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Desensitization to Mycofenolate Mofetil: a novel 12 step protocol

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Key words
desensitization; IgE reactions; adverse drug reaction

Summary
The use of MMF has become standard practice in many solid organ transplant recipients due its efficacy and favorable risk profile compared to other immunosuppressants. There has been a single case report of successful MMF desensitization. However, this protocol did not follow current Drug practice parameters. We report a successful desensitization to MMF in a double heart-kidney transplant recipient

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Introduction

Mycophenolate mofetil (MMF) has largely replaced azathioprine as the preferred drug in organ transplant recipients, and more recently has also been used as a glucocorticoid-sparing agent for the treatment of several rheumatologic diseases. It selectively inhibits T- and B-lymphocyte proliferation by reversibly inhibiting the enzyme, inosine monophosphate dehydrogenase. This enzyme is crucial to the de-novo synthesis of guanine nucleotides by catalyzing the conversion of inosine monophosphate to guanosine monophosphate. Thus, by inhibiting the synthesis of purine nucleotides, it results in decreased B- and T-lymphocyte proliferation, and decreased antibody production (1).
MMF is usually tolerated well in most patients, with the most common side effects being gastrointestinal symptoms and leukopenia. Unlike hypersensitivity reactions, these adverse effects usually resolve with dose adjustments. Hypersensitivity to MMF is rare (2,3), with only two previous case reports in the literature (4,5). When a patient is suspected of having an IgE mediated hypersensitivity to MMF, and it remains the preferred drug over other immunosuppressants, then desensitization may be a safe alternative. Drug desensitization is the induction of a temporary state of tolerance (6). Drug tolerance is defined as a state in which a patient with a drug allergy will tolerate a drug without an adverse reaction. By inducing tolerance, it modifies an individual's response to a drug temporarily, and in so doing, allows safe treatment with that drug. Desensitization is indicated where an alternative, non-cross reacting medication cannot be used or is not equally efficacious. Induction of temporary tolerance can involve both IgE and non-IgE immune mechanisms, and even undefined mechanisms (7). Desensitization involves administering incremental doses of the drug over hours to days. The state of tolerance that results from desensitization is only maintained while the patient is taking the drug. Upon discontinuation of the drug, tolerance is lost within hours to days (7).

Case Report

We report a successful desensitization to MMF in a transplant recipient. A 46-year-old African-American female with a past medical history of systemic lupus erythematosus (SLE) induced dilated cardiomyopathy and end stage renal disease was scheduled for a double cardio-renal transplant at our institution.

About 10 years prior to her planned transplant, she was placed on MMF, prednisone and cyclophosphamide during an acute flare of her underlying lupus. After a few days she started to experience pruritus of her lips several minutes after ingestion of MMF. After being on MMF for two weeks, she developed facial hives, pruritus and angioedema within 12 hours of her last dose. She was then advised to stop taking MMF and subsequently noticed complete resolution of her symptoms within 3 days while continuing on prednisone and cyclophosphamide.

Due to her history being concerning for an IgE mediated reaction to MMF, her transplant team consulted our Allergy and Immunology Department to consider a rapid drug desensitization procedure. We reviewed the literature and found two previous case reports (4,5). Upon review, both protocols utilized on the published case reports (4,5), deviated from current drug allergy practice parameters set forth by Solensky et al (7). One of the most noticeable deviations was that the protocol previously developed (4), involved giving incremental doses of MMF over 3 days, instead of several hours.

Table 1 *- Mycophenolate Mofetil Oral Desensitization.*

Step	Time (H:MM)	Dose (mg)	Oral volume (200 mg/ml1)
1	0:00	0.25	0.00125
2	0:20	0.5	0.0025
3	0:40	1	0.005
4	1:00	2	0.01
5	1:20	4	0.02
6	1:40	5	0.025
7	2:00	16	0.08
8	2:20	32	0.16
9	2:40	64	0.32
10	3:00	125	0.625
11	3:20	250	1.25
12	3:40	500	2.5
Total	3:40	999.75	4.99875

[1]Mycophenolate solution was prepared via diluting a stock solution of mycophenolate (200 mg/ml) with Ora-Plusâ until a 4 mg/ml solution was obtained.

In our patient, skin testing to MMF was planned to gain further insight on reactivity and, however the patient had a blunted response to the histamine control. Given the urgency of the situation and inability to interpret our skin tests, we decided to proceed directly with a desensitization procedure. We designed a novel 12-step desensitization protocol (**table 1**), in accordance with the current drug allergy practice parameters recommendations.

Following her back-to-back cardio-renal transplant, the patient was placed on azathioprine, tacrolimus and methylprednisolone, pending her desensitization to MMF.

In an intensive care unit setting, an oral desensitization with MMF was performed with diphenhydramine 25 mg IV and famotidine 20 mg IV given as premedication. Incremental doses were given every twenty minutes, reaching a target dose of 500 mg (cumulative 1000 mg) without adverse reactions. She was then successfully continued on the target dose of MMF 500 mg twice daily and tolerated it well. It was subsequently discontinued on a future hospitalization, four months later, due to concern that it may have contributed to an incidental finding of leucopenia. She has since been placed on azathioprine and was doing clinically well at her last follow-up, 12 months after her transplant.

Conclusion

The use of MMF has become standard practice in many solid organ transplant recipients due its efficacy and favorable risk profile compared to other immunosuppressants. Although an IgE mediated allergy to MMF is rare, it may be increasingly encountered due to its increasing use. Our protocol can be applied to other such patients to achieve a successful desensitization.

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