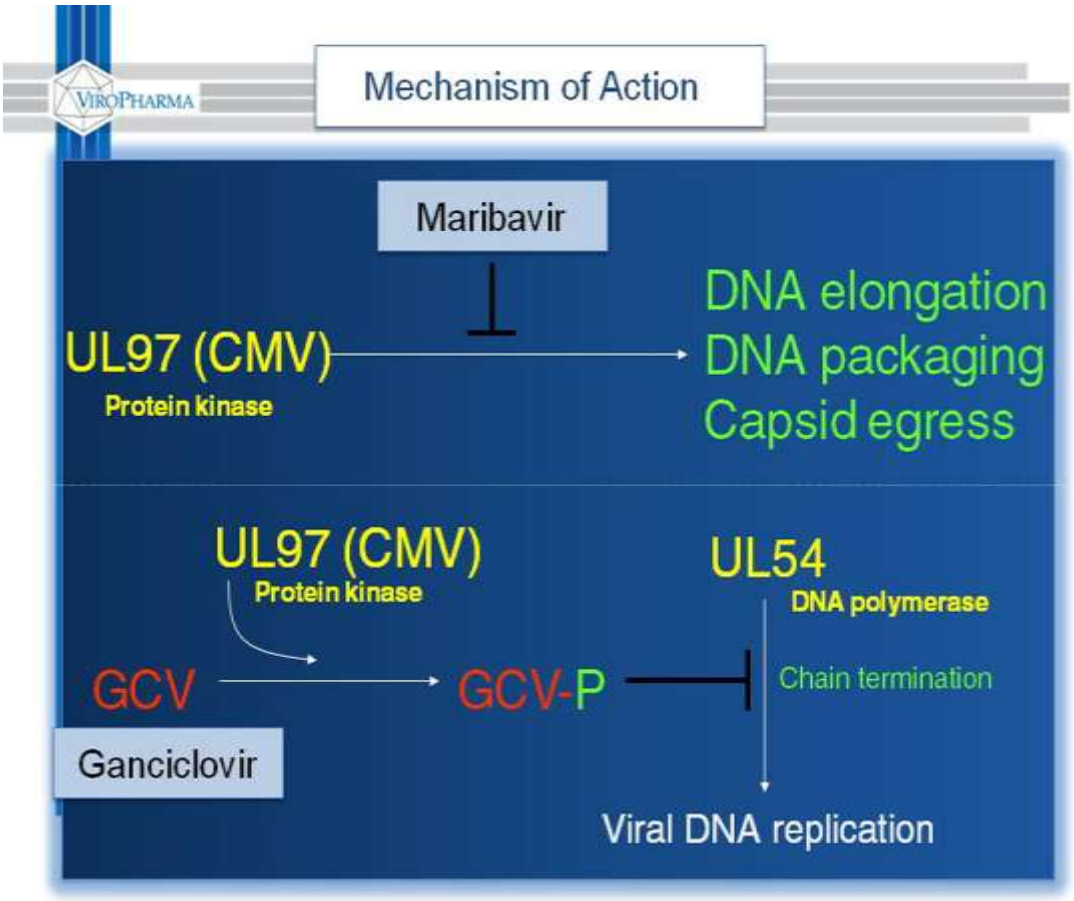

Fig 2: Mechanism of action for Maribavir.

At doses of 1uM to 15uM, maribavir's antiviral action inhibits CMV replication. Maribavir is exclusively accessible as an oral formulation, has a bioavailability of 30–40%, and is strongly plasma protein bound (>97%), resulting in free plasma concentrations being 100 times lower than total drug plasma concentrations. Maribavir concentrations are reduced by 30% when given with high-fat meals. Maribavir's pharmacokinetics (PK) are primarily linear, with a Cmax of 1–3 hours after injection and a plasma half-life of 3–5 hours. Maribavir is extensively metabolised in the liver and is predominantly removed through biliary excretion, with renal impairment (3% urine excretion) having no effect on clearance.

III.PHARMACODYNAMICS:

Maribavir, unlike classic CMV antivirals, exerts its antiviral activity through a different target, making it useful in the treatment of CMV infections that have shown resistant to normal therapy. Ganciclovir and valganciclovir should not be administered together because they both require activation through CMV pUL97 to have an antiviral effect. When combined with maribavir, an inhibitor with same enzyme, their antiviral efficacy is reduced considerably.

Clinical Significance- The clinical significance of maribavir based on study is as follow:

a. Absorption- According to population pharmacokinetic modelling, the AUC0-tau and Cmax in patients receiving maribavir 400mg twice day were 128 ug.h/mL and 17.2 ug/mL, respectively. It has an average Tmax of one to three hours..
b. Protein Binding- In all concentration ranges studied, maribavir was substantially protein-bound in plasma (98 percent),5 most likely to serum albumin and alpha-1-acid glycoprotein.
c. Route Of Elimination-Maribavir is mostly removed by hepatic metabolism. Following oral administration of radiolabeled maribavir, 61% of the dose was eliminated in the urine (2% as unaltered drug) and 14% in the faeces (5.7 percent as unchanged drug).

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d. Metabolism- Following oral administration, maribavir is substantially metabolised, principally by CYP3A4 and to a lesser amount, by CYP1A2.5. VP 44469, an inactive N-dealkylated metabolite, is the main circulating metabolite.

IV.SAFETY AND SIDE EFFECTSS:

The most common gastrointestinal side effects in a phase 2 trial of maribavir for resistant/refractory disease were dysgeusia (65.0 percent), nausea (34.2 percent), vomiting (29.2 percent), diarrhoea (23.3 percent), fatigue (20.8 percent), anaemia (20.0 percent), peripheral edoema (19.2 percent), headache (15.8%), and renal impairment (15.8 percent). Maribavir side effects were often reduced with lower doses. Despite its prevalence, dysgeusia, which is typically described as a "metallic" or "bitter" taste, was tolerated by the vast majority of patients, with only one patient quitting therapy in the phase 2 trial and relatively few patients discontinuing treatment throughout several maribavir trials. Three patients had to stop taking their medication due to gastrointestinal side effects such nausea, vomiting, and diarrhoea. Vital signs, clinical laboratory data, and electrocardiograms all showed minor changes. Neutropenia was found in 16 percent of patients at baseline and in 11 percent of patients at least once during the research; however, there was no evidence of significant myelosuppression owing to maribavir. Similar side effects, such as dysgeusia, nausea, vomiting, and rash, were found in a previous study of lower dose maribavir for prophylaxis in bone marrow transplant patients. In a randomised phase 3 trial of 352 patients comparing maribavir to investigator initiated treatment, maribavir was linked to lower rates of acute kidney injury (8.5 percent vs 21.3 percent) and neutropenia (9.4 percent vs 33.9 percent), as well as fewer patients discontinuing maribavir due to treatment-emergent adverse events (13.2 percent vs 31.9 percent). Dysgeusia was the most commonly reported treatment-associated adverse event in the maribavir group (37.2 percent versus 3.4 percent), however only 0.9 percent of patients stopped taking it. Maribavir did not cause any serious side effects in either trial.

V.DRUG INTERACTION:

Because maribavir is predominantly employed in the SOT and HSCT patient population, clinically relevant medication interactions are of special relevance. To control their co-morbidities, transplant recipients are given a variety of drugs, including immunosuppressants and other therapies, the majority of these substances are metabolised in the liver and can act as significant inducers, substrates, or inhibitors of the cytochrome P-450 enzyme system (CYP-450) system. Maribavir is mostly metabolised in the liver, where it is primarily metabolised by CYP-3A4 (70–85%) and CYP-1A2 (15–30%). P-glycoprotein and uridine diphosphate glucuronosyltransferases both use maribavir as a substrate (UGTs). Maribavir had no effect on N-acetyltransferase-2 or xanthine oxidase activity in healthy participants, according to preliminary research. Maribavir also displayed little interaction with CYP-450 isozyme substrate drugs. Maribavir inhibits CYP-2C19, P-glycoprotein, and maybe UGT1A1, but not CYP-450. Though most drugs should have low interactions with maribavir. The antifungal medication ketoconazole increased maribavir's area under the curve (AUC) by 54 percent as a substrate of CYP-3A4 and CYP-1A2, Maribavir was not impacted by voriconazole, and posaconazole, isavuconazole, or itraconazole are unlikely to influence it.Maribavir exposure was reduced by 61 percent after taking rifampin. Antacids had no effect on the metabolism of maribavir. Maribavir increased tacrolimus AUC by 51 percent in a randomised, double-blind PK study in as a moderate inhibitor of P-glycoprotein in renal transplant recipients, resulting in significant increases in both peak and trough concentrations. Increased blood immunosuppressant medication levels were found in 21 (9.0%) patients in the maribavir group (tacrolimus: n=19, sirolimus: n=2) and in 1 (0.9%) patient in the IAT (valganciclovir/ganciclovir) group in the phase 3 trial for resistant/refractory illness. To avoid supra- and subtherapeutic concentrations, it is prudent to monitor tacrolimus and other comparable medications (cyclosporine, sirolimus, and everolimus) while on maribavir and after termination.

VI.RESISTANCE AND ANTIVIRAL ACTIVITY:

UL97 mutations have been linked to maribavir resistance in vitro and in clinical studies. In patients who had recurrent infection despite lengthy maribavir therapy or who did not clear their infection while on therapy, mutations at codons 409, 411, and newly described codon 480 are primary causes of moderate-high grade maribavir resistance. Resistance documentation was not

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supplied in the earlier phase 2 or 3 prophylactic studies, but genotypic analysis was performed on patients with recurrent or persistent infections in the later phase 2 investigations. Overall, 29 patients with recurrent CMV after infection clearance or who did not respond to medication after 14 days were included in the study; 23 (79%) had UL97 genotyping data, with 17 (74%) having mutations at codon 409 or 411 (T409M or H411Y) and 5 (22%) having mutations at codon 480. (C480F). Surprisingly, resistance developed uniformly across all maribavir dosages. Resistance to maribavir can be acquired through another CMV gene, UL27, which imparts low-level resistance, albeit it is not as well understood as mutations at UL97. However, this has only been been characterised in vitro and has never been reported in CMV patients taking maribavir treatment. This mutation shows that maribavir's suppression of UL97 kinase activity resulted in a compensatory resistance mechanism.

Maribavir is unique in that it retains antiviral effectiveness even when resistance to anti-CMV drugs like (val)ganciclovir, foscarnet, and cidofovir is evident. The antiviral action of (Val)ganciclovir is dependent on its first phosphorylation by the viral UL97 enzyme. CMV resistance is predominantly caused by mutations in UL97 at codons 460, 520, and 590–607, which are separate from the codons that confer maribavir resistance. Furthermore, because maribavir does not target CMV DNA polymerase, in particular CMV gene UL54, which gives resistance to foscarnet, cidofovir, and (val)ganciclovir, cross-resistance with these drugs is unlikely.

Understanding the limitations of maribavir as a treatment for resistant/refractory CMV infection is critical given its development. Cross-resistance between ganciclovir and maribavir has been documented, with at least ten different mutations leading to cross-resistance published thus far. Low-level resistance to (val)ganciclovir is conferred by a mutation at codon 480 (C480F) that causes high-level maribavir resistance. In the phase 2 study, one patient with resistant/refractory illness who got a longer course of ganciclovir prior to receiving maribavir produced a unique UL97 mutation at codon 342 in the UL97 gene (F342Y). This mutation resulted in ganciclovir resistance as well as low-level maribavir cross-resistance, leading to a mutation at codon H411Y, which resulted in maribavir failure. More research is needed to fully comprehend the complex interaction between the cornerstone of therapy and maribavir.

As drug-resistant CMV becomes more common, expanding our arsenal and understanding the antiviral action of these medicines is critical, especially when used in combination to improve treatment outcomes for resistant or refractory illness. Maribavir has been tested in combination with various anti-CMV agents to see if there is synergy or antagonism, with both wild type and drug-resistant mutant strains being investigated. Maribavir has been demonstrated to be antagonistic to (val)ganciclovir and should not be administered together because maribavir suppresses UL97 kinase activity and (val)ganciclovir relies on UL97 kinase mediated phosphorylation for its function. Maribavir has been demonstrated to have an additive interaction when used with other anti-CMV drugs such foscarnet, cidofovir, and letermovir. Surprisingly, maribavir in conjunction with the mTOR inhibitor rapamycin (same molecule as sirolimus) demonstrated substantial synergy, suggesting that the combination could be clinically useful. Because sirolimus has been linked to a lower risk of CMV infection in transplant recipients, it is occasionally administered instead of calcineurin inhibitors like tacrolimus. However, similar to tacrolimus, it is projected that sirolimus concentrations may rise when administered in combination with maribavir, most likely due to P-glycoprotein suppression, hence sirolimus monitoring and further research are needed.

Conflict of Interest: None.

VII.CONCLUSION:

The use of currently available medications like (val)ganciclovir, foscarnet, cidofovir, and letermovir to treat and prevent CMV infection has dramatically reduced morbidity and death in SOT and HSCT recipients. Toxicities and the formation of resistance typically limit the use of innovative therapies, therefore their development and approval are still crucial. Maribavir is a unique option to the standard of therapy for resistant/refractory illness, with a more predictable PK profile and a higher margin of safety than the standard of care. The approval of maribavir for resistant/refractory illness and a phase 3 trial for pre-emptive therapy could pave the way for further real-world research, including combination therapy for CMV, as well as the approval of additional pipeline medicines.

Because treatment trials are still ongoing and maribavir failed to reach the primary endpoint in a phase 3 prophylactic study for the prevention of CMV illness in allogenic HSCT recipients, the FDA approved it only for resistant/refractory

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disease. Concerns have been raised about CMV testing and appropriate maribavir dose in the prophylaxis research. The approval of maribavir could lead to significant experience studies using 400 mg twice day as universal prophylaxis in both SOT and HSCT recipients, rather than 100 mg twice daily. Studies comparing it to pre-emptive surveillance as a prophylaxis following acute CMV treatment (particularly with resistant/refractory infection) should also be considered. In comparison to DNA polymerase inhibitors, maribavir's safety profile and oral formulation may stimulate investigator-initiated investigations and possibly off-label use.

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