

Systemic Treatment of Pediatric Atopic Dermatitis with Azathioprine and Mycophenolate Mofetil

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Abstract: Severe forms of atopic dermatitis (AD) cause significant morbidity in vulnerable pediatric populations and necessitate treatment with systemic therapy. The existing literature concerning the treatment of severe pediatric AD with azathioprine (AZ) and mycophenolate mofetil (MM) is sparse. The purpose of this case series is to examine the use of these two drugs in the treatment of severe pediatric AD. Medical records of 28 pediatric patients with AD from the University of North Carolina at Chapel Hill pediatric dermatology clinic treated using these two drugs were analyzed for laboratory values, thiopurine methyltransferase (TPMT) levels, symptoms, infections, and other relevant data. Patients were also contacted via the telephone to ascertain outcomes and any missing data. Treatment outcomes were scored into three categories: significant improvement, some improvement, and no improvement. AZ dosing was correlated to TPMT levels successfully, with comparable levels of improvement in the heterozygous and homozygous wild-type groups. Absolute eosinophil count corresponded to AD activity and treatment response across both treatment modalities in 18 of 26 (69%) patients. Seventeen of 28 (61%) patients treated with AZ and eight of 12 (66%) treated with MM reported significant improvement. We had lower rates of laboratory abnormalities and side effects with MM than with AZ but similar rates of cutaneous infections. Treatment outcomes did not appear to differ with race, sex, or TPMT level. We experienced success with AZ and MM in the treatment of severe pediatric AD. Coordinating treatment to each patient's unique morbidities is the best way to choose systemic treatments.

Affecting an estimated 10% to 20% of children in the developed world, atopic dermatitis (AD) is one of the most common conditions seen in pediatric dermatology (1). Pruritus, erythema, and scale can have significant negative effects on patients' quality of life. In more severe

forms, AD can be resistant to maximal topical approaches, and further treatment often involves a systemic approach.

The goal of this case series is to examine the use of azathioprine (AZ) and mycophenolate mofetil (MM) in

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TABLE 1. Patients Treated with Azathioprine

Patient	Gender	Race	Age at start of AZ treatment	TPMT level	TPMT class	Initial improvement at X wks	Improvement level (none, some, significant)	Total time on AZ (mos)	Infection rate (per month)	Lab abnormalities rate (per month)
A	Female	African American	15	8.5	Heterozygous	7.0	Significant	10	0.00	0.00
B	Female	African American	14	8.5	Heterozygous	None	None	2	0.50	0.00
C	Female	Caucasian	14	10.6	Heterozygous	Unknown	Some	2	0.00	0.50
D	Male	African American	12	13.1	Heterozygous	Unknown	Some	9	0.11	0.00
E	Male	Caucasian	7	14.9	Heterozygous	5.0	Significant	24	0.04	0.00
F	Female	African American	13	15.0	Homozygous WT	3.0	Significant	11	0.18	0.00
G	Male	Caucasian	4	15.7	Homozygous WT	None	None	2.5	0.00	0.00
H	Female	African American	17	16.6	Homozygous WT	9.0	Significant	25	0.00	0.00
I	Female	Caucasian	10	16.7	Homozygous WT	3.0	Significant	14.5	0.07	0.00
J	Female	Caucasian	10	16.8	Homozygous WT	9.0	Significant	28.25	0.25	0.00
K	Male	Caucasian	11	17.1	Homozygous WT	4.0	Significant	7	0.29	0.00
L	Female	African American	11	17.1	Homozygous WT	2.0	Some	17	0.06	0.00
M	Male	Caucasian	14	17.2	Homozygous WT	None	None	5	0.20	0.00
N	Female	African American	11	17.6	Homozygous WT	6.0	Significant	40	0.05	0.03
O	Female	Caucasian	11	17.6	Homozygous WT	None	None	5	0.00	0.20
P	Female	Hispanic	12	18.4	Homozygous WT	7.0	Some	2	0.00	0.00
Q	Female	Caucasian	14	18.8	Homozygous WT	4.0	Some	1	0.00	0.00
R	Male	African American	8	19.3	Homozygous WT	4.5	Significant	16	0.06	0.00
S	Female	Caucasian	12	19.5	Homozygous WT	5.5	Significant	24	0.00	0.04
T	Male	Caucasian	10	20.6	Homozygous WT	5.0	Significant	12	0.08	0.00
U	Female	Caucasian	10	21.0	Homozygous WT	6.0	Significant	11	0.00	0.00
V	Female	African American	14	21.1	Homozygous WT	2.5	Significant	3	0.33	0.00
W	Female	Caucasian	9	21.6	Homozygous WT	6.0	Significant	26	0.04	0.00
X	Female	African American	15	23.5	Homozygous WT	7.0	Significant	29	0.03	0.03
Y	Male	African American	3	25.3	Homozygous WT	5.0	Some	8	0.00	0.00
Z	Male	Hispanic	11	20.1	Homozygous WT	None	None	5	0.00	0.20
AA	Male	Caucasian	11	10.6	Homozygous WT	4.0	Significant	12	0.08	0.08
AB	Male	Caucasian	17	26.5	Homozygous WT	6.5	Significant	12	0.00	0.00

TABLE 2. *Patients Treated with Mycophenolate Mofetil*

Patient	Total time on MM (mos)	Infections per month	Lab abnormalities per month	Improvement level (none, some, significant)	Initial improvement at X wks
A	20.0	0.05	0.00	Significant	4.0
B	0.5	0.00	0.00	None	None
C	12.0	0.00	0.00	Significant	2.5
G	1.0	0.00	0.00	Significant	4.5
J	7.0	0.00	0.00	Significant	3.0
K	1.0	0.00	0.00	None	None
M	14.0	0.21	0.07	Significant	5.0
N	8.0	0.00	0.00	Significant	3.0
O	13.5	0.00	0.00	Significant	5.0
P	1.0	0.00	0.00	None	None
Q	12.0	0.00	0.00	Significant	4.5
AA	1.5	0.67	0.00	None	None

the treatment of severe pediatric AD. Although there is much literature on the treatment of AD with cyclosporine, existing literature concerning the treatment of pediatric AD with these two drugs is comparatively sparse (2).

SUBJECTS AND METHODS

Patients attending the University of North Carolina at Chapel Hill Pediatric Dermatology clinic from January 1, 2002, to March 10, 2010, who received systemic therapy for the treatment of AD were studied. Most of these patients were from the central North Carolina geographic area. All patients receiving systemic therapy had failed multiple previous therapeutic approaches (ultrapotent topical steroids, oral antibiotics, oral antihistamines, dilute bleach baths) and experienced significant detrimental effect on quality of life. A list of all patients treated systemically for AD was compiled, and their clinical records were analyzed. One provider (DSM) treated all of the participants.

Relevant data concerning patient demographics, telephone numbers, laboratory values including thiopurine methyltransferase (TPMT) activity levels, symptoms, treatments, dosing, hospitalizations, disease severity, and side effects were recorded in Microsoft Excel spreadsheets (Microsoft Corp., Redmond, WA). In addition, initial clinical outcomes were recorded and divided into three categories: significant improvement (vast and dramatic reduction in erythema, pruritus, scales, and topical steroid use and marked improvement in quality of life), some improvement (moderate reduction in erythema, pruritus, and scales; baseline topical therapy unchanged or slightly decreased; and mild improvement in quality of life), and no improvement (worsening or no reduction in erythema, pruritus, scales, and topical steroid use and worsening or no improvement in quality of life). This information was gleaned

directly from the demographic, laboratory values, medications, and clinical notes sections of the electronic medical record for each participant. AD severity was not scored objectively (e.g., using the SCORAD system). In addition, no genotyping was performed; genotype classifications discussed later are estimates from corresponding TPMT level assays. Missing data were noted. After this initial phase of data collection was completed, patients were contacted via telephone for several follow-up questions pertaining to their systemic therapy. During this call, an attempt was also made to fill in any missing data from the patient's initial record. It was impossible to contact all of our participants for telephone follow up. Incomplete patient records or patients who had started therapy < 3 months before March 10, 2010, were omitted. The University of North Carolina at Chapel Hill Institutional Review Board approved the retrospective chart review and telephone survey.

Thirty-two patients were recruited, but four were dropped (two because of missing data, and two because they were adults), leaving 28 patients (mean age 11.4 yrs, range 3–17 yrs). All patients were initially treated with AZ; those who discontinued AZ and required further therapy were then treated with MM (12 of 28).

Case Series

Of 28 patients, 15 were Caucasian, 11 African American, and two Hispanic. Sixteen were female. During the clinical visit when AZ was initiated, blood was taken for TPMT assays. AZ was initiated at a dose < 1 mg/kg per day until the result of the TPMT assay was known (within a few days). Patients with homozygous wild-type levels were increased to 3 mg/kg per day, and those with heterozygote levels were maintained at 1 mg/kg per day. We chose these doses based on our previous treatment experience. While being treated with AZ, 17 (61%) of our patients reported

significant improvement in their AD, six (21%) reported some improvement, and five (18%) reported no improvement. Seven (25%) experienced laboratory abnormalities significant enough to necessitate an adjustment in AZ dose level, the most common being abnormal liver function tests, followed by low hemoglobin and white blood cell count abnormalities. Sixteen (57%) patients experienced a cutaneous infection (most commonly folliculitis or cellulitis) during their treatment with AZ, with an average rate of infection while taking AZ for all 28 patients of 0.08 infections per month of treatment. On average, patients were treated with AZ for 13.0 months. AZ responders experienced initial improvement at a mean 5.3 weeks. AZ responders were treated for an average of 14.9 months.

TPMT level assays revealed zero homozygous recessive, five heterozygous, and 23 homozygous wild-type patients. Neither race ($t = 0.26$, $p = 0.80$) nor sex ($t = -1.05$, $p = 0.30$) affected TPMT levels, which did not correlate to infection rates ($r^2 = 0.12$) or laboratory abnormality rates ($r^2 = 0.09$). Four of five (80%) heterozygous patients and 19 of 23 (83%) homozygous wild-type patients reported significant or some improvement of their AD while taking AZ.

Twelve of our 28 patients transitioned to MM therapy (20–40 mg/kg per day) after initially trying AZ for treatment of their systemic AD. Average time of treatment with AZ before switch to MM was 9.7 months. Reasons for transition to MM from AZ were varied; four (33%) patients reported medication intolerance, six (50%) reported failure to respond to AZ, and two (17%) reported a combination of both. Of these 12 patients, eight (66%) reported significant improvement, and four (33%) reported no improvement while on MM. Only one of the 12 (8%) experienced laboratory abnormalities (low hemoglobin level) significant enough to necessitate an adjustment in MM dose. Three of our patients treated with MM (25%) experienced a cutaneous infection, an average rate of infection while on MM of 0.07 infections per month of treatment.

There was no significant difference in terms of response rates (significant or some improvement vs none) in our AZ or MM groups ($\chi^2 = 1.12$, $p = 0.28$). We were unable to find a difference between Caucasians and non-Caucasians in terms of going on to subsequent treatment with MM ($\chi^2 = 1.45$, $p = 0.23$). Mean TPMT levels were similar for Caucasians (17.7) and non-Caucasians (17.2), a difference that was not statistically significant. While being treated with AZ, Caucasians and non-Caucasians had similar rates of infection (0.07 and 0.10 infections per month, respectively, $t = -0.68$, $p = 0.51$) and laboratory abnormalities (0.06 and 0.02 abnormalities per month, respectively, $t = 0.94$, $p = 0.35$). While

on AZ, 12 of 15 (80%) Caucasians and 11 of 13 (85%) non-Caucasians reported some or significant improvement. While on AZ, 14 of 16 female patients (88%) and nine of 12 (75%) male patients experienced some or significant improvement. There was no significant difference between the sexes in terms of transitioning to treatment with MM ($\chi^2 = 0.78$, $p = 0.38$). Where data were available, absolute eosinophil count on blood differential consistently corresponded to AD activity and treatment response for both treatment modalities in 18 or 26 (69.2%) patients. See Tables 1 and 2 for a list of patients included in the final data analysis.

DISCUSSION

Azathioprine has been used in the treatment of AD with previously reported good results when titrated to a patient's TPMT level (3,4) and has been suggested as a first-line agent for severe AD in older children and teens (5). Possible side effects include headache, upset stomach, hepatotoxicity, and leukopenia, of which the last two are dose-dependent. Our most common ($n = 8$, 29%) reported physical complaint during treatment with AZ was gastrointestinal related (nausea, indigestion, and vomiting). The most common laboratory abnormality ($n = 6$, 21%) was high levels on liver function tests. In the medical literature, initial improvement while taking AZ is seen 2 to 6 weeks after start of treatment (6), and the maximum effect of AZ is reported to take at least 8 weeks after the start of treatment. These times are similar to reported response times for MM (5,7). In our patients, using TPMT-directed dosing yielded onset of AZ effect at a mean of 5 weeks.

A double-blind, randomized, placebo-controlled study of AD treated with AZ in adult patients found that AZ was significantly more likely to be correlated to an improvement in quality of life measures such as sleep quality, pruritus, and daytime activities than placebo (8). Another double-blind, placebo-controlled study found that, when titrating AZ doses according to TPMT level, patients with deficient TPMT levels obtained similar outcomes and side-effect profiles as those with wild-type TPMT levels (3). A case report also demonstrated successful treatment of severe AD in two children with deficient TPMT levels at doses of 1 to 1.25 mg/kg per day; both patients had normal blood tests at subsequent follow-up visits (4). Our results support these findings because titration of a patient's AZ dose according to TPMT level seems to nearly equalize the chance of improvement while creating similar rates of side effects and laboratory abnormalities. Like previous reports, our patients who improved while taking AZ experienced mean onset of initial improvement at approximately

1 month. There have been reports of AZ being more efficacious in females (9). Our results do not fully support this, but a larger sample might produce differences. A possibility that we failed to address was that all 12 of our patients with MM had been treated with AZ before, so a lag effect from AZ treatment might have caused some of the improvement attributed to MM in these patients. We did not incorporate a “break time” into our study (a transition time between the two therapies in which a patient did not use either systemic therapy, improvement during this time could possibly be at least partially attributed to a latent improvement from AZ treatment).

Mycophenolate mofetil is considered to be less toxic than other immunosuppressants (10) and is used off-label for AD treatment. Possible side effects include gastrointestinal (nausea, vomiting, diarrhea), leukopenia, hypertension, and nephrotoxicity. Like with AZ, our most common ($n = 3$, 25%) side effect with MM was gastrointestinal. These complaints were generally mild and lessened with continued MM treatment. Our patients who improved while taking MM experienced mean onset of initial improvement of 3.9 weeks. Previous reports have described an initial response time for MM of approximately 4 to 8 weeks and have suggested that, if no effect is seen by 8 weeks, MM should be discontinued (11). MM has a longer typical time to clinical response than cyclosporine and oral corticosteroids but fewer side effects (7).

There is even less literature concerning treatment of AD with MM than for treatment with AZ, but studies thus far indicate good results (10). A retrospective chart review of 20 adults with refractory AD treated with MM showed improvement in the majority of participants and complete clearance in 50% while being generally well tolerated (12). A retrospective study by Heller et al (13) of 14 pediatric patients also had positive results, with more than 50% of patients attaining 90% improvement without major side effects; most responses occurred within 2 months of treatment initiation. We experienced success with MM, with two-thirds of our patients reporting significant improvement. Our findings support prior reports indicating that cumulative rates of infection on MM seem to be similar to those seen in AZ (14). Because we had an overall lower rate of laboratory abnormalities and seemingly less-severe side effects with MM, our experience reinforces the idea that MM may be better tolerated and safer than AZ (although both drugs had similar rates of gastrointestinal complaints).

CONCLUSION

As other researchers have noted, each patient's case of AD, as well as response to treatment, is unique (7). There is no one “silver bullet” in terms of an AD treatment. We

experienced success with AZ and MM in the treatment of pediatric AD. Coordinating treatment to each patient's unique morbidities is the best way to choose systemic treatments. In addition, rotating therapies, as Ballester initially published, might be a viable approach to minimize toxicities (7). MM is more expensive than AZ, which may play a role in treatment decisions concerning some patient populations (15). AZ and MM offer attractive options for safer and longer systemic treatment in patients who cannot use cyclosporine (16). Our approach in severe AD requiring systemic treatment is to maintain good control of the patient's AD for 1 to 2 years before discontinuation of the effective and tolerated systemic agent. For both treatment modalities, absolute eosinophil count correlated to AD severity and treatment response in more than two-thirds of our patients, lending support to the idea that it is possible to monitor clinical effect according to absolute eosinophil count (17). Because only five of our study patients (four AZ, one MM) have completed therapeutic courses, longer follow-up of patients with AD treated with these systemic agents is necessary to determine long-term efficacy and safety profiles. Additionally, it would be interesting to compare infection rates before and after systemic treatment initiation.

A randomized, controlled clinical trial of all three major systemic treatment options (cyclosporine, AZ, and MM) of pediatric AD is needed. Other future areas of study include comparison of treatment successes and morbidities according to race and sex in larger samples, perhaps using populations from multiple centers. Because severe AD causes significant morbidity in children, affecting psychosocial development and families' quality of life, more research is needed to delineate the safest and most efficacious treatment.

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