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

Thousand Oaks High School

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Abstract

Cytomegalovirus (CMV) is an infectious disease which affects postoperative patients who have undergone solid organ transplant, as well as others who have a weakened immune system. Renal transplant patients are at risk for acquiring CMV either 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 used to treat patients, but each antibiotic faces high resistance rates. Because of this, oral ganciclovir is no longer commercially available for CMV patients due to their negative effects which often places patients at a higher risk for further infections or invasive diseases. Overall, due to the increasing necessity of antibiotic treatment for solid organ transplant recipients, drugs such as maribavir and brincidofovir are being studied to try and improve treatment for CMV patients by minimizing resistance, thus lowering recurrence rates. Through a systematic literature review, the antibiotics were evaluated and analyzed to understand the effectiveness for patients, and to determine if there was a statistical difference between the treatments. In conclusion, the maribavir is found to be more successful in lowering the morbidity and mortality rates of postoperative renal transplant patients with cytomegalovirus.

Introduction

Cytomegalovirus infection (CMV) is a double stranded DNA virus that causes significant morbidity and mortality in solid organ transplant (SOT) patients. These patients have an impaired immune system following each transplant due to the immunosuppressive drugs prescribed to each patient to prevent rejection of the new organ. CMV occurs from transmission

of transplanted organs due to reactivation of latent infection or activation of a primary infection in seronegative patients. This means those involved are either affected because the donor was seropositive while the recipient was seronegative and does not have the antibodies to fight of CMV infection, or they contracted the infection after the transplantation (Chon et al., 2015). About thirty to seventy-five percent of patients contract CMV following their transplant, and recent studies on renal transplant patients have a recovery time ranging from 38 to 458 days, with a median of 219 days (Chacko et al., 2010; Chon et al., 2015). Also, the overall crude mortality rate associated with congenital CMV is 0.17 per 1 million persons each year (Bristow et al., 2011).

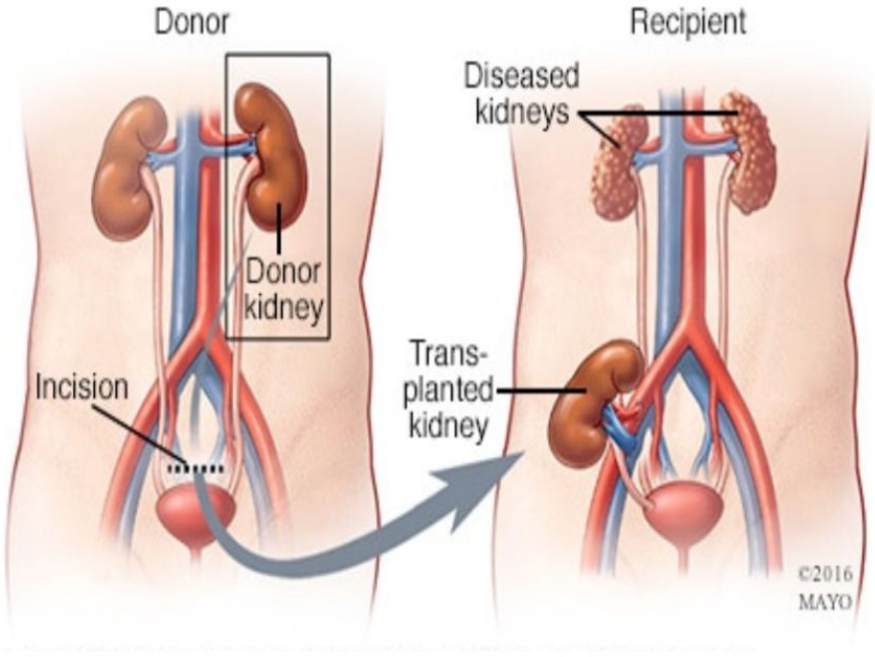

Figure 1. This diagram shows a renal transplant from the donor to a patient with end stage renal failure. During this process, CMV can be passed on from the donor who already has it, or after the transplantation contracts the virus (Mayo Clinic, 2018).

Antibiotic Treatments

CMV infection occurs most often between 30 and 90 days after transplantation, but can be contracted outside of this range (Genovefa et al., 2018). Common treatments for postoperative renal transplant patients with CMV include valganciclovir (ValGCV), oral ganciclovir (GCV), leflunomide (LEF), and foscarnet (FOS). ValGCV is the most common treatment for postoperative renal transplant patients with CMV, as it has the capability to treat some cases of the virus while keeping resistance rates relatively low compared to the other antibiotics. However, it still fails in treating the majority of patient groups because despite the slightly improved resistance rate, it still has many cases of recurrence. A second antibiotic treatment, GCV, is used to reduce symptoms of CMV and treat the infection caused by viruses in patients with congenital immunodeficiency syndromes (Pavlopoulou et al., 2005). These patients suffer from a deficiency, absence, or defect in the immune system. In most cases, patients take doses of GCV daily, which is determined by the patient's physician depending on their condition following the first round of treatment. Recent studies on renal transplant patients have a recovery time ranging from 38 to 458 days, with a median of 219 days

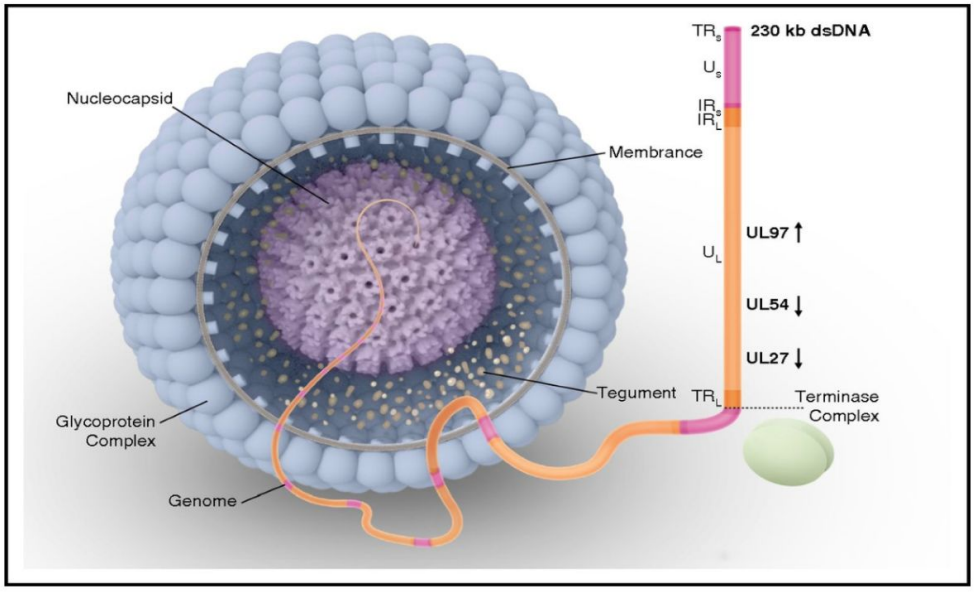

Figure 2. This diagram shows the cell infected with CMV. The CMV virus infects certain section of the DNA such as UL97, UL54, and UL27 (Chaer et al., 2016).

(Chon et al., 2015). Currently, GCV is no longer commercially available because of its long term resistance to the drugs used for treatment, caused by the mutations in CMV genes coding for protein kinase and DNA polymerase (Genovefa et al., 2018).

Although treatment has been found successful in certain lower risk patients, about 60% of patients are either resistant to the antigen during the treatment, or overtime become resistant to this drug due to the mutating genes (James et al., 2013). Overall, the continual use of GCV treatment for CMV draws out the side effects that are present with CMV and time in a hospital setting, as well as creates a higher frequency of the drug resistant gene in bacterial cells.

Furthermore, patients are also being treated with the antibiotic foscarnet. This antiviral medication is a sodium injection that is widely used to treat CMV, but is also considered highly likely to increase the frequency of a resistance gene in bacteria after the treatment to rid the body of clinically significant CMV, therefore prevent the recurrence of CMV. Due to this, the antiviral drug is considered to be an ineffective treatment because the resistant strain of bacteria becomes substantially noticeable and thus dangerous to the patients being exposed to the drug. Moreover, patients who have treatment involving FOS injections become less susceptible to other antiviral treatments which places the patient in a worse condition than when the treatment began, and also causes patients to have severe stomach, head, and joint pain. Although CMV has multiple options for antibiotic treatment, FOS, similarly to oral GCV has high rates in resistance which hinders the care of those with CMV. Also, FOS may potentially worsen the preexistent impaired renal function, increasing the probability of rejection of the new organ (Menghi et al., 2013).

Another antibiotic, leflunomide, reports of a successful low-dose treatment which possesses immunosuppressive properties in transplant patients with very high viral replication

(Chon et al., 2015). The viral replication lowers the effectiveness of immune systems at ridding the body of illness and increases the risk of infection such as cytomegalovirus. Research also concludes that the treatment is unsuccessful because patients are also becoming more resistant to the antigen. At the present, less common treatments such as the LEF seem to have more benefits compared to the GCV, and also better long-term outcome. Despite few beneficial results with both treatments, many factors must be considered such as how long a patient is receiving treatment after their transplant, as well as how long they must be in the direct care of the physicians and finally, how many episodes of CMV recurrence there is following antibiotic treatment.

Newly approved treatments such as maribavir and brincidofovir have presented with successful results. Maribavir is an oral antiviral drug candidate licensed by ViroPharma in 2003 for the prevention and treatment of human cytomegalovirus disease. Brincidofovir, an antiviral drug being developed for the treatment of cytomegalovirus, adenovirus, smallpox, and ebola virus infections. Brincidofovir is a prodrug of cidofovir (Genovefa et al., 2018). Overall, treatment with brincidofovir has been used for patients who have contracted CMV through hematopoietic stem cell transplantations. Despite this, current treatments for SOT patients who have CMV are being treated with brincidofovir as well as maribavir in order to find a solution to the current problem involving the lack of viable treatment options for cytomegalovirus.

Due to the nature of bacterial cells in the body, and the various ways which they are able to reproduce and evolve with a resistance gene towards antibiotic treatments, it is necessary for future success in renal transplant patients with CMV to find a treatment that either has a controllable resistance or none at all. With the use of GCV in the past, patients have been left

untreated or their conditions have worsened because of the resistance which appeared after they were being treated for long periods of time with the older antibiotics. With a higher frequency of the resistance gene for GCV, there is a urgent need for an antibiotic, which could include maribavir as well as brincidofovir, that causes significantly less resistance, meaning a lower rate of recurrence for CMV infected patients.

Effects of CMV

There are many considerations when choosing a antibiotic treatment for cytomegalovirus because of the direct and indirect effects which it has on the patients. CMV pneumonia, a direct effect of the virus, is an infection of the lungs which can occur most prominently with patients with a suppressed immune system. Another direct effect is viral syndrome, meaning the differing symptoms caused by a virus which include coughing, sneezing, fever, inflammation, vomiting, diarrhea, fatigue, and cramping, all of which are ways the immune system tries to rid the body of infectious organisms. Also, the a direct danger of the CMV is the problems which may occur within the organ systems, shutting them down, or rejecting the newly transplanted organ, such as the kidney. The indirect effects include considerable medical expenses, as well as a risk of fungal and Gram-negative bacteria (GNB) infections, which cause pneumonia, bloodstream infections, wound or surgical site infections, and meningitis. Also, GNB has been known to cause resistance to multiple drugs and to most available antibiotics, thus making the CMV difficult to treat for renal transplant patients, and an increasing need for new, effective antibiotics.

Overall, this study is important to the public because CMV is the most common infection in any full organ transplant. Furthermore, current treatment has been found to work against the

body by making it drug resistant, and it cannot treat patients who are already resistant to the antigen. Without studies on such treatments, there will be higher mortality rates and patients will not receive the high level of care that is necessary to have a successful recovery after their transplant procedure, and eventually reach remission status.

Keywords: cytomegalovirus, renal transplant, resistance, recurrence, maribavir, brincidofovir

Purpose

The purpose of this research to investigate which of the different antibiotic treatments for cytomegalovirus is more effective and less resistant than the other. The use of maribavir and brincidofovir as antibiotic treatments for CMV has the potential to decrease the mutation rate in patients bacterial cells which create a resistance gene, causing the recurrence of the infection, as well as making CMV more difficult to treat. Overall, the antibiotic treatments used in past research such as ganciclovir, foscarnet, and leflunomide do not have high success rates because of the resistance that occurs in many patients, causing the infection to become increasingly more life threatening. Physicians are using specific drugs to target the infection, but are concluding unsuccessful results with the patient's progressive resistance to the past, more commonly used antigen.

Research Question

Is Maribavir more effective than Brincidofovir as cytomegalovirus treatment for postoperative renal transplant patients?

- This research question will investigate the effect of above treatments on the mortality and morbidity rate in patients, as well as how the resistance levels differ.

Hypothesis

Alternative: Maribavir will be more effective in treating the postoperative renal transplant patients with cytomegalovirus as compared to brincidofovir.

- The overall outcome of maribavir should provide lower recurrence rates and therefore less drug resistance for the patients.

Null: Maribavir and brincidofovir treatment has no significant improvement providing patients with a less recurrence of CMV.

Methods

To begin research, a complete search through online databases for the basic understanding of renal transplants and common problems which occur for these patients was executed. Cytomegalovirus has become increasingly more prevalent in patients following renal transplants, and therefore, the demand for new antibiotic treatment for CMV due to high resistance rates is rising. There were few antibiotics which are currently being evaluated in this field of research, but after careful consideration and learning the different uses which each antibiotic had in the past, I decided to further investigate maribavir as well as brincidofovir.

After gathering substantial knowledge on the subject from October through February,a systematic literature review was decided upon to display results, and began data collection. A

systematic literature review of all of the data gathered from sources was able to describe the treatments for cytomegalovirus. A collection of around 35 academic papers related to cytomegalovirus infection found on databases such as Transplant Infectious Disease, Clinical Microbiology and Infection, Pediatric and Clinical Transplantation, Informa Healthcare, Wiley Interscience Journals, and Infectious Diseases Society of America were read through thoroughly, annotated, summarized, and searched for biases. Due to certain biases such as papers including authors that worked for companies which promoted certain antibiotics, the papers were discarded and not used to further this research. After a thorough review of each paper, the time frame of 2000 to 2019 was decided to retrieve data that was relevant to the field today, and accurate. This study retrieved data through literature review at Thousand Oaks High School in addition to the academic papers received from expert advisors. Also, using surrounding collegiate level schools such as California Lutheran University, and Moorpark College, academic papers were gathered.

Following the conclusion of this process, I had a complex understanding of the topic, and the determination of which treatments were most valuable for CMV infected patients. Valganciclovir, maribavir and brincidofovir, were analyzed and discussed throughout the paper. After determining what treatments to analyze, data was extracted from the academic research papers. To do so, the data had to be from postoperative renal transplant patients with CMV. Also, with the data ranges of patients which were treated effectively along with those who were not, were averaged to illustrate effectiveness. Next, a series of one-tailed t-tests was used to show the efficiency of maribavir and brincidofovir compared to valganciclovir, as well as a control of receiving no treatment. If the P-values $\leq .05$, they were considered to be statistically significant, and the null hypothesis was rejected. Through this, a more adequate antibiotic was determined,

and the data and conclusions were drawn from the research to expose the complication with having few antibiotic treatments for CMV patients which has a statistically inefficient outcome, and support this specific research. Finally, the evidence was synthesized into an academic research paper.

Results

Study Selection

The search results for this study on online databases provided about ten thousand. Overall, 17 studies were considered for the results after reviewing and annotating relevant sources. These studies were chosen for data collection because they were the only clinical trials directly testing maribavir, brincidofovir, and valganciclovir for renal transplant patients who have contracted CMV. Although these papers provided data with maribavir and brincidofovir antibiotics, two of the papers were excluded because it involved another antibiotic used alongside the MBV and brincidofovir (Piret et al., 2019; Frange et al., 2018).

Participants

One thousand two-hundred eight patients were involved in the across all of the papers evaluated. Participants were all postoperative renal transplant patients which contracted CMV following the procedure. The age groups varied from thirty-nine to sixty-eight years of age, with the mean age of 53.5.

Table 1. In this data table, the description of patients involved in data collection who had solid organ transplants and contracted CMV, then were treated with maribavir because patients did not respond to other, older treatments.

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)

All participants developed CMV between one and sixteen months after the renal transplant, with an average of 5.8 months. Because all seven of these patients were treated with ValGCV, GCV, FOS, and LEF as stated earlier, they grew resistance through the mutations in the bacterial cells, which then survived after the use of more antibiotic treatment and then

reproduced making them more abundant within the patient. Each treatment was presented to the patient at a different time throughout their treatment to make sure the strains of bacteria with a resistance gene, which had already been found within the patient did not worsen. Six out of the seven patients grew resistance to the treatment, most commonly GCV. Other resistance came from FOS. As this situation became increasingly dangerous for each patient, MBV was implemented into the patients' treatments, and were able to reduce the level of CMV infection. After receiving a 400 mg dose of MBV twice a day for approximately eight weeks, patients were found to have UL97 mutations which confer MBV resistance (Strasfeld et al., 2010). Also, the development of CMV retinitis occured, but is easily treated and controlled with immunosuppressive therapy. Although this occurred during the treatment period, the MBV-resistant CMV mutants were isolated after the viral propagation, and there was no more signs of drug resistance because it was extensively monitored (Strasfeld et al., 2010).

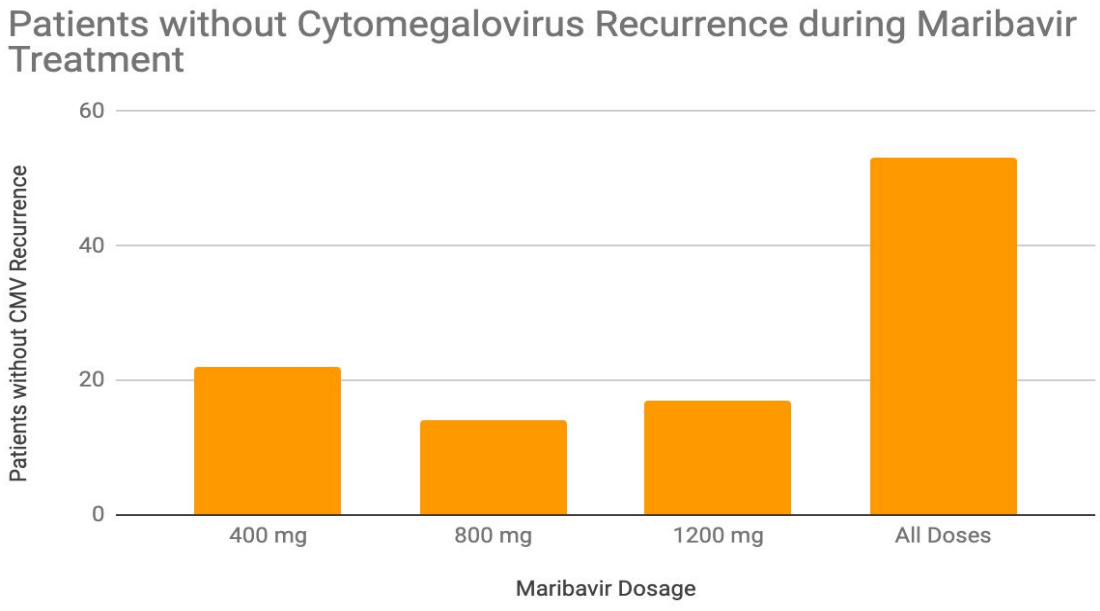

Figure 3. In this bar graph, data was taken from the trials of 120 patients treated with maribavir who were evaluated after six weeks. Overall, about 75.9 percent patients who received 400 mg doses of maribavir had success in having no recurrence of cytomegalovirus.

The data illustrates the recurrence of CMV in SOT patients that were treated with different dosages of MBV. Following this treatment for six weeks, patients were evaluated and they found how many patients did not have, as well as those who did still suffer from recurrence of the virus (Papanicolaou et al., 2018). From the 34.9 percent of patients who had CMV recurrence at anytime throughout the six weeks of treatment, the majority came from 800 mg MBV treatment group (40.7%) and the 1200 mg MBV treatment group (40.0%) (Papanicolaou et al., 2018). Although 61.6% of patients treated with MBV had no recurrence, and were able to be in remission, the highest percent of patients were found with no recurrence in the 400 mg treatment group (75.9%).

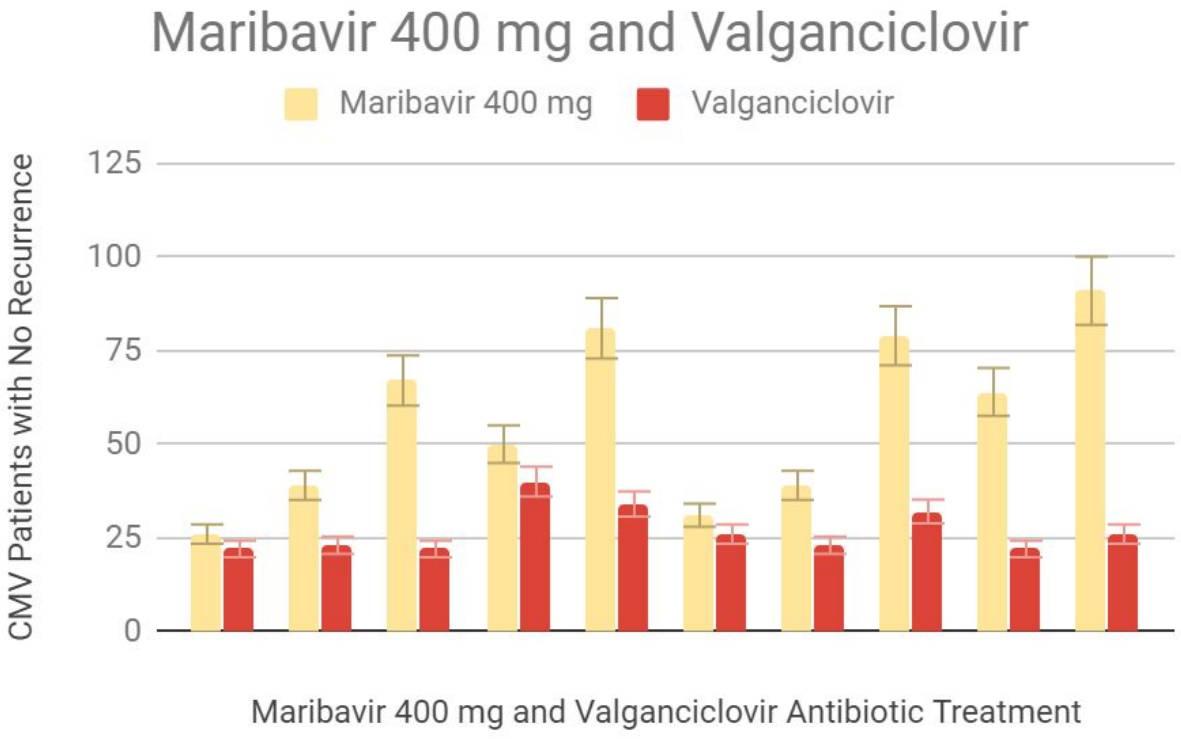

Figure 4. In this graph, the plots confirmed undetectable plasma CMV DNA at any time during the study. Overall, the DNA affected by CMV is shown with the dose of 400 mg of maribavir tested alongside valganciclovir, a common, and still available antibiotic treatment for solid organ transplant recipients.

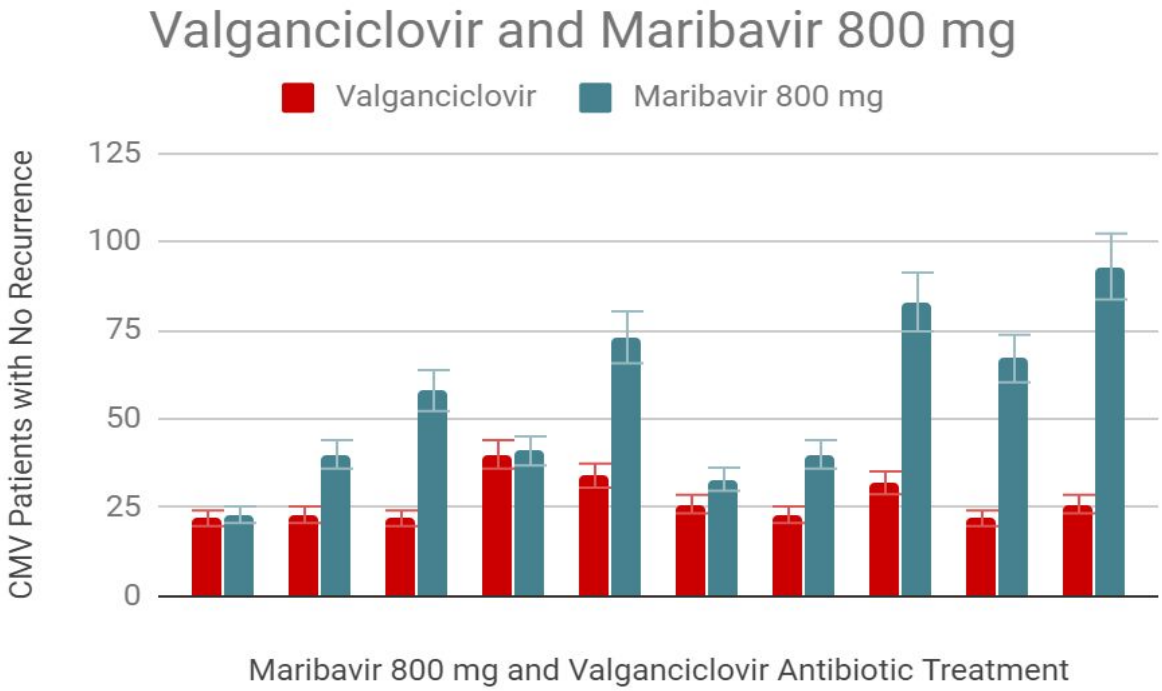

Figure 5. This bar graph compares the antibiotic treatments of valganciclovir as well as maribavir with a 800 mg dose. Patients considered no longer had CMV recurrence following the treatment which was administered.

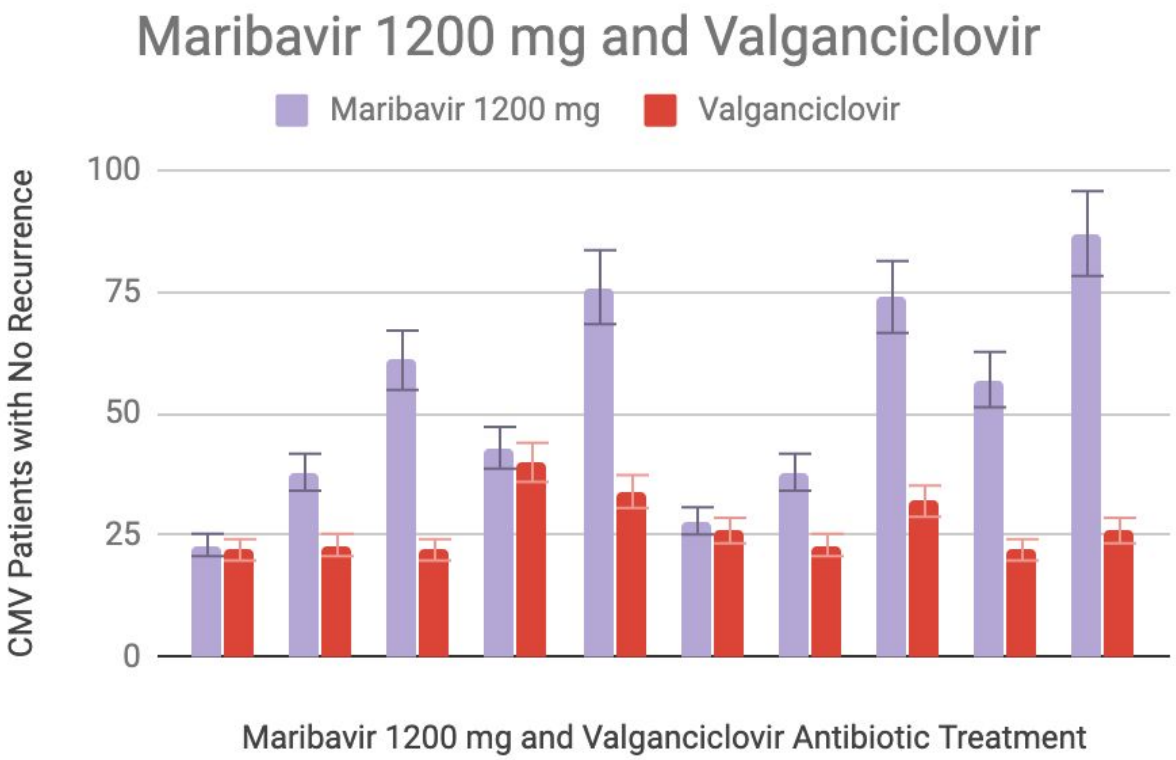

Figure 6. Similar to previous figures, this graph directly compares the antibiotics valganciclovir and a 1200 mg dose of maribavir for treating CMV patients.

The results which were gathered after treating groups of patients that are infected with CMV who have undergone a solid organ transplant procedure with differing amounts of Maribavir. Following the antibiotic treatment of valganciclovir, treatment groups of 100 SOT patients with CMV, the range of the success of reaching remission, meaning no recurrence, was twenty-two to forty patients with an average of twenty-seven. Comparatively, the MBV 400 mg dose ranged from twenty-six to ninety-one patients, with an average of 56.7 (Fig 4). With a higher dose of maribavir treatment administered daily, patients given 800 mg ranged from twenty-three to ninety-three, with an average of 55.1 (Fig 5). Also, the patients who received

1200 mg ranged from twenty-three to eighty-seven, with an average of 52.5 who were in remission following treatment (Fig 6). After conducting one-tailed t-tests on the differing treatments, the p-values of approximately 0.0025 for MBV 400 mg, 0.0040 for MBV 800 mg, and 0.0049 for MBV 1200 mg, all are ≤ 0.05.

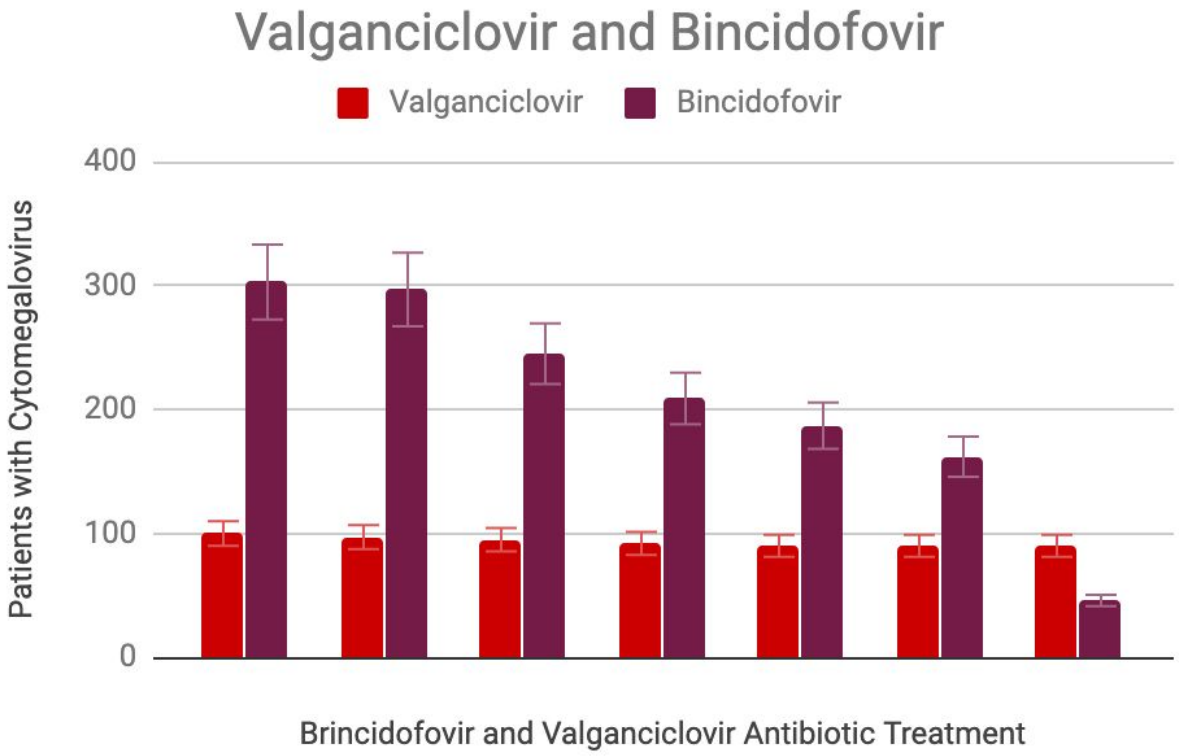

Figure 7. Shown in this bar graph the antibiotics, valganciclovir and brincidofovir, are treating CMV in SOT patients. Each antibiotic was used on a starting number of 404 patients with CMV.

Although success is found in some cases of CMV, the range of CMV patients left with recurrence after brincidofovir is forty-six to three-hundred three patients, with an average of two-hundred seven, contrasting to the range of patients after treatment from valganciclovir, ninety to one hundred, with an average of 93.4 with unsuccessful treatments (Fig 7).

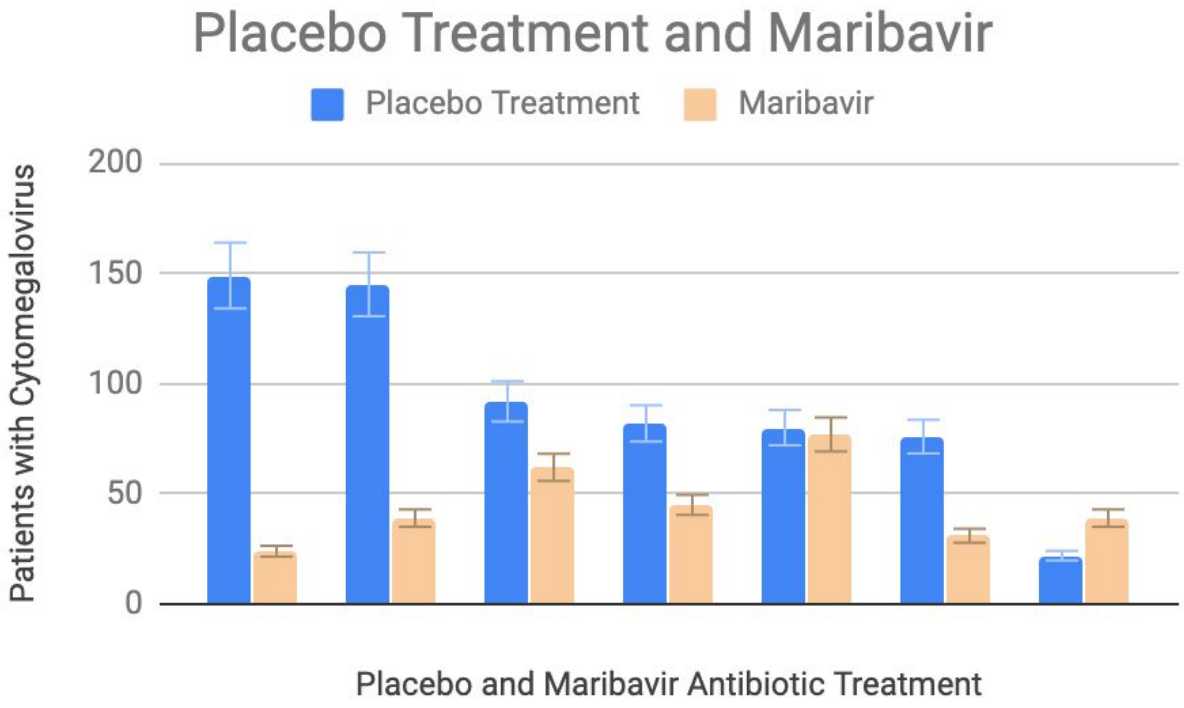

Figure 8. This graph depicts the number of patients with CMV after being treated randomly with either maribavir or a placebo to test the efficiency of the antibiotic.

This graph shows the differing outcomes of patients with CMV after treatment with the antibiotic, maribavir, as well as placebo treatment which caused a very small range of change in recurrence of CMV for patients. Although the placebo is less effective for treatment, the maribavir left treatment groups with twenty-two to seventy-seven patients, average of 45.3, with resistance, while the placebo had a range of twenty-two to one hundred forty-nine, with an average of 92.3 patients (Fig 8).

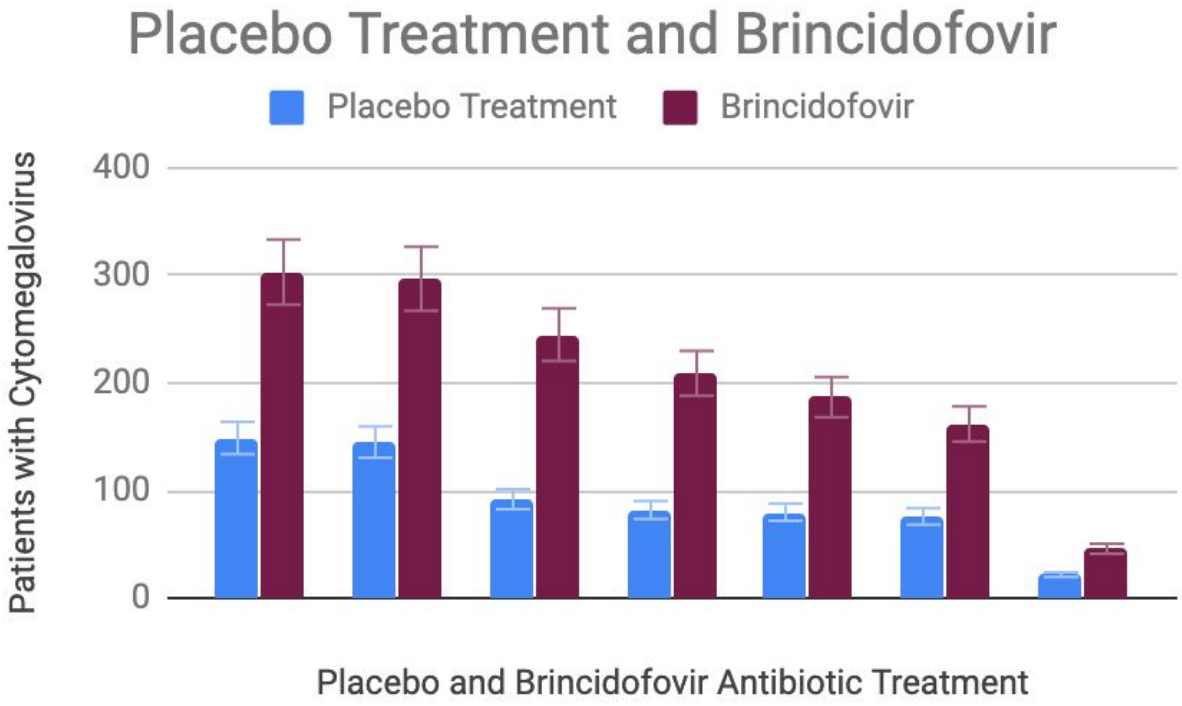

Figure 9. This graph illustrates the differing numbers of patients with clinically significant CMV after treatment of brincidofovir as well as a placebo. Each patient group contained about 306 solid organ transplant patients with CMV.

The patients who were in the control group of placebo, were no more successful than those treated with the antibiotic, brincidofovir. Because the range of patients treated with brincidofovir was forty-six to three-hundred three, average of two-hundred seven, as in figure 7, compared to the relatively low range of twenty-two to one hundred forty-nine, average of 92.3, seen in figure 8, patients with CMV after treatment of a placebo, the antibiotic is seen to have significant resistance and no less morbidity than the antibiotics no longer available such as oral ganciclovir (Fig 9).

Discussion

Despite the numerous antibiotics which have been used to treat CMV, there are bacterial strains which have mutated to become resistant in each treatment. In Table 1, it is clear that many patients suffer from an elongated treatment due to the resistance. Despite changing the antibiotic which the patient was being treated with, it did not stop the resistance gene from mutating with other treatments and reproducing. When this occurs, physicians must provide other antibiotics which could be used to treat the CMV, and have a better outcome of less mutation and a successful treatment for postoperative renal transplant patients.

All but one of the patients in the table became resistant to at least one of the antibiotics which were used to treat their CMV infection. The most common starting place for treatment for these patients is valganciclovir, but high levels of resistance occur with this antibiotic as well as oral ganciclovir, foscarnet and leflunomide. As the virus infects the DNA in the cell, the bacteria multiplies and mutates because there are no checkpoints in the process of translation of ribonucleic acid (RNA). With this occurrence, CMV patients are put at severe risk of organ failure, as well as other infection that can be life threatening with their weakened immune system. Furthermore, the organ disease which is common among patients who contracted CMV are far more dangerous because the immune system is working to fight off the bacteria which is constantly mutating with differing antibiotic treatments focused on the CMV, and cannot fight off the diseases which are often contracted with these patients. Pneumonia, CMV retinitis, and early rejection of the renal transplant are all difficult to endure for the human body, but are seen in most cases of CMV as increasingly more life threatening. Moreover, due to the early contraction of CMV within as little as one month to up to about nine months post renal

transplantation, patients become susceptive to the vast number of organ diseases quickly after their transplant surgery, when the body is recovering and there is a slight, three percent chance of rejection that may be increased with CMV.

Furthermore, the antibiotic was able to help rid the body of the GCV, ValGCV, FOS, and in some cases LEF resistant bacteria, but there is evidence that suggests patients grew a small resistance to the MBV over a suspended period of time (Avery et al., 2010). Although some patients had recurrence due to mutations that caused a resistance gene to form in the bacterial cells, and these mutants were able to displace the strains from the GCV and FOS treatments, few patients affected by this were quickly treated with ease and contracted no recurrence after immunosuppressive treatment.

Moreover, MBV is important to the CMV field of research because it is a new drug for the CMV treatment. Because the other treatments have caused multiple, dangerous strains of resistant bacteria, the maribavir was able to work to eliminate this bacteria as well as treat CMV. Overall, the treatment was successful and reduce morbidity and mortality rates, but with the wrong dose it became resistant similar to the outcome of oral ganciclovir and valganciclovir that was rendered dangerous to the patients and made commercially unavailable. Also, due to the statistical significance of the maribavir compared to the valganciclovir which is the most commonly used treatment in modern medicine, the alternative hypothesis can be accepted with about ninety-five percent confidence that maribavir is the stronger candidate for cytomegalovirus treatment. Additionally, maribavir was also much more effective when seen against the use of a placebo for patients also suffering from CMV after their solid organ transplant, placing more confidence with the use of maribavir. Also, although brincidofovir has been seen to successfully

lower CMV for solid organ transplant patients until it is no longer clinically significant, it fails to be proven as more effective than valganciclovir.

The patients who received the dose of 400 mg maribavir had the greatest success (Fig 4). Although the dose of 800 mg maribavir was not much worse, the 1200 mg dose along with all of the doses together had a significantly worse outcome. Overall, in this study the varying doses were tested and the greatest result in treating CMV in postoperative solid organ transplant patients was the 400 mg dose of maribavir. The MBV drug has been found 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 maribavir is due to its favorable toxicity profile, it shows early clinical trial evidence of anti-CMV activity, even though there is still 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 in 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.

Limitations

Throughout this research there have been multiple barriers to work around. Because maribavir and brincidofovir are relatively new antibiotic treatments for cytomegalovirus, there

was limited data which could be extracted for this research. Although there have been many cases that were individually treated with the antibiotic, there was only a few papers which evaluated higher numbers of patients. Overall, data was gathered, but to have a more significant conclusion, more trials with various solid organ transplants is necessary. Moreover, due to the differing number of treatment groups between both maribavir and brincidofovir, there is no ability to test the antibiotics directly, but through more common treatments, and through a control.

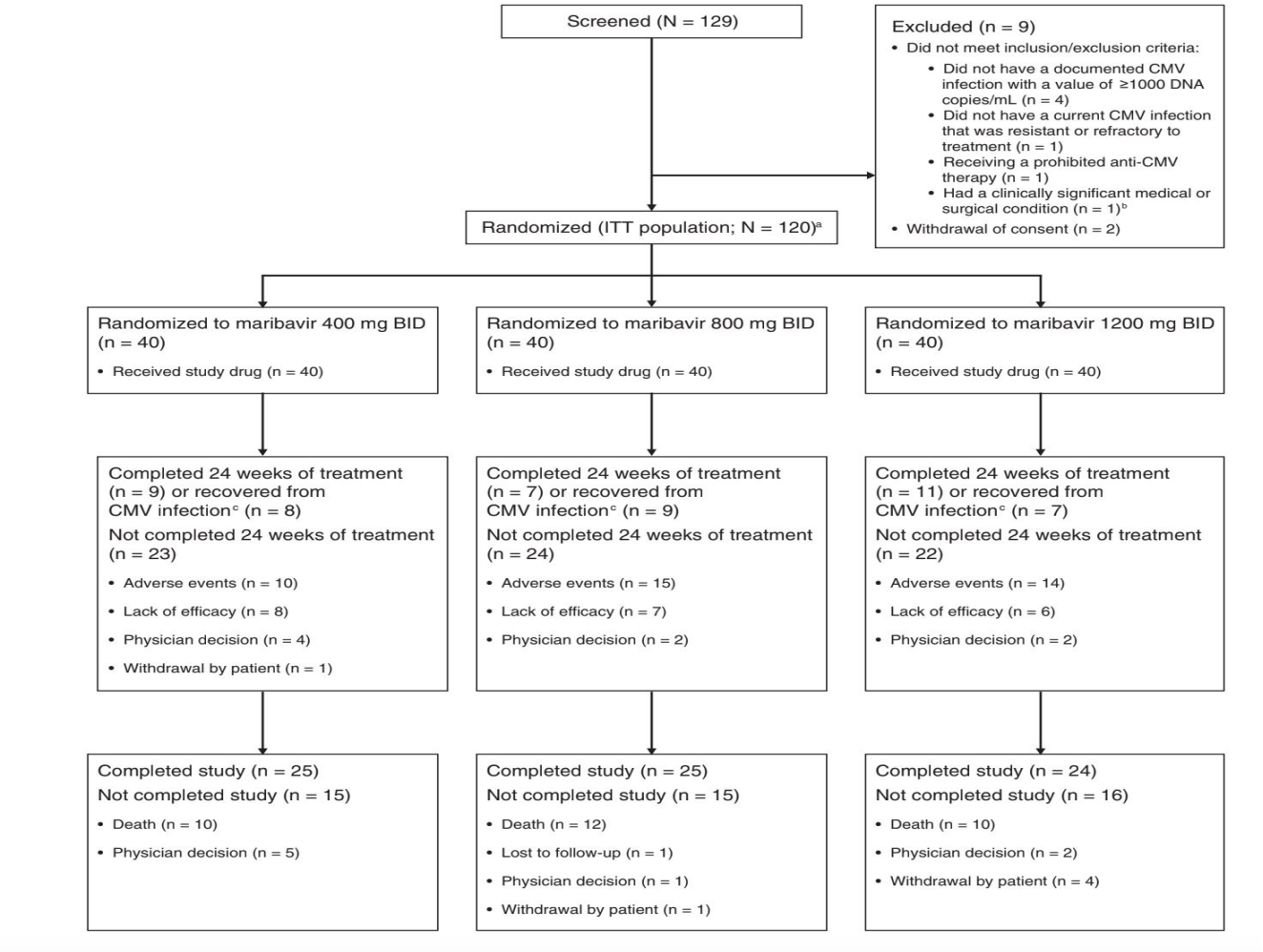

Figure 10. This chart explains how postoperative renal transplant patients were evaluated for treatment or MBV. Although the trial began with 129 patients, only 74 were able to complete the treatment due to not meeting criteria, a physician decision to discontinue treatment, or the patient passed away (Genovefa et. al., 2018).

Although data collection came from a numerous different academic research papers which begun with large treatment groups, overtime patients had to drop out of the trial because their body was no longer fit for treatment. At certain points throughout maribavir and brincidofovir treatment or before the trial began, physicians reviewed the status of each patient to determine if they met the requirements. If a patient had persisting diseases following treatment, they were released from the trial, as well as if they did not have significant CMV viral load, or resistance to prior treatments. Ultimately, research was concluded with sufficient data, but because each patient reacts differently to the antibiotics, altering the timeframe of trials and creating smaller treatment groups.

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 cytomegalovirus. All of the paper analyzed throughout this review support this conclusion, that maribavir provides patients with less risk of recurrence due to a lower mutation rate throughout their course of treatment, than brincidofovir.

Further Work

To continue this research, treatments using maribavir on more patients with CMV after solid organ transplants with differing doses that are more specific to each individual patient. This along with the use of other new treatments such as brincidofovir can help further the research for CMV research. If this research could be extended, the focus would shift onto patients being

treated with multiple antiviral drugs. Because many patients have been exposed to GCV and other common, and no longer used antibiotics, their bacterial strains may have more dangerous variations. Due to this, research would be conducted using these new, more effective antibiotics along with the other treatments they were given in the past. This research would conclude whether or not the drugs are able to work together to create an interaction which causes an increase in the effects of one or both of the drugs, called a synergistic effect. Also research could be conducted to see whether maribavir and brincidofovir are able to work synergistically or antagonistically. Overall, this would allow for more effective CMV treatments, and help patients who develop any resistance gene to any of the treatments have other options to help rid the virus from their systems after their renal transplant.

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