Atopic dermatitis: phototherapy and systemic therapy

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■ Abstract

The majority of atopic dermatitis (AD) patients respond satisfactorily to gentle bathing, frequent moisturizing, and topical medications. Second-line therapies for AD should be used in recalcitrant cases or in patients with uncontrolled disease despite compliance with first-line measures and avoidance of allergens. Recommended advanced therapies include phototherapy, especially narrowband ultraviolet B, systemic immunosuppressants, and a new biologic agent. Few studies have compared head-to-head efficacy of the different immunosuppressant therapies such as cyclosporine, methotrexate, azathioprine and mycophenolate mofetil. Therefore, the agent used is based on provider and patient preferences and can be decided on a case-by-case basis.

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Atopic dermatitis (AD) is a chronic inflammatory skin disease. Patients should be treated so they have adequate control of their disease, with minimal rash and pruritus and optimal quality of life. Many patients achieve this control with first-line measures (gentle bathing, frequent moisturization, avoidance of allergens) and topical prescription treatments (topical steroids, calcineurin inhibitors); however, systemic treatment is indicated for a number of patients. Phototherapy is used during acute flares and also for patients whose chronic disease is uncontrolled while using topical therapy. Systemic immunomodulatory medications are recommended for patients who cannot be controlled on a topical and/or phototherapy treatment plan. With further studies and scientific advancements, the pathogenesis of AD is better understood. As such, a new systemic treatment was recently approved for AD, involving inhibition of the IL-4 receptor alpha subunit. With continual knowledge expansion, the discovery of additional treatments is anticipated and welcomed.

Phototherapy

Phototherapy has been used to treat AD since the early 20th century. It was first used to treat AD after Morison et al noticed that the skin of AD patients, while refractory to other treatments, improved after sun exposure.[1] The group subsequently found that oral psoralen used with ultraviolet (UV) light improved AD in these patients. The American Academy of Dermatology (AAD) recommends phototherapy as a second-line therapy, after patients have not adequately responded to emollients, topical corticosteroids (TCS), and topical calcineurin inhibitors (TCI).[2] Phototherapy can be used as maintenance therapy in chronic AD patients.[2] The AAD advises phototherapy only be used under the guidance of a physician who has adequate knowledge to supervise its use.[2] Several factors should influence the decision regarding which light modality to use, such as availability, cost, patient skin type, skin cancer history, and patient use of photosensitizing medications.[2] The minimal erythema dose and/or Fitzpatrick skin type should guide the phototherapy treatment plan in terms of dose and schedule.[2] Lastly, home phototherapy should be an option for those patients who are unable to obtain phototherapy in an office, under the guidance of an experienced physician (Table 1).[2]

While phototherapy attempts to mimic natural sunlight, phototherapy ultraviolet light limits harmful wavelength exposure, and

■ TABLE 1 Overview of phototherapy use recommendations

- Considered second-line treatment after first-line therapies: moisturizers, topical corticosteroids, and topical calcineurin inhibitors

- Can be used in chronic disease as maintenance treatment

- Should only be used under physician supervision

- Treatments based on availability, cost, patient's skin type, personal and family skin cancer history, and medical history

- Light therapy dose based on minimal erythema dose and/or patient's skin type

- Home therapy is appropriate for some patients

Adapted from Sidbury R, Davis DM, Cohen DE, et al. Guidelines of care for the management of atopic dermatitis: section 3. Management and treatment with phototherapy and systemic agents. *J Am Acad Dermatol.* 2014;71(2):327-349.[2]

provides dose predictability and consistency. Many studies have shown that phototherapy is effective.[3-8] Although no head-to-head trials have been conducted to determine which type of light therapy is the most effective, several forms are used including natural sunlight; narrowband (NB) UVB; broadband (BB) UVB; UVA; topical and systemic psoralen plus UVA (PUVA), UVA, and UVB (UVAB); and Goeckerman.[2] The most widely used phototherapy is NB-UVB secondary to its limited side effects, efficacy, accessibility, and knowledge about its use.

Risk
Phototherapy is thought to be relatively low risk. Studies have shown that few patients discontinue light therapy secondary to adverse effects.[3,5-8] Various modalities have different side effects, the most common being local transient changes, including actinic damage, local soreness and redness, pruritus, burning, and stinging. Other less common and sometimes more serious adverse effects include nonmelanoma skin cancer, melanoma (particularly with PUVA),[9] lentigines, photosensitive eruptions, folliculitis, photoonycholysis, herpes simplex virus reactivation, and facial hypertrichosis. Noncutaneous side effects may uncommonly occur, particularly with UVA therapy. These include cataract formation, headaches, nausea, vomiting, and even hepatotoxicity with the addition of psoralen.[10]

Practical considerations
The protocols for phototherapy treatment are based on clinical practice guidelines developed by the AAD for psoriasis.[2,11] Several factors contribute to the provider's decision on the type of light therapy to use on a particular patient. The convenience of the treatment and the cost are important variables to consider. The light therapy protocols are generally based on the patient's minimal erythema dose (MED) and/or Fitzpatrick skin type.[12] For BB-UVB, once the initial UVB dose is set, the subsequent treatments have higher doses dependent upon the initial UVB treatment and based on missed doses. In comparison, NV-UVB

has a different protocol based on Fitzpatrick skin type or MED, and augments the dose after each treatment with a suggested maximum dose and recommendations for maintenance therapy.[11] The Joint Task Force on Practice Parameters (JTF), representing the American Academy of Allergy, Asthma & Immunology; the American College of Allergy, Asthma & Immunology also has AD treatment guidelines, which are comparable to the AAD guidelines, and suggests using UVA1 for acute exacerbations, UVB modalities for chronic AD, and photochemotherapy with PUVA only for patients with severe widespread AD.[13,14]

Important considerations for the provider to remember are the patient's medical history and physical exam. The physician must adjust the treatment plan accordingly if the patient has a history of skin cancer or is using skin products or systemic medications (prescription and over-the-counter) that may be photosensitizing.[2] Phototherapy can be used in conjunction with emollients and TCS, but should be limited with TCI use, according to the manufacturers.[15]

Oral systemic agents
Both AAD and JTF guidelines recommend using systemic immunomodulating agents in a subset of patients with severe AD recalcitrant to topical regimens and phototherapy.[14] Only a few randomized control trials have compared systemic treatments to one another, making it difficult to recommend one treatment over another.[16-18] However, the current consensus among dermatologists suggests that cyclosporine, methotrexate (MTX), mycophenolate mofetil (MMF), and azathioprine (AZA) are the most effective (Table 2).[2,19] The newest agent, dupilumab, is recently approved by the US Food and Drug Administration (FDA) approved for adults, and it stands as the only FDA-approved systemic option for atopic dermatitis, apart from of prednisone.

Cyclosporine
Cyclosporine is a powerful immunosuppressant that works by suppressing cytokine gene expression and therefore decreases the number of T-cells and interleukin-2 in circulation. It has been shown to be effective in treating other immune-mediated skin diseases such as psoriasis and graft versus host disease. Its first use in AD patients was in 1991.[20,21] Cyclosporine is considered the first line of systemic therapies for severe AD and is the most prescribed systemic medication for severe AD in the pediatric population in the United States and Canada.[22,23] In one of the few randomized controlled trials on cyclosporine compared to placebo, 23 patients receiving cyclosporine showed significantly reduced severity and surface area involvement after 6 weeks of treatment, with 15 of 19 of patients on cyclosporine showing at least moderate improvement compared to 6 out of 19 on placebo.[24] Another study showed that cyclosporine A used continuously in children over a 1-year period provided more control as compared to intermittent therapy.[25] A systematic review found cyclosporine to be effective in treating AD as compared with placebo, but that adverse effects or rare liver and kidney complications may limit its long-term use.[20] One head-to-head trial between cyclosporine and methotrexate showed no statistical significance between the 2 drugs in their ability to improve the severity scoring for atopic dermatitis (SCORAD) score from baseline to 12 weeks in severe AD children.[26] Moreover, continued use is often necessary to pre-

■ **TABLE 2** Oral systemic agents overview.

	CYCLOSPORINE A	AZATHIOPRINE	METHOTREXATE	MYCOPHENOLATE
Decrease in clinical score (%)	54-95	26-39	42-52	55-68
Treatment period in trials (weeks)	Max 52	Max 24	Max 24	Max 30
Treatment period in trials (weeks)	Max 52	Max 24	Max 24	Max 30
Time to respond (weeks)	2	8-12	8-12	8-12
Most important side effects	↑Serum creatinine ↑Blood pressure	Hematological ↑Liver enzymes Gastrointestinal	Hematological ↑Liver enzymes Gastrointestinal	Hematological Skin infections Gastrointestinal
Pregnancy	Possible	Little information Possible with strict indication	Teratogenic, absolutely contraindicated	Conflicting data, better not to use
Fathering	Possible	Little information Possible with strict indication	Contraindicated	Little information, better not to use

Adapted from Wollenberg A, Oranje A, Deleuran M, et al. ETFAD/EADV Eczema task force 2015 position paper on diagnosis and treatment of atopic dermatitis in adult and paediatric patients. *J Eur Acad Dermatol Venereol.* 2016;30(5):729-747.[19]

vent relapse; therefore, its superiority over other systemic medications remains unknown.[20] It has a relatively quick onset within 1-2 weeks of initiation, with the microemulsion formulation being even more effective than nonmodified formulations.[27]

Cyclosporine has several significant side effects, and lab monitoring is required. The well-known adverse effects include: nephrotoxicity, hypertension, infection, tremor, hypertrichosis, headache, gingival hyperplasia, and increased risk of skin cancer and lymphoma.[2] Evaluation of blood pressure (2 measurements), renal function, urinalysis (UA) with microscopic analysis, fasting lipid profile, complete blood count (CBC) with differential and platelets, liver function, magnesium, potassium, uric acid, tuberculosis testing, human immunodeficiency virus (HIV; if indicated), and human chorionic gonadotropin (hCG; if indicated) are recommended at baseline.[2] Follow-up monitoring should include a blood pressure check at every visit, and labs (renal function, liver function, lipids, CBC with differential and platelets, magnesium, potassium, uric acid) every 2 weeks for 2 to 3 months, then monthly thereafter. If the provider increases the dose of cyclosporine, labs values should be rechecked 2 to 4 weeks thereafter. An annual TB test should be performed along with hCG, if indicated.[2] Since cyclosporine has several significant side effects, the FDA only recommends cyclosporine for psoriasis for 1 consecutive year at a time.[28]

Methotrexate
Methotrexate (MTX) functions as a folic acid antagonist, which

interferes with purine and pyrimidine synthesis and thus blocks the production of DNA and RNA. By interfering with DNA and RNA synthesis, it also interferes with T-cell function. MTX is used for several cancers and dermatologic conditions, such as psoriasis, and is used off label for AD. There is a lack of consistent, randomized controlled trials evaluating the efficacy of MTX for AD. However, a few studies have been conducted and show it is efficacious. An open-label, dose-ranging trial done in adults with moderate to severe AD demonstrated a decrease in the subjects' dermatitis by 52% over a 24-week period and remained improved even after 12 weeks of discontinuation of MTX.[29] A randomized control trial comparing efficacy and safety of methotrexate versus azathioprine showed they were comparable in terms of efficacy and safety in the short term.[16] The maximum efficacy is achieved usually within 10 weeks, with little improvement seen after 12 to 16 weeks even after further dose progression.[16,28-30]

The AAD recommends folate supplementation during treatment with methotrexate to decrease the risk of hematologic and GI side effects.[2] The side effect profile in AD patients has not been well studied. However, MTX has well-documented adverse effects in treatment of other cutaneous diseases. Nausea and GI upset are usually secondary to oral administration, and these symptoms usually subside if MTX is given parenterally. Other side effects include liver damage, lung fibrosis, and bone marrow suppression. The bone marrow suppression is usually reversible with a decrease in dose or discontinuation of MTX.[29,30] The risk of pulmonary fibrosis may preclude patients with pulmonary dis-

IGA score of 0 to 1 with ≥2 points reduciton from baseline to 16 weeks
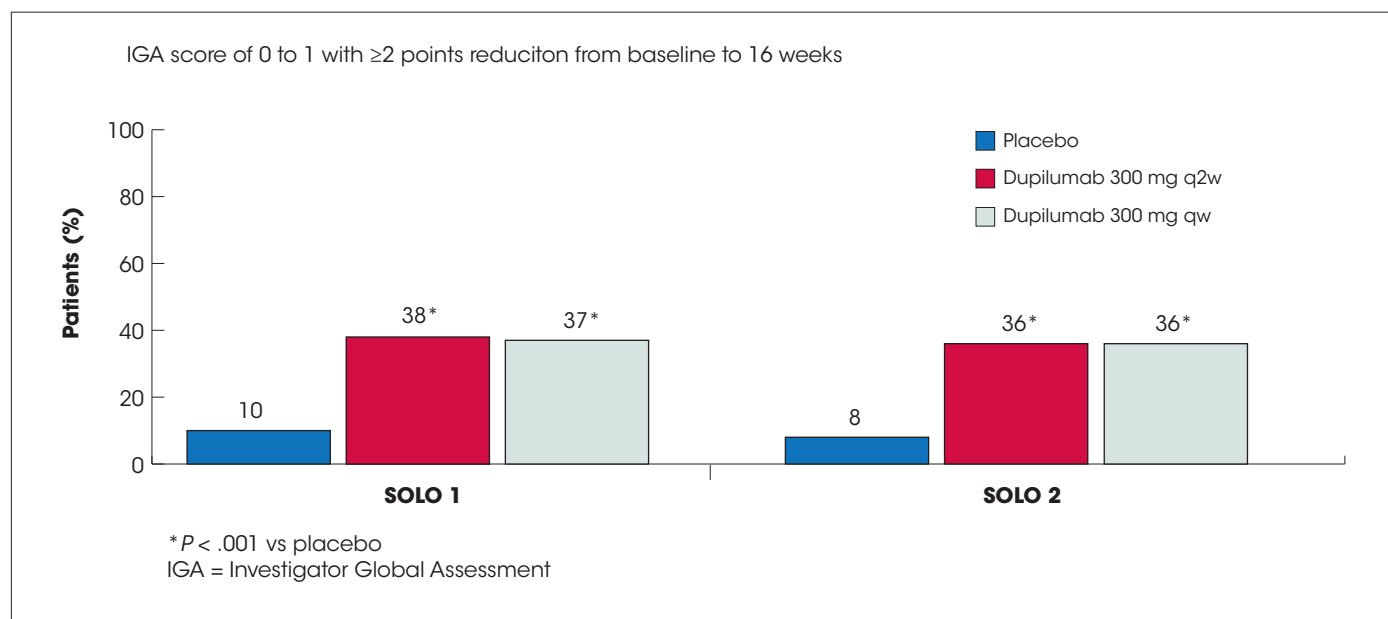
■ **FIGURE** Efficacy of dupilumab compared to placebo measured by IGA score.
Adapted from Simpson EL, Bieber T, Guttman-Yassky E, et al. Two phase 3 trials of dupilumab versus placebo in atopic dermatitis. *N Engl J Med.* 2016;375(24):2335-2348.[38]

eases such as asthma and chronic cough from MTX treatment. The data on liver damage is from patients with psoriasis, and therefore the cumulative dose of MTX and its relationship to hepatic toxicity in patients with AD remains unknown.[28,31] Baseline labs should consist of a CBC with differential and platelets, liver function tests, renal function, Hepatitis B and C, TB, HIV, hCG, and pulmonary function tests, if indicated. Regular CBC and liver function panels should occur weekly for 2 to 4 weeks after treatment initation and 1 week after any large dose increase. After 1 month of treatment, the labs should be ascertained every 2 weeks for 1 month, and then every 2 to 3 months when on a stable dose.

Azathioprine

Azathioprine (AZA) is a purine analog that inhibits DNA production. It affects rapidly dividing cells such as B and T cells, therefore preferentially affecting inflammatory diseases with increased immune cell proliferation. AZA is currently approved for transplant rejection prophylaxis and also for rheumatoid arthritis.[2] It is used off-label to treat AD.[2] In 2 randomized, double-blinded, placebo-controlled trials, AZA was found to be efficacious as compared with placebo.[32,33] Meggitt et al showed that the AZA-treated patients had a 37% improvement in their AD compared with a 20% improvement in the placebo group and also significant improvements in patient-reported itch, area of involvement, global assessment, and quality of life outcomes.[32]

The adverse effects associated with AZA cause many patients to voluntarily discontinue treatment, specifically due to nausea and vomiting.[2] Therefore, progressive dosing is preferred in order to limit side effects and optimize compliance.[2] Other gastrointestinal (GI) symptoms are also common, such as bloating, anorexia, and cramping.[2] Less common side effects include headache, hypersensitivity reactions, elevated liver enzymes, and leukope-

nia. There is a paucity of data linking the true relevance of AZA therapy with increased risk of infections and other cancers. It is unknown if this risk increases with long-term treatment.

AZA's metabolism is dependent upon a patient's thiopurine methyltransferase (TPMT) activity level and therefore can affect how it should be prescribed. TPMT is an enzyme necessary in the thiopurine pathway, and a decrease in enzyme activity can lead to AZA toxicity. A homozygous carrier for a decreased or absent TPMT enzyme activity is at risk for myelotoxicity.[32,33] Testing a patient's TPMT level is strongly recommended by the AAD before AZA initiation.[2] Studies have found TPMT levels may change over the course of a patient's lifetime; therefore, regular blood count and liver enzyme monitoring are indicated.[33-36] A delayed response to treatment may be found in some patients (possibly due to enzyme activity), and a patient may need 12 weeks or more of medication to achieve clearance of their AD.[2] Lab monitoring at baseline includes: TPMT, CBC with differential, platelets, renal and liver function, Hepatitis B and C, TB testing, and HIV and hCG (if indicated). Follow-up labs should include CBC with differential, platelets, liver function, and renal function twice a month for 2 months, then monthly for 4 months, then every other month. An annual TB test should be performed and hCG, if indicated.

Mycophenolate mofetil

Mycophenolate mofetil (MMF) blocks the production of purines by inhibiting inosine monophosphate dehydrogenase, which selectively works on B and T cells since other cells have a purine scavenger pathway that overcomes MMF's blockade. Its current indication for use is solid organ transplant rejection prophylaxis. The efficacy of MMF in treating AD in studies has been inconsistent. A study comparing cyclosporine and MMF found that dur-

ing the initial 10 weeks of the study, patients who received both drug treatments had better disease control, while 7 patients who were treated with MMF alone required adjunct oral corticosteroid therapy.[17] After 10 weeks, treatments were found to have similar efficacy and side effects, suggesting that MMF has a slower onset to efficacy. The AAD considers this treatment to be less efficacious than the other immunomodulatory drugs mentioned above, but still considers it an alternative for refractory AD.[2]

MMF is a well-tolerated medication, with GI side effects being the most common adverse effects. Abdominal cramping, headaches, and fatigue are not dose dependent and generally do not affect adherence to the medication. Other less common adverse effects include anemia, leukopenia, thrombocytopenia, and genitourinary symptoms. There is also a risk of increased infections; however, the rate of infections in patients with AD is unknown. Baseline monitoring should include a CBC with differential and platelets, renal function, liver function, TB testing, and HIV and hCG, if indicated. Regular monitoring of CBC with differential, platelet count, and LFTs should occur every 2 weeks for 1 month, then monthly for 3 months thereafter, then every 2 to 3 months once stable (presuming no dose adjustments).

Dupilumab

Advances in the understanding of the disease mechanism of AD has led to the development of dupilumab which is a new, recently FDA-approved systemic therapy. Dupilumab is an interleukin-4 receptor alpha subunit, thus inhibiting both IL-4 and IL-13 signaling.[37] Two phase 3 studies involving adult patients with mild to moderate AD using dupilumab have been published.[38] These trials randomized patients to 1 of 3 active treatment arm groups or a placebo arm. The treatment groups received different doses of dupilumab. The treatment groups had AD clearance that was statistically significant compared with the placebo group. The primary outcome was the reduction of the Investigator's Global Assessment (IGA) to a score of 0 or 1 and an improvement of 2 or more points from baseline. Eighty-five patients (38%) in SOLO 1 who received dupilumab every other week achieved this endpoint and 83 patients (37%) with weekly treatment achieved this outcome versus only 10% of placebo. In SOLO 2, 36%, 36%, and 8% of patients receiving every other week, weekly, and placebo, respectively, achieved these outcomes. Both of these primary endpoints were statistically significant as compared with placebo. These early studies are promising (Figure).[38] The most common side effects were injection site reactions and conjunctivitis. Fortunately, the injection site reaction did not lead to any nonadherence, although 1 subject dropped out of the study secondary to conjunctivitis. The pediatric trial for dupilumab monotherapy is currently underway to assess its dosing, adverse effect profile, long-term safety and efficacy.

Conclusion

Systemic therapy for AD is not well studied, especially in the pediatric population. Much of the data on phototherapy and systemic agents stems from other disease processes. However, with the recent approval of a systemic agent for AD and after improved understanding of the pathogenesis of the disease and a great need for new and improved therapy, a drive exists for continued innovation and development. Systemic therapy is an important aspect of recalcitrant AD, as the treatment goal for patients should be to minimize inflammation, decrease surface area and intensity of rash, alleviate pruritus, and allow for optimal quality of life. Development of new systemic therapies will improve disease control and improve the quality of life for patients with AD.

References

1. Morison WL, Parrish J, Fitzpatrick TB. Oral psoralen photochemotherapy of atopic eczema. *Br J Dermatol*. 1978;98(1):25-30.
2. Sidbury R, Davis DM, Cohen DE, et al. Guidelines of care for the management of atopic dermatitis: section 3. Management and treatment with phototherapy and systemic agents. *J Am Acad Dermatol*. 2014;71(2):327-349. https://doi.org/10.1016/j.jaad.2014.03.030.
3. Meduri NB, Vandergriff T, Rasmussen H, Jacobe H. Phototherapy in the management of atopic dermatitis: a systematic review. *Photodermatol Photoimmunol Photomed*. 2007;23(4):106-112. https://doi.org/10.1111/j.1600-0781.2007.00291.x.
4. Rombold S, Lobisch K, Katzer K, Grazziotin TC, Ring J, Eberlein B. Efficacy of UVA1 phototherapy in 230 patients with various skin diseases. *Photodermatol Photoimmunol Photomed*. 2008;24(1):19-23. https://doi.org/10.1111/j.1600-0781.2008.00328.x.
5. Clayton TH, Clark SM, Turner D, Goulden V. The treatment of severe atopic dermatitis in childhood with narrowband ultraviolet B phototherapy. *Clin Exp Dermatol*. 2007;32(1):28-33. https://doi.org/10.1111/j.1365-2230.2006.02292.x.
6. Jekler J, Larko O. UVB phototherapy of atopic dermatitis. *Br J Dermatol*. 1988;119(6):697-705.
7. Grundmann-Kollmann M, Behrens S, Podda M, Peter RU, Kaufmann R, Kerscher M. Phototherapy for atopic eczema with narrow-band UVB. *J Am Acad Dermatol*. 1999;40(6 Pt 1):995-997.
8. Tay YK, Morelli JG, Weston WL. Experience with UVB phototherapy in children. *Pediatr Dermatol*. 1996;13(5):406-409.
9. Stern RS, Nichols KT, Vakeva LH. Malignant melanoma in patients treated for psoriasis with methoxsalen (psoralen) and ultraviolet A radiation (PUVA). The PUVA follow-up study. *N Engl J Med*. 1997;336(15):1041-1045. https://doi.org/10.1056/NEJM199704103361501.
10. Grundmann SA, Beissert S. Modern aspects of phototherapy for atopic dermatitis. *J Allergy (Cairo)*. 2012;2012:121797. https://doi.org/10.1155/2012/121797.
11. Menter A, Korman NJ, Elmets CA, et al. Guidelines of care for the management of psoriasis and psoriatic arthritis: Section 5. Guidelines of care for the treatment of psoriasis with phototherapy and photochemotherapy. *J Am Acad Dermatol*. 2010;62(1):114-135. https://doi.org/10.1016/j.jaad.2009.08.026.
12. 1Sidbury R, Tom WL, Bergman JN, et al. Guidelines of care for the management of atopic dermatitis: Section 4. Prevention of disease flares and use of adjunctive therapies and approaches. *J Am Acad Dermatol*. 2014;71(6):1218-1233. https://doi.org/10.1016/j.jaad.2014.08.038.
13. Schneider L, Tilles S, Lio P, et al. Atopic dermatitis: a practice parameter update 2012. *J Allergy Clin Immunol*. 2013;131(2):295-299.e1-27. https://doi.org/10.1016/j.jaci.2012.12.672.
14. Eichenfield LF, Ahluwalia J, Waldman A, Borok J, Udkoff J, Boguniewicz M. Current guidelines for the evaluation and management of atopic dermatitis: A comparison of the Joint Task Force Practice Parameter and American Academy of Dermatology guidelines. *J Allergy Clin Immunol*. 2017;139(4):S49-S57. https://doi.org/10.1016/j.jaci.2017.01.009.
15. Astrellas. Prescribing Information Protopic (tacrolimus). https://www.accessdata.fda.gov/drugsatfda_docs/label/2011/050777s018lbl.pdf. Accessed May 4, 2017.
16. Schram ME, Roekevisch E, Leeflang MM, Bos JD, Schmitt J, Spuls PI. A randomized trial of methotrexate versus azathioprine for severe atopic dermatitis. *J Allergy Clin Immunol*. 2011;128(2):353-359. https://doi.org/10.1016/j.jaci.2011.03.024.
17. Haeck IM, Knol MJ, Ten Berge O, van Velsen SG, de Bruin-Weller MS, Bruijnzeel-Koomen CA. Enteric-coated mycophenolate sodium versus cyclosporin A as long-term treatment in adult patients with severe atopic dermatitis: a randomized controlled trial. *J Am Acad Dermatol*. 2011;64(6):1074-1084. https://doi.org/10.1016/j.jaad.2010.04.027.
18. Schmitt J, Schakel K, Folster-Holst R, et al. Prednisolone vs. ciclosporin for severe adult eczema. An investigator-initiated double-blind placebo-controlled multicentre trial. *Br J Dermatol*. 2010;162(3):661-668. https://doi.org/10.1111/j.1365-2133.2009.09561.x.
19. Wollenberg A, Oranje A, Deleuran M, et al. ETFAD/EADV Eczema task force 2015 position paper on diagnosis and treatment of atopic dermatitis in adult and paediatric patients. *J Eur Acad Dermatol Venereol*. 2016;30(5):729-747. https://doi.org/10.1111/jdv.13599.
20. Hoare C, Li Wan Po A, Williams H. Systematic review of treatments for atopic

eczema. *Health Technol Assess*. 2000;4(37):1-191.

21. Sowden JM, Berth-Jones J, Ross JS, et al. Double-blind, controlled, crossover study of cyclosporin in adults with severe refractory atopic dermatitis. *Lancet*. 1991;338(8760):137-140.

22. Totri CR, Eichenfield LF, Logan K, et al. Prescribing practices for systemic agents in the treatment of severe pediatric atopic dermatitis in the US and Canada: The PeDRA TREAT survey. *J Am Acad Dermatol*. 2017;76(2):281-285. https://doi.org/10.1016/j.jaad.2016.09.021.

23. Ring J, Alomar A, Bieber T, et al. Guidelines for treatment of atopic eczema (atopic dermatitis) Part II. *J Eur Acad Dermatol Venereol*. 2012;26(9):1176-1193. https://doi.org/10.1111/j.1468-3083.2012.04636.x.

24. van Joost T, Heule F, Korstanje M, van den Broek MJ, Stenveld HJ, van Vloten WA. Cyclosporin in atopic dermatitis: a multicentre placebo-controlled study. *Br J Dermatol*. 1994;130(5):634-640.

25. Harper JI, Ahmed I, Barclay G, et al. Cyclosporin for severe childhood atopic dermatitis: short course versus continuous therapy. *Br J Dermatol*. 2000;142(1):52-58.

26. 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. *Eur J Pediatr*. 2013;172(3):351-356. https://doi.org/ 10.1007/s00431-012-1893-3.

27. Zurbriggen B, Wuthrich B, Cachelin AB, Wili PB, Kagi MK. Comparison of two formulations of cyclosporin A in the treatment of severe atopic dermatitis. A double-blind, single-centre, cross-over pilot study. *Dermatology*. 1999;198(1):56-60.

28. Menter A, Korman NJ, Elmets CA, et al. Guidelines of care for the management of psoriasis and psoriatic arthritis: section 4. Guidelines of care for the management and treatment of psoriasis with traditional systemic agents. *J Am Acad Dermatol*. 2009;61(3):451-485. https://doi.org/10.1016/j.jaad.2009.03.027.

29. Weatherhead SC, Wahie S, Reynolds NJ, Meggitt SJ. An open-label, dose-ranging study of methotrexate for moderate-to-severe adult atopic eczema. *Br J Dermatol*. 2007;156(2):346-351. https://doi.org/10.1111/j.1365-2133.2006.07686.x.

30. Lyakhovitsky A, Barzilai A, Heyman R, et al. Low-dose methotrexate treatment for moderate-to-severe atopic dermatitis in adults. *J Eur Acad Dermatol Venereol*. 2010;24(1):43-49. https://doi.org/10.1111/j.1468-3083.2009.03351.x.

31. Kalb RE, Strober B, Weinstein G, Lebwohl M. Methotrexate and psoriasis: 2009 National Psoriasis Foundation Consensus Conference. *J Am Acad Dermatol*. 2009;60(5):824-837. https://doi.org/10.1016/j.jaad.2008.11.906.

32. Meggitt SJ, Gray JC, Reynolds NJ. Azathioprine dosed by thiopurine methyltransferase activity for moderate-to-severe atopic eczema: a double-blind, randomised controlled trial. *Lancet*. 2006;367(9513):839-846. https://doi.org/10.1016/S0140-6736(06)68340-2.

33. Berth-Jones J, Takwale A, Tan E, et al. Azathioprine in severe adult atopic dermatitis: a double-blind, placebo-controlled, crossover trial. *Br J Dermatol*. 2002;147(2):324-330.

34. el-Azhary RA, Farmer SA, Drage LA, et al. Thioguanine nucleotides and thiopurine methyltransferase in immunobullous diseases: optimal levels as adjunctive tools for azathioprine monitoring. *Arch Dermatol*. 2009;145(6):644-652. https://doi.org/10.1001/archdermatol.2009.81.

35. Caufield M, Tom WL. Oral azathioprine for recalcitrant pediatric atopic dermatitis: clinical response and thiopurine monitoring. *J Am Acad Dermatol*. 2013;68(1):29-35. https://doi.org/10.1016/j.jaad.2012.07.001.

36. Evans WE, Hon YY, Bomgaars L, et al. Preponderance of thiopurine S-methyltransferase deficiency and heterozygosity among patients intolerant to mercaptopurine or azathioprine. J Clin Oncol. 2001;19(8):2293-2301. https://doi.org/10.1200/JCO.2001.19.8.2293.

37. Eichenfield LF, Gold LFS. Addressing the immunopathogenesis of atopic dermatitis: advances in topical and systemic treatment. *Sem Cutan Med Surg*. 2017;37(Suppl 2):S45-S48. https://doi.org/10.12788/j.sder.2017.012.

38. Simpson EL, Bieber T, Guttman-Yassky E, et al. Two phase 3 trials of dupilumab versus placebo in atopic dermatitis. *N Engl J Med*. 2016;375(24):2335-2348. https://doi.org/10.1056/NEJMoa1610020.