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Uptitrating mycophenolate mofetil therapy in a patient with lupus cerebritis doesn't increase risk of infection compared to cyclophosphamide

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Uptitrating mycophenolate mofetil therapy in a patient with lupus cerebritis doesn't increase risk of infection compared to cyclophosphamide

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ABSTRACT A clinical decision report using:

Appel GB, Contreras G, Dooley MA, et al. Mycophenolate mofetil versus cyclophosphamide for induction treatment of lupus nephritis. *J Am Soc Nephrol*. 2009;20(5):1103-1112. https://doi.org/10.1681/ASN.2008101028

for a patient with neuropsychiatric lupus.

Keywords: *MMF, Mycophenolate mofetil, SLE, lupus cerebritis, neuropsychiatric lupus*

Clinical-Social Context

Alexis Burke [pseudonym] is a 52-year-old African-American woman with discoid lupus and a three-year history of neuropsychiatric lupus who presented to the emergency department (ED) with a one-week history of slurred speech and right-sided weakness.

Ms. Burke had bouts of neuropsychiatric lupus in 2018 and 2019 that made her dependent on a walker for ambulation. She also had an associated discoid lupus which presented as patchy hair loss and skin rash. Back then, the flares were resolved with pulse steroids and plasmapheresis. The patient worked diligently during rehabilitation therapy and had a nearly complete recovery in function. During this time, her family, and especially her mother, were strong pillars of support for the patient. The mother accompanied Ms. Burke from the time she received her lupus diagnosis. She kept track of what medications Ms. Burke should be taking, ensured her adherence to the treatment, monitored for side effects, and monitored for lupus symptoms. Our rheumatology service managed her long-term lupus treatment. Hydroxychloroquine caused her intolerable side effects, so we prescribed 1500 mg twice daily mycophenolate mofetil (MMF) instead. She and her family had refused cyclophosphamide and rituximab at that time. During a visit to our clinic in 2021, Ms. Burke presented with leukopenia, likely due to MMF. As a result, we reduced the dose to 1000 mg twice daily. We were not concerned about Ms. Burke's ability and will to be adherent to her current medication regimen given her support system.

One week prior to admission, Ms. Burke started having frequent falls, followed sequentially by weakness in her right upper extremity and right lower extremity. Five days ago, she developed slurred speech and her limb weaknesses progressed to the point of being unable to use her walker anymore and being unable to move her right upper extremity at all.

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At admission, a stroke code was called for Ms. Burke. The neurology service evaluated her and ordered a magnetic resonance imaging study (MRI) which showed multiple infarcts reminiscent of her MRIs in 2018 and 2019 when she was first diagnosed with neuropsychiatric lupus. The neurologists started pulse steroids due to their suspicion of neuropsychiatric lupus flare with vasculitis. Her symptoms improved with steroids. Afterward, the neurology service consulted our rheumatology service since we were prescribing the MMF and managing her lupus.

Like almost all her prior admissions, Ms. Burke was accompanied by her mother ("Mrs. Burke") and daughter who spoke for her when she was too tired to speak for herself. Ms. Burke was passive during the discussion, saying that "I trust my mom will do the best for me since she has helped many family members deal with lupus, and she has been here for me since the start." We explained to them that Ms. Burke's lupus is causing these autoimmune central nervous system (CNS) attacks and that the twice daily 1000 mg of MMF is insufficient for stopping these attacks, given the fact that she was admitted for neuropsychiatric lupus. We recommended cyclophosphamide and continuing outpatient follow-up with our service.

The Burkes were grateful and relieved that our service was involved since we had been there with them since Ms. Burke's lupus diagnosis. As a result, they were initially agreeable to the treatment course. After thinking over it, Mrs. Burke asked us: "Is cyclophosphamide a chemo drug?". Once we replied in the affirmative, Mrs. Burke said that "Alexis will not be getting any chemo drugs" with Ms. Burke nodding in agreement. The Burkes had witnessed family members on chemotherapy drugs for lupus and various cancers with horrible side effects like mood changes, mucositis, and persistent fatigue. Ms. Burke was not directly involved, but Mrs. Burke saw many family members becoming "skin and bones" and living with poor quality of life even after cancer remission. We explained that not all chemotherapy drugs have the same side effects and that we would be monitoring for side effects very closely, but Mrs. Burke did not want her daughter to run the risk.

While her mother was concerned about the side effects, Ms. Burke was considered about the costs of a chemotherapy drug. Ms. Burke was only getting money from disability and most of it was going to her rent and groceries. She was registered for Medicare but was not certain how much chemotherapy drugs would cost her. Regardless, her mother thought that they may be able to manage the copays given that family members in similar situations were able to do so. Ms. Burke was not concerned about the financial costs hearing this from her mother.

Given the Burkes' aversion to cyclophosphamide due to the possible adverse effects, our team was considering the potential ramifications of increasing the dose of MMF back to 1500 mg twice daily since that had prevented the lupus flares in the past. This is also what Mrs. Burke was advocating for; despite the leukopenia in our clinic, Ms. Burke and her family had not noticed any side effects, fevers, or infections when she was taking this dose of MMF. Besides one instance of leukopenia during her admission, her white blood cell count stayed within normal limits. Nevertheless, both the family and the team were not comfortable sending the patient home with a higher dose of MMF without first reviewing the literature for the likelihood of MMF-induced infection.

Clinical Question

Does uptitrating mycophenolate for patients with neuropsychiatric systemic lupus erythematosus and a history of MMF-induced asymptomatic leukopenia increase their risk of infections?

Research Article

Appel GB, Contreras G, Dooley MA, et al. Mycophenolate mofetil versus cyclophosphamide for induction treatment of lupus nephritis. *J Am Soc Nephrol*. 2009;20(5):1103-1112. https://doi.org/10.1681/ASN.2008101028 [1]

Description of Related Literature

Literature searches were performed via PubMed. The publication date was limited to the last 20 years.

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The search string ("MMF" OR "mycophen*" OR "Cellcept" OR "mofetil" OR "Mycophenolic Acid"[MeSH]) returned 1,652 results when filtered for clinical trials.

The next search string used was (SLE OR "systemic lupus erythematosus" OR "lupus" OR "Lupus Erythematosus, Systemic"[Mesh] OR "Lupus Vasculitis, Central Nervous System"[MeSH]) AND ("MMF" OR "mycophen*" OR "Cellcept" OR "mofetil" OR "Mycophenolic Acid"[MeSH]). This returned 105 results when filtered for clinical trials.

The next search string used was (SLE OR "systemic lupus erythematosus" OR "lupus" OR "Lupus Erythematosus, Systemic"[Mesh] OR "Lupus Vasculitis, Central Nervous System"[MeSH]) AND ("MMF" OR "mycophen*" OR "Cellcept" OR "mofetil" OR "Mycophenolic Acid"[MeSH]) AND ("infection*" OR "Infections"[MeSH]). This returned 29 results when filtered for clinical trials.

The next search string tested was (SLE OR "systemic lupus erythematosus" OR "lupus" OR "Lupus Erythematosus, Systemic"[MeSH] OR "Lupus Vasculitis, Central Nervous System"[MeSH]) AND ("MMF" OR "mycophen*" OR "Cellcept" OR "mofetil" OR "Mycophenolic Acid"[MeSH]) AND ("infection*" OR "Infections"[Mesh]) AND ("Immunocom*" OR leukopenia OR "Leukopenia"[MeSH] OR "Immunocompromised Host"[Mesh]). This yielded no matches.

We manually screened the 29 results obtained in the third search.

We could not find any RCTs examining the efficacy and safety of MMF on neuropsychiatric SLE during manual screening. This lack was confirmed by adding "Neuropsy*" to our search string, which yielded zero clinical trials. The clinical trials in these 20 PubMed results mainly studied lupus nephritis. Despite not having lupus nephritis herself, this is the best the literature could offer Ms. Burke.

We were examining the safety of long-term high-dose MMF only since its efficacy had already been proven in Ms. Burke's case with the two-year stint of no neuropsychiatric lupus flares while on 1.5 g MMF twice daily. There were no studies comparing the infection risks of different dosages of MMF, so we tried to select studies where one of the arms got the full 3 g per day of MMF since that was the proposed treatment for Ms. Burke. As a result, the articles by Dooley et al.[2], Zeher et al.[3], Lu et al.[4], Li et al.[5], Yap et al.[6], Zhao et al.[7], Grootscholten et al.[8], Ong et al.[9], Chan et al.[10], Contreras et al.[11], El-Shafey et al.[12], and Laskari et al.[13] had to be removed from consideration as they did not have any treatment arm that received 3 grams of MMF per day.

Articles that studied MMF used in combination with other drugs like volcosporin, cyclosporin, or tacrolimus had to be excluded since it was outside the scope of the clinical question and not relevant to Ms. Burke. As a result, the articles by Furie et al.[14,15], Contreras et al.[16], Rovin et al.[17,18], Kaballo et al.[19], Mysler et al.[20], Ginzler et al.[21] (published in 2012), and Arriens et al.[22] were removed from consideration.

There were other articles that were interesting but not relevant to the Burkes. Yuki et al.'s article studied the effect of MMF on covid vaccines.[23] Kittanamongkolchai et al. talked about using serum MMF level to guide dosing, which would not be feasible for our practice and unnecessary for the Burkes given Ms. Burke's flare-free track record on 1.5 grams twice daily MMF in the past.[24] Villaverde Verdejo et al. studied graft rejection in patients with lupus nephritis who received kidney transplants and MMF immunosuppression.[25] Filler et al. described the pharmacokinetics of MMF in children with vasculitis and other connective tissue diseases affecting the kidney.[26] Guthridge et al. studied the efficacy of herpes zoster vaccination for patients with SLE but specifically excluded patients taking MMF.[27]

After this screening, the articles by Appel et al., Ginzler et al. (published in 2005), and Isenberg et al. were chosen for further review.[1,28-29]

The article by Ginzler et al.[28] was a 24-week RCT that compared MMF to cyclophosphamide for lupus nephritis treatment with 140 patients and found that it was more effective. MMF had less severe infections, but more instances of diarrhea compared to cyclophosphamide. The article by Appel et al.[1] was an RCT that compared MMF to cyclophosphamide for induction treatment of lupus nephritis using 370 patients. They concluded that the two treatments were equivalent in effect and safety, both caused infections and there was no statistically significant difference between the two. The article by Isenberg et al. is a prospective planned primary efficacy analysis of the paper by Appel et al. that analyzed the data by self-reported race and determined that black patients had a statistically insignificant lower response rate to cyclophosphamide treatment.[1,29] The Appel et al. article is more recent than the Ginzler article and has a larger study population.

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Out of all the studies searched, the Appel et al. study is the best fit for Ms. Burke. Granted, it's not a perfect match for Ms. Burke: they also use a prednisone taper at the start for both groups because they are doing induction therapy[1], whereas we would be using a steroid taper for her lupus flare. There's no way to compare Ms. Burke's current risk of infection on 2 grams MMF daily to the proposed 3 grams MMF daily, and the patients have lupus nephritis, whereas Ms. Burke has neuropsychiatric lupus; However, it's the best the lupus literature has for her since it examines MMF monotherapy and compares it to the standard of care (cyclophosphamide). Additionally, there are no RCTs focusing on neuropsychiatric lupus. The shorter duration of treatment is not as much of a detracting factor for Ms. Burke because she is due for a follow-up appointment in our outpatient rheumatology clinic in 3 months anyway. Based on SORT criteria, the grade of recommendation is B.[30] Even though infections, a major concern for the Burkes, were directly assessed in this study, the patient population studied had lupus nephritis, not neuropsychiatric lupus.

Critical Appraisal

This study is a prospective, randomized, open-label, parallel-group, multicenter study comparing cyclophosphamide and MMF for patients with newly diagnosed lupus nephritis. This was an open-label RCT since the side effect profiles of the two drugs are distinct enough that the patients could identify what drug they were being treated with. The SORT level for evidence is 1 since this is an RCT.[1,30] An intention-to-treat analysis was used. The study was funded by Aspreva Pharmaceuticals Corporation, which has given honoraria to multiple authors. In addition, one of the authors is an employee of Aspreva, which opens the study to more funding bias.

370 patients with biopsy-confirmed lupus nephritis class III or higher were enrolled across 88 centers in North America, South America, Asia, and Europe. Patients who had MMF or cyclophosphamide treatment in the past year or had a current infection were excluded. The former exclusion criterion limits the applicability of the study to Ms. Burke since she had been taking MMF for multiple years.

The trial randomized participants and stratified by race and biopsy type. Oral MMF was given to 0.5 g twice daily and titrated up to 1.5 g twice daily in two weeks along with a 60 g steroid taper. Cyclophosphamide was given intravenously in monthly infusions per the National Institutes of Health protocol. Patients followed up at weeks 2 and 4 and every 4 weeks thereafter.

Of the 186 participants in the MMF group, 1 was lost to follow-up, 1 didn't receive treatment for unspecified reasons, 24 withdrew due to adverse effects, 6 took back consent and 5 withdrew for other reasons. Of the 185 participants in the cyclophosphamide group, 7 didn't receive treatment, 13 withdrew due to adverse effects, 5 took back consent, and 11 withdrew for other reasons. There may be some attrition bias due to adverse events, but the authors' analysis captured all the adverse events even if the patients withdrew.

Per intention-to-treat analysis, the proportion of patients reporting adverse events in the MMF group was 96.2% and 95% for cyclophosphamide, the difference was not statistically significant. However, there were 40.6% more adverse events reported in the cyclophosphamide group because some patients experienced multiple adverse events. Most of the adverse events reported in both groups were infections, and there was no statistically significant difference in the proportion of adverse events that were infections in the two groups.

The study has a large, diverse study population and frequent follow-ups which makes it a strong study.

Clinical Application

Ms. Burke presented to the ED with a neuropsychiatric lupus flare after a decrease of her MMF dosage. She refused to reconsider taking cyclophosphamide and refused to consider other chemotherapy drugs due to their side effects. Her mother felt strongly that her quality of life would decline if she started taking chemotherapy drugs for her lupus, and the patient agreed.

The study concluded that MMF is as safe as cyclophosphamide for SLE treatment over the six-month period studied. These results were shared with Ms. Burke and her mother, the latter of whom felt justified in refusing cyclophosphamide given that it had caused more adverse events than MMF. Ms. Burke was getting a steroid taper

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after her recent flare, so that was another way she matched the study. However, there were limitations to applying this study to Ms. Burke since the patients studied had lupus nephritis, which Ms. Burke did not have. Nevertheless, the resumption of her old treatment of 3 grams of MMF daily was offered to Ms. Burke, and she and her mother agreed.

New Knowledge Related to Clinical Decision Science

At the start of this venture, the care team was frustrated with Ms. Burke's and her mother's refusal to accept the next step in treatment: cyclophosphamide. However, considering their values regarding the proposed allowed the team to better understand their perspectives and establish rapport with them. This clinical case is a good reminder that guidelines just serve as recommendations and do not replace clinical decision-making. Additionally, a certain medication does not have to be avoided just because the patient has experienced side effects with prior use.

In Ms. Burke's case, we chose to increase the dosage of MMF and consequently risk leukopenia and future infections. These risks were more acceptable to her and her mother than the risks associated with a strong chemotherapy drug like cyclophosphamide. Considering what the patient wants from her life and her healthcare is what makes good patient care, and knowing patients may be willing to accept certain side effects can inform how we tailor the guidelines to the patient.

Research Question Related to Clinical Decision Science

Fear of potential side effects frequently affects patients' choice of therapy and if left unvoiced, affects adherence. Simply measuring patients' fears of side effects could potentially alter clinical care decisions, as illustrated in this Clinical Decision Report. Clinicians are familiar with pain scales (Visual Analog Scales 1-10).[31] These are used clinically to make sure the issue is addressed in patient care settings. A Visual Analog Scale (VAS) to assess a patient's perceived risk of side effects when initiating new medication could screen for treatment hesitancy similar to how the Parent Attitudes about Childhood Vaccines questionnaire screens for vaccine hesitancy.[32] This would facilitate research of how clinical decisions are made in practice.

Conflict Of Interest Statement

The author declares no conflicts of interest.

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