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Drug survival for azathioprine and enteric-coated mycophenolate sodium in a long-term daily practice cohort of adult patients with atopic dermatitis

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To the Editor,

Results from clinical studies indicate that azathioprine and enteric-coated mycophenolate sodium (EC-MPS) are safe and potent drugs in the treatment of atopic dermatitis (AD).¹⁻⁵ However, published data from large groups of non-selected patients is non-existent to date which hampers generalization to daily practice. In addition, head-to-head trials in which azathioprine and EC-MPS are compared, have never been performed.

The primary objective was to perform an analysis of drug survival for azathioprine and EC-MPS in a long-term daily practice cohort of patients with AD. The secondary objective was to identify determinants of drug survival. Drug survival is a reflection of daily practice and explores the time on a particular drug using the Kaplan-Meier survival technique, which allows for censoring.

Data was retrospectively collected in two tertiary referral centers in the Netherlands (University Medical Center Groningen and Utrecht). Patients with AD, diagnosed based on the criteria of Hanifin and Rajka⁶ and the criteria of Williams⁷, treated in the period from 1995 (azathioprine) and 2004 (EC-MPS) until data lock in December 2013 were included. Patients were treated according to the standard follow-up protocol to minimize differences between physicians (azathioprine 150/200 mg/day; EC-MPS 1440 mg/day).

Drug survival was analysed using Kaplan-Meier survival curves. Determinants of drug survival (age, gender, oral corticosteroids concomitantly used at the moment of discontinuation and the azathioprine maintenance dose) were selected using a univariate Cox regression analysis and

analyzed with a multivariate Cox regression analysis with backward selection. Statistical analyses were performed in SPSS (for Windows version 21, SPSS Inc).

Drug survival of 94 patients (median duration of treatment 180 (range 4-1095) days; 82 patient-years) treated with azathioprine and drug survival of 84 patients (median duration of treatment 324 (range 14-1095) days; 110 patient-years) treated with EC-MPS was analysed (Table 1). Twenty-two patients were counted twice as they were both treated with AZA as with EC-MPS.

In the azathioprine group, 24 (25.5%) patients were still actively treated at the moment of data lock. Ten (10.6%) patients had discontinued treatment owing to controlled AD, of which 3 patients concomitantly used oral corticosteroids at the moment of discontinuation. Controlled AD was defined as a relief of AD symptoms mentioned by the patient and a satisfactory result reported by the physician. In case of controlled AD the dose could be gradually reduced and finally discontinued. Side effects were a reason for discontinuation of azathioprine in 34 (36.2%) patients and 18 (19.1%) patients discontinued owing to ineffectiveness. Two patients (2.1%) discontinued azathioprine owing to both side effects and ineffectiveness. Six (6.4%) patients stopped azathioprine owing to another event.

Twenty-two (26.2%) patients were still actively treated with EC-MPS at the moment of data lock and 3 (3.6%) patients were lost to follow-up. Nine (10.7%) patients had discontinued owing to controlled AD, none of them concomitantly used oral corticosteroids or CsA at the moment of stopping.

Ineffectiveness was a reason for discontinuation of EC-MPS in 32 (38.1%) patients. Side effects were the reason for discontinuation in 12 (14.3%) patients. Three (3.6%) patients stopped EC-MPS owing to both side effects and ineffectiveness and 3 (3.6%) patients stopped owing to another event.

The median overall drug survival for azathioprine was 201 days and for EC-MPS 322 days. The percentage of patients using azathioprine was 44%, 26%, and 14% and using EC-MPS was 45%, 36%,

and 27% after 1, 2 and 3 years, respectively (Figure 1a). The drug survival split by reason for discontinuation is shown in Figure 1b, c and d. Six percent, 21%, and 44% discontinued azathioprine and 6%, 15%, and 28% discontinued EC-MPS owing to controlled AD after 1, 2 and 3 years, respectively. Forty percent, 44%, and 47% discontinued azathioprine and 20%, 20%, and 23% discontinued EC-MPS owing to side effects after 1, 2 and 3 years, respectively. Twenty-three percent, 36%, and 41% discontinued azathioprine and 40%, 47%, and 51% discontinued EC-MPS owing to ineffectiveness after 1, 2 and 3 years, respectively.

The overall drug survival ($p=0.04$) and drug survival related to side effects ($p=0.01$) of EC-MPS was significantly better compared to azathioprine. The drug survival curves related to ineffectiveness cross with a trend towards better drug survival for azathioprine compared to EC-MPS. No significant difference between the drug survival distributions was found with respect to controlled AD.

Multivariate Cox regression analysis for azathioprine showed that concomitant oral corticosteroids at the moment of discontinuation was associated with a decreased drug survival related to side effects (HR 2.16, 95%CI 1.07-4.34). Older age was associated with an increased drug survival related to ineffectiveness (HR 0.81, 95%CI 0.69-0.95).

Multivariate Cox regression analysis for EC-MPS showed that concomitant oral corticosteroids at the moment of discontinuation was associated with a decreased drug survival related to side effects (HR 3.82, 95%CI 1.33-10.97) and a decreased drug survival related to ineffectiveness (HR 2.22, 95%CI 1.02-4.80). Male sex was associated with an increased drug survival related to ineffectiveness (HR 0.48, 95%CI 0.25-0.94).

The results show that the course of overall drug survival of azathioprine and EC-MPS was almost identical. Remarkably, discontinuation of treatment owing to side effects and/or ineffectiveness for both azathioprine and EC-MPS is higher in our drug survival study compared to earlier clinical trials.¹⁻

⁵ An explanation might be that patients who participate in clinical trials are often very motivated to fulfill the trial period, despite ineffectiveness or side effects.⁸ In addition, the longer treatment duration in daily practice may account for a higher discontinuation rate. A recent study of Thomsen *et al.*⁹ also reports a less favorable outcome of 60 patients treated with azathioprine in daily practice compared to those in clinical trials.

Patients with severe AD have uncontrolled eczema despite the use of high amounts of topical corticosteroids. Discontinuation of the oral immunosuppressive drug leads to exacerbations of AD and excessive use of topical corticosteroids, which can cause side effects. Therefore, in daily practice, no upper time limit exists for treatment with oral immunosuppressive drugs in AD.

There are differences between clinical trials and drug survival studies. Drug survival analysis is not a study of efficacy, but a reflection of daily practice. Clinical decisions made by physician and patient together taking into account effectiveness and side effects determine the outcome instead of clinical skin scores at fixed time points. Furthermore, clinical trials use strict inclusion and exclusion criteria, while in daily practice studies all patients are included. Patients' characteristics such as comorbidity, susceptibility to side effects and earlier treatment failure, may influence treatment success.

Oral corticosteroids at the moment of discontinuation of azathioprine or EC-MPS treatment may influence the reason for stopping. The number of patients using concomitantly oral corticosteroids at the moment of discontinuation was comparable in both groups ($p=0.59$). A significant effect on drug survival in the multivariate Cox regression analysis was found for the azathioprine group that discontinued owing to side effects and for the EC-MPS groups with respect to discontinuation owing to side effects and owing to ineffectiveness.

The determinants in the Cox regression model do not fully explain the outcome. Other factors for example disease severity, physicians' preferences, adherence to treatment and the availability of other treatment options may influence the outcome as well. A limitation of this study might be the

low explained variance of the results of the Cox regression analysis. Another limitation is the retrospective design, which brings dependency on quality of medical records.

In conclusion, drug survival of azathioprine is mainly limited by discontinuation owing to side effects, while drug survival of EC-MPS is mainly limited by discontinuation owing to ineffectiveness.

Concomitant use of oral corticosteroids in the more advanced phase of treatment has a negative effect on drug survival.

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Figure 1 – Azathioprine and enteric-coated mycophenolate sodium drug survival split for reasons of discontinuation.

Median drug survival overall (discontinuation owing to controlled AD, side effects, ineffectiveness and other reasons): azathioprine 201 days; EC-MPS 322 days. The median drug survival with respect to controlled AD, side effects and ineffectiveness could not be estimated, as > 50% of the patients still used the drugs after 3 years.

Overall drug survival: log rank test $p = 0.04$; discontinuation owing to controlled AD: curves cross, no trend towards a difference between drug survival is seen; discontinuation owing to side effects: log rank test $p = 0.00$; discontinuation owing to ineffectiveness: curves cross, after 3 months a trend towards better drug survival for azathioprine is seen.

Table 1 – Patient and treatment characteristics.

patient characteristics			
mean age (SD)	42.9 (13.9)	43.7 (13.3)	0.68 ^a
male (%)	54 (57.4%)	50 (59.5%)	0.88 ^b
ethnicity			
Caucasian	89 (94.7%)	82 (97.6%)	
Non-Caucasian	5 (5.6%)	2 (2.4%)	
oral immunosuppressive drugs history			
prior oral immunosuppressive drugs	83 (88.3%)	78 (92.9%)	0.32 ^b
naïve for oral immunosuppressive drugs	11 (11.7%)	6 (7.1%)	
concomitant use of			
oral corticosteroids	55 (58.5%)	46 (54.8%)	0.65 ^b
median % of total treatment episode ^c	82.8 (3.2-100.0%)	41.4 (0.5-100.0%)	0.04 ^d
used at moment of discontinuation	23 (24.5%)	17 (20.2%)	0.59 ^b
cyclosporin A	-	21 (25.0%)	na
median % of total treatment episode ^c	-	25.6 (1.6-100.0%)	na
used at moment of discontinuation	-	3 (3.6%)	na
status of use at the moment of data lock ^e			
active	24 (25.5%)	22 (26.2%)	0.18 ^b
discontinued	70 (74.5%)	59 (70.2%)	
lost to follow-up	0 (0.0%)	3 (3.6%)	

^a independent sample t-test, ^b Pearson chi-square test, ^c the percentage of total treatment episode is the duration of concomitant therapy divided by the duration of total azathioprine/EC-MPS episode, ^d Mann-Whitney U, ^e data lock: December, 2013.

