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Drug survival and post-drug survival of systemic treatments in a national French cohort of children with atopic dermatitis.

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Dear Editor,

Systemic immunosuppressive treatments (IS) are restricted to severe atopic dermatitis (AD) in children. We described the IS use (first and second-line) for children with AD in a French retrospective national cohort, by using two survival analyses: 'drug survival' (DS, defined as the duration of treatment) and 'post-drug survival' (PDS, defined as the time between the end of first-line and the beginning of second-line).

Children with AD aged 0 to 18 years, started with at least one IS from 2008 to 2018 and seen by members of French research groups (15 specialized centres), were included in the DS analysis. Discontinuation of IS was the event of interest in DS analysis; observations were censored if patients were lost to follow-up or still under treatment at the end of the study. Children who discontinued their first-line IS were included in the PDS analysis. The event was the start of a second-line IS; data were censored in case of loss-to-follow-up or absence of event after a 24-month period. DS and PDS were analysed with Cox regression models in patients on ciclosporin (CIC) and methotrexate (MTX), because of the small numbers of patients treated with other IS.

Eighty-three children (mean age 11± 8.7 years, 53% boys, 75% with age of AD onset before 2) were included. Among them, 65% had asthma, 49% allergic rhinitis and 42% allergic conjunctivitis. Previous treatments included topical corticosteroids (100%), topical calcineurin inhibitors (67%), and phototherapy (11%). The first-line IS was CIC for 60 patients (mean starting dose 3.2 ±5.6 mg/kg); MTX for 18 (mean starting dose 0.2 ±0.2 mg/kg/week); acitretin for 3, dupilumab (DUPI) and omalizumab for 1 patient. The reasons for discontinuation (n=60) were: failure for 17 (36%) children under CIC and 8 (80%) with MTX; controlled AD for 18 (38%) patients under CIC and 2 (20%) with MTX; adverse events for 11 (18%) children under CIC and no patient with MTX. Although the distribution of the 3 reasons for discontinuation was not globally statistically significant (p=0.88), CIC and MTX tend to have distinct profiles.

The median DS for first-line was 11.5 (IQR: 6.3-20.7) and 22.3 (IQR: 5.8-38.2) months for CIC and MTX respectively (p=0.01). The only predictive factor for longer DS was the MTX use (Table 1). A second-line IS was prescribed to 39 patients: CIC for 10 (25.6%), MTX and DUPI for 13 each (33.3%), mycophenolate mofetil, azathioprine and acitretin for one patient.

The median PDS was 8.0 and 4.1 months for CIC and MTX respectively (p=0.58). Age at AD onset under 2, respiratory allergy and controlled AD at the end of first-line were predictive factors of longer PDS. The predictive factors for shorter PDS were high-dose of first-line treatment and male gender (Table1).

The median DS for the second-line IS was 31.5 (IQR:8.5-78.3) and 13.5 (IQR:5.5-50.1) months for CIC and MTX respectively (p=0.88). No determinant of DS for second-line was found.

This first comparative study of the different first and second-line IS among AD children, in a daily-practice cohort, shows different treatment profiles: time under treatment was longer for MTX than for CIC but second-line IS seemed to be required sooner.

A few studies focused on 'DS in AD[1–6] (only 2 included children[5,6]). The median DS of 12 months for CIC as first-line is slightly longer than in previous studies[1,5,6]. However, they were conducted in adults or in both

adults and children. Our findings could be explained by a better safety profile in paediatric populations. A similar median DS for MTX (22 months) was reported in two studies[4,6], while one study reported only half that duration[2]. These results potentially illustrate a tendency to consider that the MTX safety profile is identical for adults and children. However, 'DS' analysis is difficult to interpret, depending on the physicians and patients' behaviour, drugs available[7], expert recommendations, etc.. This context is likely to vary significantly, so a comparison is difficult to make in the different contexts. For AD, the advent of DUPI for adults has already changed practices; here, it is the second most prescribed second-line IS (equal to MTX).

'PDS' analysis [6] provides information about both the benefit of first-line and of treatment-free period. The only result available for PDS showed a median shorter time for CIC (2 months) than for MTX (12 months)[6]. Contrasting with these results, we found a tendency for longer median PDS with CIC (8 months) vs MTX (4 months). The large proportion of patients who discontinued the MTX because of failure could explain the shorter PDS. However, treatment discontinuation could also be decided on a combination of arguments (efficacy or failure, adverse events, patient compliance).

To conclude, in addition to clinical trials, DS and PDS analyses give comprehensive information on the IS use for children with AD. Further studies should be performed with drugs that are becoming available, DUPI in particular.

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Table 1. Determinants of 'drug survival' (first and second-line) and 'post-drug survival' after first-line immunosuppressive treatments, using univariate and multivariate Cox regression analyses.

	Univariate model			Multivariate model		
Variable	**HR**	**95%CI**	***p***	**HR**	**95%CI**	***p***
Drug survival (first-line)						
Age*	0.97	0.90 – 1.05	0.48	1.02	0.95 – 1.10	0.52
Gender (ref: female)	0.70	0.41 – 1.19	0.2	0.62	0.35 – 1.11	0.11
Age of onset of AD < 2 years (ref > 2 years)	1.22	0.55 – 2.72	0.62	-	-	-
Rhinitis†	0.61	0.36 – 1.02	0.06	0.71	0.39 – 1.27	0.25
Conjunctivitis†	0.60	0.36 – 1.02	0.06	0.79	0.43 – 1.46	0.47
Food allergy†	0.99	0.59 – 1.65	0.96	-	-	-
Respiratory allergy†	0.78	0.45 – 1.34	0.37	-	-	-
Overweight*†‡	1.42	0.63 – 3.20	0.39	-	-	-
Treatment for asthma*†	0.72	0.43 – 1.21	0.21	0.86	0.48 – 1.54	0.63
MTX (ref CIC)	0.40	0.19 – 0.83	0.01	0.37	0.17– 0.80	0.01
Post-drug survival						
Age*	1.08	0.98 – 1.18	0.11	1.07	0.95 – 1.19	0.23
Gender (ref: female)	2.42	1.18 – 4.89	0.15	2.48	1.06 – 5.80	0.03
Age at onset of AD < 2 years (ref > 2 years)	0.51	0.20 – 1.35	0.18	0.23	0.07 – 0.76	0.01
Asthma†	0.67	0.34 – 1.31	0.24	-	-	-
Rhinitis†	0.96	0.48 – 1.89	0.90	-	-	-
Conjunctivitis†	1.23	0.62 – 2.43	0.55	-	-	-
Food allergy†	0.57	0.29 – 1.12	0.10	0.42	0.18 – 1.01	0.05
Respiratory allergy†	0.49	0.25 – 0.95	0.04	0.22	0.08 – 0.54	< 0.01
Overweight*†‡	1.11	0.38 – 3.19	0.84	-	-	-
MTX (ref: CIC)	1.38	0.62 – 3.06	0.43	2.01	0.67 – 6.03	0.20
High dose of treatment†**	1.62	0.81 – 3.21	0.17	2.87	1.09 – 7.57	0.03
Long duration of first-line treatment†§	1.00	0.50 – 2.01	1.00	2.58	0.94 – 7.09	0.06
Controlled AD†¶	0.47	0.23 – 0.96	0.04	0.24	0.08 – 0.66	< 0.01

All data were collected from medical records using a standardized questionnaire

* At the initiation of first-line immunosuppressive treatment.

† Reference: none.

‡ Defined as a Body Mass Index greater than the 97th percentile for the correlated age and gender category.

** Defined as > 0.3 mg/kg/week for MTX; > 3.5 mg/kg/day for CIC.

§ Defined as a duration of treatment > 12 months for MTX and > 6 months for CIC.

¶At the end of first-line immunosuppressive treatment.