Analysis of Maribavir and Brincidofovir, Antibiotic Treatments for Postoperative Renal Transplant Patients with Cytomegalovirus

Lydia Sheppard

The Center for Advanced Studies and Research at Thousand Oaks High School

Hypothesis: Maribavir will provide CMV patients with a more effective antibiotic treatment

Abstract

Cytomegalovirus (CMV) is an infectious disease affecting postoperative patients who have undergone solid organ transplant, and those with a weakened immune system. Renal transplant patients are at risk for acquiring CMV through their donor due to the seropositive and seronegative difference, or due to a suppressed immune system following the procedure. Treatments such as valganciclovir, ganciclovir, foscarnet, and leflunomide are commonly used for treatment, but each antibiotic faces high resistance rates. As a result, oral ganciclovir is no longer commercially available for CMV patients due to their negative effects, placing patients at higher risk for additional infections or invasive diseases. However, due to the increasing necessity of antibiotic treatment for solid organ transplant recipients, drugs such as maribavir and brincidofovir are being studied to improve treatment for CMV patients by minimizing resistance, thus lowering recurrence rates. In conclusion, Maribavir was found to be more successful in lowering the morbidity and mortality rates of postoperative renal transplant patients with CMV.

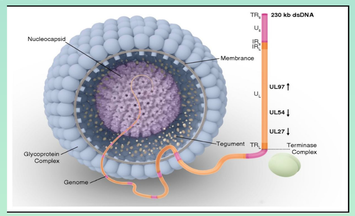

Fig 1. This diagram shows the cell infected with CMV at certain sections of DNA.

Introduction

CMV is a double stranded DNA virus that results in significant morbidity and mortality in solid organ transplant (SOT) patients. CMV occurs from transmission of transplanted organs due to reactivation of latent infection or activation of a primary infection in seronegative patients. Infections are acquired by seropositive donors in seronegative recipients without antibodies to fight the CMV infection, or by contracting the infection after the transplantation (Chon et al., 2015). Approximately thirty to seventy-five percent of patients contract CMV following their transplant. Recent studies demonstrate a recovery time ranging from 38 to 458 days.

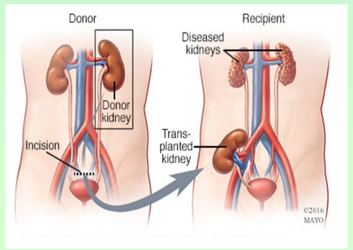

Fig 2. Diagram of renal transplant from donor to patient with end stage renal failure.

There are many considerations when choosing an antibiotic regime for CMV because of the direct and indirect effects of treatment. The direct effects include viral syndrome and organ injury or failure. The symptoms of the virus include coughing, sneezing, fever, inflammation, vomiting, diarrhea, fatigue, and cramping, all of which are ways the immune system tries to rid the body of the infectious organism. The other direct danger of CMV occurs within the organ systems, shutting them down, or rejecting the newly transplanted organ. The indirect effects include considerable medical expenses, as well as a risk of fungal and Gram-negative bacteria (GNB) causing pneumonia, bloodstream infections, wound or surgical site infections, and meningitis. GNB is also known to develop resistance to most available antibiotics, making CMV difficult to treat for renal transplant patients, and increasing the need for new, effective antibiotics.

Purpose

To determine which antibiotic regime is most efficacious in the treatment of Cytomegalovirus in postoperative renal transplant recipients

Methods

-Collection of peer-reviewed, academic articles
-Systematic review of related studies and articles
-Collection of data from related studies
-Writing of academic paper
-Statistical analysis of data

Results

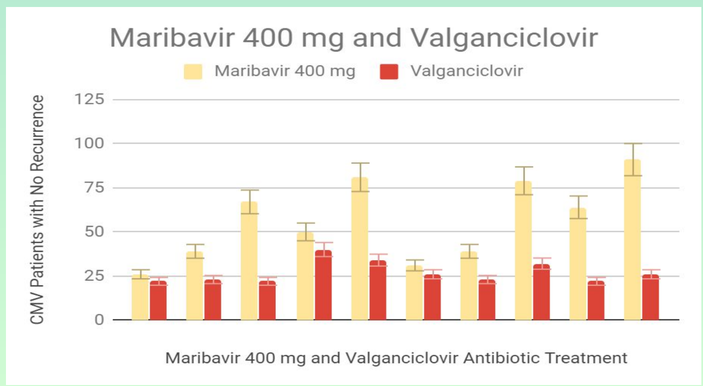

Fig 3. In this graph, the plots confirmed undetectable plasma CMV DNA at any time during the study. Overall, the DNA affected by CMV is shown with the dose of 400 mg of maribavir tested alongside valganciclovir, a common, and still available antibiotic treatment for solid organ transplant recipients.

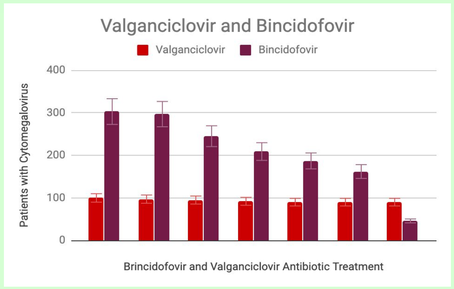

Fig 4. Shown in this bar graph the antibiotics, valganciclovir and brincidofovir, are treating CMV in SOT patients. Each antibiotic was used on a starting number of 404 patients with CMV.

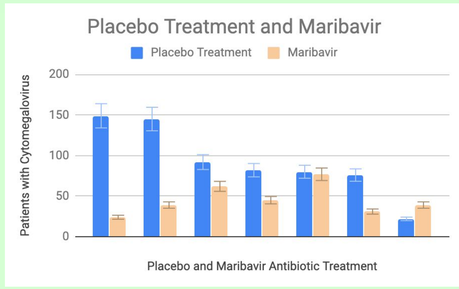

Fig 5. This graph depicts the number of patients with CMV after being treated randomly with either maribavir or a placebo to test the efficiency of the antibiotic.

Patient No.	Age (years)/ Gender	CMV Serostatus	Months Post Transplantation	Months Since First CMV+	CMV Organ Disease	Prior CMV Treatment	Known Genotypic Resistance (to)
1	39/ Female	D+/R-	12	11	Glomerulitis, retinitis	ValG CV, FOS, CMVIg, CDV, LEF	Yes (GCV)
2	65/Male	D+/R-	16	11	Pneumonia	ValGCV, GVC, FOS, LEF, CMVIg	Yes (GCV)
3	68/ Female	D+/R-	33	30	Duodenitis, retinitis	ValGCV, GCV, FOS, IVIg, CDV	Yes (GCV, FOS, CDV)
4	44/Male	D+/R-	17	8	-	GCV, FOS, CMVIg, ValGCV	Yes (GCV, FOS)
5	47/Male	D+/R-	5	1.5	Enteritis	GCV, ValGCV, FOS, LEF, CMVIg	No
6	68/ Female	D+/R-	26	6	CMV Retinitis	ValGCV, GCV, FOS, CDV	Yes (GCV, FOS, CDV)
7	44/ Male	D+/R-	9	6	Early rejection of Transplant	ValGCV, CMVIg, GCV, FOS	Yes (GCV, FOS)

Discussion

Numerous antibiotics have been used to treat CMV, resulting in bacterial strains which have mutated, becoming resistant to treatment. In Table 1, many patients suffer from an elongated treatment course due to such resistance. Despite changing antibiotic therapy, it did not stop the resistance gene from mutating with other treatments and reproducing. When this occurs, physicians must provide other antibiotics to treat the CMV to achieve a better outcome with less mutation in the postoperative renal transplant population. Patients receiving 400 mg Maribavir (MBV) had the greatest success (Fig 4). with reducing outcomes shown as dosing levels increased up to 1200 mg. The MBV drug has been found to be more successful because it inhibits the viral UL97 kinase, an antiviral mechanism which differs from the drugs used in the past to treat the CMV virus such as GCV, Foscarnet (FOS), and Cidofovir (CDV) (Table 1). The success of MBV is due to its favorable toxicity profile showing early clinical trial evidence of anti-CMV activity and despite evidence of MBV resistance, the mutants were able to be isolated and contained (Strasfeld et al., 2010). Overall, this is an important addition to CMV treatment because the other antibiotics which are used to treat the virus allow mutations to occur which lead to the resistance of the drug. With the addition of MBV, patients who have contracted CMV after a renal transplant are able to be treated with a higher success rate with less resistance, less organ failure post transplant, and longer periods of remission, meaning the patients had a diminution of the seriousness or intensity of CMV and were considered to be in a temporary recovery.

Conclusion

This systematic literature review provides ample evidence to support the alternative hypothesis that states Maribavir provides a more effective treatment for postoperative renal transplant patients with CMV. All of the papers analyzed also demonstrate that Maribavir provides patients with less risk of recurrence due to a lower mutation rate throughout their course of treatment, than Brincidofovir.

Further Work

Further research is recommended to focus on patients treated with multiple antiviral drugs. Exposure to GCV and other common, and no longer used antibiotics, promote bacterial strains with more dangerous variations. Research should be conducted using these new, more effective antibiotics along with the other treatments previously administered. This body of evidence might determine whether or not the drugs are able to work together to create an interaction improving the effects of one or both of the drugs, known as a synergistic effect. Additional research could be conducted to discover whether Maribavir and Brincidofovir are able to work synergistically or antagonistically.

Acknowledgements

I would like to thank Dr. Nikki Malhotra for all of her time and help while researching along with the help of my expert advisors, Dr. Camille Kotton and Dr. Maureen Metzger for all of their support in helping me finalizing a topic, gather data and correctly analyze it.