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Cyclosporine shows benefit as compared to methotrexate for treatment of pediatric atopic dermatitis refractory to topical medications when rapidity of clinical response is of key importance to the patient

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ABSTRACT A clinical decision report appraising El-Khalawany MA, Hassan H, Shaaban D, Ghonaim N, Eassa B. Methotrexate versus cyclosporine in the treatment of severe atopic dermatitis in children: a multicenter experience from Egypt. *European Journal of Pediatrics*. 2012;172(3):351-356. <https://doi.org/10.1007/s00431-012-1893-3> for a pediatric patient with severe atopic dermatitis.

Keywords: atopic dermatitis, pediatrics

Clinical Context

Jacob Williams [pseudonym], an 8-year-old Caucasian male, presented with a chief complaint of atopic dermatitis refractory to several months of high-potency topical corticosteroids, narrowband UV-B light, and oral antihistamines. On exam, the patient had xerosis, lichenification, and pruritic erythematous scaly patches and plaques on flexor surfaces of the elbows, wrists, and ankles. The patient's father stated that the patient had been home-taught in the past calendar year due to his symptoms, but was very interested in returning to public school and his friends in the next month. The father also stated that he did not feel the family had adequate resources and time to provide an optimal education at home for the patient in the long term, though transportation to and from school and appointments would not be an issue. There were no significant socioeconomic factors preventing the pursuit of additional treatment. The father anticipated his son being prescribed low-dose methotrexate, due to prior conversations with healthcare professionals. He was against the use of systemic corticosteroids due to the potential for hypothalamic-pituitary axis suppression. He was wondering whether methotrexate would be better than a different systemic therapy to control his son's symptoms and allow school attendance.

Clinical Question

Is methotrexate more effective in rapidly controlling severity of symptoms of atopic dermatitis in children 8 years old compared to other non-steroid systemic therapies after failure of topical steroids and oral antihistamines?

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Research Article

El-Khalawany MA, Hassan H, Shaaban D, Ghonaim N, Eassa B. Methotrexate versus cyclosporine in the treatment of severe atopic dermatitis in children: a multicenter experience from Egypt. *European Journal of Pediatrics.* 2012;172(3):351-356.
<https://doi.org/10.1007/s00431-012-1893-3>.

Related Literature

We sought out evidence from clinical trials to best guide our decision, rather than expert opinion or society guidelines. A PubMed search using the keywords "atopic dermatitis" "children" and "trial" returned 644 results, proving far too general to be useful for our purposes. By adding the additional term "systemic," as our patient had now failed the first-line treatment of topical corticosteroids, narrowband UV-B, and antihistamines, we reduced the number of applicable results to 56. We also added "pediatric" and the British spelling variant "paediatric" to our query, for a final query of "atopic dermatitis" AND "systemic" AND "trial" AND ("pediatric" OR "paediatric" OR "children"). This search returned 64 total results, proving that the addition of "pediatric" and "paediatric" had identified additional studies. Of these 64 results, 1 was an industry guideline, 1 was a survey report of prescribing practices, 4 were case reports or series, 6 were published protocols for ongoing studies, 8 were studies of pharmacokinetics and/or safety, 10 were review articles or editorials, and 34 were clinical trials. Of the 34 clinical trials, only 6 investigated systemic non-steroid treatment of atopic dermatitis. After excluding those studies whose outcome did not report severity or quality of life measures, those whose population did not include children age 8, those that had excluded patients with severe atopic dermatitis, and those investigating systemic antihistamines, on which our patient had already failed, we were left with only a single study comparing methotrexate treatment with cyclosporine treatment for atopic dermatitis after failure of topical therapies.

This finding mirrored a literature review of systemic treatments for atopic dermatitis published four months prior,¹ in which the only well-controlled study found comparing methotrexate to other systemic therapies for atopic dermatitis in children was the one found in our own literature search. There were only five other studies found that specifically investigated treatment modalities in pediatric populations, those being a study showing cyclosporine's superiority as compared to IVIG,² a study comparing different dosing regimens for cyclosporine,³ a study comparing montelukast to placebo,⁴ a study of short-course flunisolide (a steroid) while awaiting response to other systemic therapy,⁵ and a study showing that omalizumab is no better than placebo in treating severe atopic dermatitis in children.⁶ The overall paucity of results reflects the lack of well-controlled trials of treatment for severe atopic dermatitis in pediatric populations, though several trials are now currently ongoing, including those whose protocols appeared in our literature search.

The article chosen is thus superior to all other articles found, as it is the only study whose methods compare methotrexate to another non-steroid systemic treatment among a pediatric population including children age 8, and thus is the only study which can answer the clinical question posed by our patient scenario. As this study is the only good quality randomized controlled trial to address our clinical question, the grade of recommendation (using SORT criteria) of any finding from this study would be Grade B.

Critical Appraisal

This manuscript was the only study found that compared methotrexate to other systemic medications in pediatric atopic dermatitis refractory to topical medications, making this study's results most relevant to the clinical question. Patients were enrolled in this study from outpatient clinical care by virtue of being age 8-14 with atopic dermatitis refractory to topical medications, similar to our patient. Patients were excluded if they suffered from uncontrolled systemic diseases, had a history of organ transplantation or cancer, or had suffered from herpes zoster infection within 2 months of the study. The patients included in this study were therefore similar to our patient, and our patient would have been eligible for treatment in this study. However, this study, by virtue of the geography of the participating treatment clinics, included only Egyptian children, whereas our patient resided in Detroit, Michigan. This difference in ethnicity might manifest in different response to systemic immunomodulatory medications. However, no such advisory on medication use in Egyptians versus US children could be found, and thus we concluded that this difference likely does not bear significantly on our use of the study for clinical purposes.

Patients in the study were randomized by computer to two treatment groups (methotrexate or cyclosporine) of 20 persons each, after which they received 12 weeks of treatment followed by an additional 12 weeks of follow-up with otherwise equal treatment.

There was no true control group receiving only topical medications and placebo. There was no statistically significant difference between both groups regarding age of patients, duration of the disease, distribution of lesions, or clinical stage of lesions. No patients in either group were lost to follow-up or needed to be removed from care during the course of the study. The authors did not disclose any deviations from the study protocol, although it is unclear if the study was registered prospectively. Patients' severity score for atopic dermatitis (SCORAD) scores were assessed at 4, 8, 12, and 24 weeks. These scores encompass both objective and subjective criteria related to the severity of atopic dermatitis, and thus encompass all clinically relevant outcomes from the treatment as regards our patient's ability to return to school. Patient scores were then analyzed in the groups to which they were randomized. The effect size at the end of the treatment as compared to pre-study SCORAD score was comparable in both arms of the study, with a 51% reduction in symptoms in the methotrexate group and a 55% reduction in the cyclosporine group ($p=0.93$). However, cyclosporine showed a more rapid (2-3 week) onset of action as compared to methotrexate (3-5 weeks). There were no adverse side effects that necessitated discontinuing or decreasing dosage, and all adverse effects had dissipated by the conclusion of the study. It is possible that a larger sample size than used in this study would have seen a significant difference in treatment outcomes between the groups.

Methodologically, the study benefits from the randomization of patients into treatment groups, an appropriate follow-up period, clearly stated inclusion and exclusion criteria, and a clear scoring system. Using the SORT criteria for evaluating level of evidence, this individual randomized controlled trial is a Level 1 study, providing good-quality patient-oriented evidence. This study was also not sponsored in any way, leading to less risk of bias. However, the small cohort size ($n=20$ in each arm) is a notable drawback, and it is unclear whether participants, clinicians, or both were blinded to the treatment regimen. In addition, it is not clear how patients were recruited for the trial. A stronger study would have included more patients as well as a placebo group for direct comparison, and a stronger manuscript would have clearly stated both level of blinding and recruitment tactics to allow for adequate assessment of performance, detection, and participation biases.

Clinical Application

Atopic dermatitis is one of the most commonly encountered medical issues in pediatric patients, affecting nearly 1 in 10 children in the United States.² However, there is little literature on the relative efficacy of systemic therapies for atopic dermatitis refractory to topical medications in the pediatric population. In our clinical context, our patient needed systemic treatment for atopic dermatitis that had proven refractory to topical medications. The chosen study provides good quality evidence that methotrexate and cyclosporine are equally effective options, and both of these medications are available in our practice. Given the quality of evidence in the study cited, it would have been reasonable to treat our patient with either drug. However, our patient's social context indicated that rapidity of action should also be an important determinant of appropriate care, given the patient and family's desire to begin school again in roughly one month from the visit. Therefore, in the spirit of shared decision making, treatment with cyclosporine was preferred, based on the analysis of this study, given comparable level of clinical response to methotrexate with more rapid onset.

Other aspects of our patient's social context also played a role in this decision, though they had not been part of the trial. Cyclosporine necessitates more frequent laboratory monitoring for liver and kidney injury than methotrexate and also requires the patient to protect against exposure to the sun's ultraviolet rays. The family affirmed access to transportation and willingness to bring the patient to the clinic for frequent laboratory monitoring, and Jacob agreed to wear sunscreen and protective clothing. Had our patient lived in Florida instead of Michigan, exposure to the sun may have played into the decision even further. Jacob also did not mind giving up grapefruit juice, though those children who truly love grapefruit juice may be better suited for methotrexate, as grapefruit juice is forbidden for the duration of cyclosporine treatment.

This study has good external validity for application to our patient scenario at the time of our visit, yet the several protocols of large ongoing studies in this area found in our literature search and the dawn of targeted biologic therapy for immunomodulation in atopic diseases will likely alter the available and acceptable treatment modalities in children significantly in coming years.¹ It would be advisable for clinicians to treat with the medications currently supported by the literature, yet to also keep a close eye on new evidence in this important area of care.

New Knowledge Related to Clinical Decision Science

Our case proves instructive for those interested in the interface of the clinical research evidence and the social contexts of their patients. The literature showed that either methotrexate or cyclosporine would be safe and effective for atopic dermatitis in children who have failed topical treatments, but that cyclosporine would have earlier onset of action. In our patient's social context, this more rapid onset of action was a key deciding factor that proved respectful of his preferences, his social network, and his family's time and resources. Other factors, such as transportation to the clinic for monitoring, willingness to wear sunscreen, and ability to avoid grapefruit juice were also important to consider in making this decision. Thus, the case and the decision-making process described herein highlight the need to avoid developing a simple decision rule for all patients, and instead bringing the social context into dynamic interplay with the literature evidence.

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