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Prescribing practices for systemic agents in the treatment of severe pediatric atopic dermatitis in the US and Canada: The PeDRA TREAT survey

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Background: There is a paucity of literature to direct physicians in the prescribing of immunomodulators for patients with severe atopic dermatitis (AD).

Objective: To survey systemic agent prescribing practices for severe childhood AD among clinicians in the United States and Canada.

Methods: The TREatment of severe Atopic dermatitis in children Taskforce (TREAT), US&CANADA, a project of the Pediatric Dermatology Research Alliance (PeDRA), developed an online multiple-response survey to assess clinical practice, gather demographic information and details of systemic agent selection, and identify barriers to their use in patients with recalcitrant pediatric AD.

Results: In total, 133 of 290 members (45.9%) of the Society for Pediatric Dermatology completed the survey, and 115 of 133 (86.5%) used systemic treatment for severe pediatric AD. First-line drugs of choice were cyclosporine (45.2%), methotrexate (29.6%), and mycophenolate mofetil (13.0%). The most commonly used second-line agents were methotrexate (31.3%) and mycophenolate mofetil (30.4%); azathioprine was the most commonly cited third-line agent. The main factors that discouraged use of systemic agents were side-effect profiles (82.6%) and perceived risks of long-term toxicity (81.7%).

Limitations: Investigation of the sequence of systemic medications or combination systemic therapy was limited. Recall bias may have affected the results.

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Drs Totri and Eichenfield contributed equally to this work.

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Conclusion: Great variation exists in prescribing practices among American and Canadian physicians using systemic agents for treatment of pediatric AD. (J Am Acad Dermatol http://dx.doi.org/10.1016/j.jaad.2016.09.021.)

Key words: atopic dermatitis; azathioprine; cyclosporine; methotrexate; mycophenolate mofetil; oral antimicrobials; oral steroids.

Atopic dermatitis (AD) affects nearly 20% of children in the United States, Europe, and Japan.[1] While the majority of pediatric patients can be treated with topical therapy alone, a small subset with refractory or severe AD requires systemic immunomodulatory therapy with medications such as cyclosporine (CSA), methotrexate (MTX), mycophenolate mofetil (MMF), and azathioprine (AZA).

CAPSULE SUMMARY

- A paucity of literature exists to direct physicians in the prescribing of systemic therapies for children with refractory atopic dermatitis.
- There is wide variation in the prescribing practice of systemic immunomodulators for pediatric atopic dermatitis.
- There is a need for comparative effectiveness studies of commonly used immunomodulators and investigation of new biologic agents.

The European TREatment of severe Atopic eczema in children Taskforce (TREAT) survey confirmed wide variation in prescribing practice of systemic immunomodulators across 8 European countries.[2] In 2014, the Pediatric Dermatology Research Alliance (PeDRA) launched the TREAT US&CANADA survey in collaboration with the European TREAT team: (i) to produce data on the current systemic agent prescribing practices of pediatric dermatologists for severe AD in the United States and Canada; (ii) to investigate factors influencing the use of specific systemic agents; and (iii) to inform the design of future intervention studies.

METHODS

The TREAT US&CANADA survey team developed an anonymous, online multiple-response survey to gather information on demographics, clinical practice data, and systemic agent selection, as well as factors impacting systemic medication use for refractory pediatric AD. The survey was modeled after the European TREAT survey and was extensively piloted among PeDRA members before going live.

From September to December 2014, the survey was distributed among select members (n = 319) of the Society for Pediatric Dermatology. Unique, anonymized survey links were delivered through email and staggered reminder emails were sent. Responders who did not prescribe systemic immunomodulating drugs were directed to the end of the survey, while those who did were presented with a clinical scenario of an adolescent patient who had failed treatment with potent topical corticosteroids, antihistamines, and phototherapy. Participating clinicians were asked to record their first-, second-, and third-line systemic drugs of choice. Preferred dosing regimens, including initiating and maximal doses, length of treatment, and discontinuation regimens were also queried. Use of treatment guidelines to direct systemic treatment in severe pediatric AD was assessed, and perceived barriers to the use of systemic agents were recorded.

RESULTS

Study population

A total of 319 invitation emails were sent to Society for Pediatric Dermatology members. Twenty-seven failed emails and two ineligible participants (ie, not practicing in the United States or Canada) were identified, leaving 290 potential respondents. The survey was completed by 133 members (45.9%) of whom 115 (86.5%) used systemic treatment for severe pediatric AD. Demographic characteristics of the participants are summarized in Table I. Of the respondents, the majority (74.4%) were dermatologists with Pediatric Dermatology Board certification. The majority (66.4%) of the cohort practiced in a pediatric dermatology setting, while 34.6% treated both children and adults.

Systemic agents and dosing schedules

The first-line systemic agents of choice were CSA (45.2%) and MTX (29.6%). The most commonly chosen second-line agents were MTX (31.3%) and MMF (30.4%). AZA was the most commonly used third-line agent (33.0%) followed by MMF (24.3%). A

Abbreviations used:

AD: atopic dermatitis
AZA: azathioprine
CSA: cyclosporine
MTX: methotrexate
MMF: mycophenolate mofetil
PeDRA: Pediatric Dermatology Research Alliance
RCT: randomized controlled trial
SCORAD: SCORing Atopic Dermatits
TREAT: TREatment of severe Atopic eczema in children Taskforce

complete list of the systemic agents can be found in Table II. Detailed dosing schedules including initiation and maximum dose of each drug, length of treatment, and discontinuation regimens of respondents are provided in Table III.

Practice arrangement

Nearly 63% of the physicians had facilities available for inpatient care, and 8.7% had topical treatment facilities for children as outpatients or within a day treatment center. Approximately half (48.7%) had access to nursing support for patient/caregiver AD education, while only 13.0% had dedicated AD education programs and schools for patients, caregivers, or both. Drug monitoring clinics for children on systemic therapies were available to 14.8% of physicians.

Factors discouraging the use of systemic agents

Elements discouraging the use of systemic agents were assessed in the survey (Table IV). Side-effect profiles (82.6%) and risk for long-term organ toxicity (81.7%) were factors that discouraged the use of these agents. A large number of respondents (65.2%) were discouraged by concerns expressed by patients and their families. Approximately half (49.6%) did not use AD guidelines or protocols to direct their prescription of systemic treatments.

DISCUSSION

With a response rate of 45.9%, our study is likely a true representation of practice patterns among providers utilizing systemic therapy for children with severe AD in North America. Limitations of the study include a small Canadian sample of 18 practitioners, preventing intercountry comparison of clinical practice. Due to the survey methodology, we did not query doctors about the sequence of prescribing systemic medications or use of combination systemic therapy. Because chart audits were not required from respondents, recall bias is another potential limitation.

Our study reveals great variation in prescribing practices among North American physicians prescribing systemic agents for pediatric AD. The results differ from those seen in the European TREAT study, which queried 343 individuals from 8 different European countries, and found CSA to be the most commonly used first-line agent (43.0%), followed by oral corticosteroids (30.7%) and AZA (21.7%). CSA was the most commonly used second-line agent (33.6%) and MTX the most commonly used third-line systemic treatment (26.2%). While both our study and its European counterpart found CSA to be the most commonly prescribed first-line agent, the use of MTX differed greatly. MTX was most often a third-line agent in Europe but commonly used as first-line therapy in the United States and Canada. An

Table I. Demographic characteristics of participants

Characteristic	n (%)
Sex	
Female	90 (67.7)
Male	43 (32.3)
Age (years)	
31-40	50 (37.6)
41-50	40 (30.1)
51-60	24 (18.0)
>60	19 (14.3)
Country of work	
United States	115 (86.5)
Canada	18 (13.5)
Primary specialty	
Board Certified Dermatologist with Pediatric Dermatology Board Certification	99 (74.4)
Board Certified Dermatologist without Pediatric Dermatology Certification	21 (15.8)
Pediatrician but not Dermatology Board Certification	9 (6.8)
Other	4 (3.0)
Practicing location	
University teaching hospital/clinic	94 (70.7)
Single-specialty group practice	17 (12.8)
Multi-specialty group practice	10 (7.5)
Solo community based practice	7 (5.3)
Integrate Health Maintenance Organization	5 (3.8)
Caseload	
Pediatrics only	87 (65.4)
Pediatrics and adults	46 (34.6)
Years of experience	
0-4 years	29 (21.8)
5-10 years	30 (22.6)
11-20 years	37 (27.8)
>20 years	37 (27.8)

Table II. Treatment of choice

Drug selection, n (%)	Cyclosporine	Methotrexate	Mycophenolate mofetil	Azathioprine	Oral corticosteriods	Other
First Line	52 (45.2)	34 (29.6)	15 (13.0)	8 (7.0)	6 (5.2)	0 (0.0)
Second Line	21 (18.3)	36 (31.3)	35 (30.4)	23 (20.0)	0 (0.0)	0 (0.0)
Third Line	20 (17.4)	22 (19.1)	28 (24.3)	38 (33.0)	2 (1.7)	5 (4.3)*

*Includes dapsone, intravenous immunoglobulin.

Table III. Dosing schedules

	Initial dose (%)	Maximum dose (%)	Average duration of treatment (%)	Maximum duration of treatment (%)	Regimen to discontinue treatment (%)
Azathiprine	2 mg/kg/day (55.1%)	3 mg/kg/day (70.0%)	4-12 months (60.9%)	>12 months (73.9%)	Taper dose over 1 month (52.2%)
Cyclosporine	3-5 mg/kg/day (53.8%)	3-5 mg/kg/day (71.0%)	4-12 months (65.6%)	4-12 months (62.4%)	Taper dose over 1 month (48.4%)
Methotrexate	300 mcg/kg/ week (26.1%)	>400mcg/kg/ week (47.8%)	4-12 months (70.7%)	>12 months (78.3%)	Taper dose over 1 month (34.8%)
Mycophenolate mofetil	10 mg/kg/day (39.7%)	>20 mg/kg/day (41.0%)	4-12 months (66.7%)	>12 months (64.1%)	Taper dose over 1 month (51.3%)
Oral corticosteroids	1 mg/kg/day (87.0%)	2 mg/kg/day (75.0%)	2-4 weeks (62.5%)	1-2 months (50.0%)	Variable* among n = 8

*Includes taper dose over 1 month, half dose every 2 weeks, discontinue without a taper, taper dose over 1 week, and 3-4 week taper.

Table IV. Factors that discouraged the use of systemic agents

	Strongly agree, % (n)	Agree, % (n)	Neutral, % (n)	Disagree, % (n)	Strongly disagree, % (n)
Perceived risk of long-term organ toxicity	25.2% (29)	56.5% (65)	13.0% (15)	3.5% (4)	1.7% (2)
Side-effect profile	23.5% (27)	59.1% (68)	10.4% (12)	4.3% (5)	2.6% (3)
Concerns expressed by patient/family	11.3% (13)	53.9% (62)	22.6% (26)	9.6% (11)	2.6% (3)
Need for blood monitoring	5.2% (6)	27.8% (32)	30.4% (35)	25.2% (29)	11.3% (13)
Lack of guidelines	4.3% (5)	29.6% (34)	30.4% (35)	25.2% (29)	10.4% (12)
Lack of prescribing indication for atopic dermatitis in children	2.6% (3)	25.2% (29)	33.9% (39)	26.1% (30)	12.2% (14)
Lack of personal experience	2.6% (3)	10.4% (12)	21.7% (25)	41.7% (48)	23.5% (27)
Financial constraints	1.7% (2)	19.1% (22)	30.4% (35)	33.0% (38)	15.7% (18)
Colleagues with more experience in the use of systemic agents to whom I would refer the child	0.0% (0)	4.3% (5)	15.7% (18)	48.7% (56)	31.3% (36)

explanation for this difference may be that the European TREAT study was completed shortly after publication of a randomized controlled trial (RCT) comparing MTX with AZA, which supported a role for MTX in the management of adults with AD.[3] Since this publication, MTX use in Europe may have increased.

There is only one published RCT looking at systemic treatments for severe AD in children. El Khalawany et al compared CSA and MTX in 40 children with severe AD. At week 12, patients in the MTX group had a mean (±standard deviation [SD]) absolute reduction in SCORing Atopic Dermatits (SCORAD) of 26.25 ± 7.03, compared with 25.02 ± 8.21 in the CSA group (P = .93). Both drugs were associated with minor adverse effects, none of which necessitated changing the treatment regimen. The authors concluded that, when used in low doses, both drugs are clinically effective, relatively safe, and well tolerated.[4] This study was statistically underpowered and had a relatively short treatment period of 12 weeks. Furthermore, a fixed low dose of MTX was used in the study, inconsistent with usual clinical practice. The onset of benefit from both drugs appeared to be similar, which also does not reflect clinical experience (CSA has the most

rapid onset of action among the conventional immunomodulating agents).[5,6]

To date, no systemic therapies are approved by the Food and Drug Administration for the treatment of AD in children. CSA is approved for the treatment of AD in adults in various countries and children over 16 years of age in Germany and France.[7] Additional RCTs are needed to determine the optimal dosing and duration of therapy for pediatric patients with AD and to compare the efficacy of different systemic agents. A national RCT comparing cyclosporine and methotrexate is currently underway in the United Kingdom (TREAT, trial registration 15837754). Comparative studies of commonly used therapies and novel systemic agents, such as biologics, should also be pursued.

Our data displays a high rate of concern about side-effect profiles and risks for long-term toxicity with presently used systemic agents. There is a clinical need for development and testing of new systemic agents for pediatric AD.

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