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Outcome of treatment with azathioprine in severe atopic dermatitis: a five-year retrospective study of adult outpatients

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Dear Editor,

Azathioprine is one of several immunomodulatory drugs used in the treatment of severe atopic dermatitis [1]. Two double-blinded, randomized, placebo-controlled trials (n=37 [2] and n=63 [3]) and one single-blinded, randomized, controlled trial comparing azathioprine with methotrexate (n=42 [4]) have evaluated the efficacy and safety of azathioprine in patients with atopic dermatitis. These studies indicate that azathioprine is superior to placebo and with a clinical efficacy equal to that of methotrexate in controlling atopic dermatitis with an expected average reduction in disease activity of about 40%. Furthermore, these studies have shown that adverse effects, particularly gastrointestinal disturbances, are common with azathioprine accounting for premature discontinuation of treatment in about 30% of patients. There are no definite recommendations for the duration of treatment of atopic dermatitis with azathioprine [5], and data on long-term adherence and on the causes for discontinuation of azathioprine for this indication is lacking.

We retrospectively reviewed patient records from two Danish dermatological hospital departments (Bispebjerg and Roskilde Hospitals). Patients ≥ 18 years of age with atopic dermatitis according to the UK Working Party's criteria [6], who had an ICD-10 diagnosis of atopic dermatitis (L20), and who began treatment with azathioprine due to refractory eczema were included consecutively from 1st of January 2008 to 31st of December 2012. The shortest observation time per patient was one year. Only immunosuppressant-naïve patients were included; i.e. patients who had never before been treated with a systemic immunomodulatory drug, except prednisolone. Azathioprine was used in doses ranging between 25 and 200 mg/day in 74 patients during the period of observation. Of these, 60 patients (22 men and 38 women) were immunosuppressant-naïve (Table 1).

After one year, 31 patients (52%) were still treated or had stopped due to significant improvement of the disease, whereas 9 patients (15%) had discontinued due to lack of clinical benefit; 12 patients (20%) because of adverse effects, primarily gastrointestinal disturbances (accounted for 58% of all discontinuations due to adverse effects); and another 8 patients (13%)

had discontinued or were withdrawn from treatment due to personal concerns over potential harmful effects of the treatment or because they were non-adherent to scheduled ambulatory visits. These 8 patients (4 men and 4 women) were, on average, approximately 11 years younger than the other patients who discontinued treatment due to other reasons within the first year (mean age 28.4 vs. 39.3 years), $p=0.055$. No severe (harmful) adverse effects (such as azathioprine hypersensitivity syndrome, severe myelotoxicity, cancer or severe infections related to azathioprine treatment) occurred in the population.

During the second year of treatment, another 10 of the remaining 26 patients discontinued treatment: 3 patients because of complete or almost complete clearance of eczema; 2 patients because of lack of clinical benefit of the treatment; 1 patient due to adverse effects; 4 due to concerns over potentially harmful effects of the treatment or because they were non-adherent to scheduled ambulatory visits. Another 6 patients benefitted clinically from treatment but had observation times under two years.

A total of 10 remaining patients (16.7% of the original cohort) entered their third year of consecutive treatment. Eight of these patients had long-term remission of their eczema, whereas 2 patients discontinued during the third year of treatment due to serological disturbances or adverse effects (Figure 1).

High serum total IgE, $HR=1.48$ (0.87-2.51), $p=0.153$ and eosinophil count, $HR=1.33$ (0.61-2.92), $p=0.469$ were non-significantly associated with treatment discontinuation. Also, we found no significant influence on the risk of premature discontinuation of TPMT activity, $HR=0.98$ (0.87-1.09), $p=0.653$ or *TPMT* heterozygosity, $HR=0.81$ (0.27-2.39), $p=0.701$.

Of all patients who discontinued azathioprine treatment prematurely due to adverse effects or lack of clinical benefit, or both, 14 (6 men and 8 women) initiated treatment with a second systemic drug during the five-year period of observation; 1 patient was treated with cyclosporine A, 2 with alitretinoin, 4 with mycophenolate mofetil, and 7 were re-treated with azathioprine. Overall, the three-month adherence rate among azathioprine *re-treated* patients was 42%, and at one year was reduced to 34%. The 7 patients re-treated with azathioprine, discontinued azathioprine during their *first* treatment round due to quite heterogeneous reasons: lack of clinical benefit (1 patient), gastrointestinal adverse effects (1 patient), concern over possible long-term harmful effects (1 patient), and non-adherence to scheduled ambulatory visits (4 patients). Among the 14 patients who were treated again with a systemic drug, the discontinuation rate of the second drug was 64% (9 patients), whereas 36% (5 patients) benefitted clinically from the second treatment and experienced no severe adverse effects.

Our data shows that around half of adult patients who begin treatment with azathioprine for severe atopic dermatitis have clinical benefit of the treatment after one year and tolerate the treatment without significant adverse effects. The other half of patients discontinue at some stage within the first year due to a lack of clinical benefit or due to adverse effects, predominantly gastrointestinal disturbances. We did not observe any serious adverse effects in this cohort, which is somewhat surprising.

We observed no significant influence on the risk of premature discontinuation of azathioprine of TPMT activity or *TPMT* heterozygosity. However, adverse effects of azathioprine can be dose-dependent, non-allergic and idiosyncratic dose-independent, presumed allergic, and the majority of adverse events cannot be explained by variations in TPMT activity or thiopurine metabolite patterns [5]. Furthermore, there were no *TPMT* null variants in our patient sample and we reduced the initial dosage of the drug in heterozygotes to minimize risk of myelotoxicity.

We found a tendency for patients with higher values of blood eosinophil count and serum total IgE to prematurely discontinue treatment with azathioprine. These results could indicate that patients with extrinsic atopic dermatitis have a higher risk of treatment failure and that these patients should be evaluated more carefully during treatment. However, our analyses were not adjusted for severity of atopic dermatitis, and patients with high IgE and eosinophil count, may have more severe eczema, which could be expected to respond poorer to azathioprine.

Among a small subgroup of patients who had discontinued treatment prematurely, we observed that re-treatment with azathioprine did not necessarily result in a poorer treatment outcome during the *second* round of treatment. This finding indicates that although a patient has discontinued treatment due to lack of efficacy, anxiety related to treatment, or (mild) adverse effects, re-treatment at a later stage to obtain disease control in the same patient is possible.

A limitation of the study was the lack of prospectively collected clinical data on disease severity and duration. Particularly, it is a limitation that we did not assess the severity of atopic dermatitis systematically from baseline and at follow-up so we were able to judge the effect of the treatment objectively. Also, it is a limitation that we did not measure azathioprine dose systematically. Azathioprine was prescribed by different physicians with different therapeutic approaches. However, when TPMT activity was low or when the patient was *TPMT* heterozygous azathioprine was prescribed more cautiously.

Larger, prospective studies are needed to fully explore possible differences in treatment response according to subtypes of atopic dermatitis. Also, since at present there is no

consensus as to whether azathioprine should be prescribed first for refractory atopic dermatitis, it is necessary to establish a hierarchy of immunomodulatory treatment choices for this condition.

Legend for figure

Figure 1. Result of treatment with azathioprine among 60 adult patients with severe atopic dermatitis.

Note: Adverse effects represent gastrointestinal disturbances, serological abnormalities, infections, and other adverse effects (general malaise or night sweats). Personal concern is concerns over potential long-term harmful effects of the treatment. Non-adherence is failure to comply with scheduled ambulatory visits. Censored patients denote patients who at the time of censoring have clearance of eczema but whose follow-up times end before entering the next treatment interval.

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Table 1. Descriptive characteristics of 60 immunosuppressant-naïve adult patients with severe atopic dermatitis treated with azathioprine.

	Data	Men	Women	All	P-
	availability	N=22	N=38	N=60	value
Department	60 (100)				0.726
Bispebjerg		16 (72.7)	26 (68.4)	42 (70.0)	
Roskilde		6 (27.3)	12 (31.6)	18 (30.0)	
Age	60 (100)	36.9 (13.2)	34.4 (13.4)	35.3 (13.3)	0.488
Eosinophil count	59 (98)	0.29 (0.30)	0.21 (0.38)	0.25 (0.34)	0.961
Total serum IgE	26 (43)	2421 (5038)	431 (2278)	895 (3407)	0.646
Positive skin prick test	23 (38)	6 (75.0)	10 (66.7)	16 (69.6)	0.679
Type 1 allergy	49 (82)	13 (68.4)	15 (50.0)	28 (57.1)	0.204
Type 4 allergy	48 (80)	1 (5.6)	13 (43.3)	14 (29.2)	0.005
TPMT heterozygosity	35 (58)	2 (15.4)	4 (18.2)	6 (17.1)	0.832
TPMT enzyme activity	38 (63)	13.2 (5.4)	14.0 (2.4)	13.7 (3.8)	0.585
Senior physician	60 (100)	11 (50.0)	24 (63.2)	35 (58.3)	0.319
Number of physicians	42 (70)	2 (2)	1 (2)	2 (2)	0.342

Data availability is number (%) of patients with information on the particular variable. Age, TPMT (thiopurine methyltransferase) activity, and number of physicians are mean values (standard deviation); eosinophil count, total serum IgE and number of physicians are medians (interquartile range); all other values are numbers (%). Type 1 allergy and type 4 allergy are self-reported.

P-value is for difference between men and women.

Numbers are calculated from available data.

