

Systemic Therapy for Atopic Dermatitis in Older Adults and Adults With Comorbidities: A Scoping Review and International Eczema Council Survey

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Background: Clinical trials of systemic therapies for atopic dermatitis (AD) often exclude patients based on age and comorbidities.

Objectives: We conducted a scoping review of observational studies and survey of International Eczema Council (IEC) members on the treatment of AD in patients with liver disease, renal disease, viral hepatitis, HIV, or history of malignancy.

Methods: We searched MEDLINE via Ovid, Embase via Ovid, and Web of Science from inception to September 14, 2020. We mapped the available evidence on the use of cyclosporine, methotrexate, azathioprine, mycophenolate, systemic corticosteroids, and dupilumab for AD in older adults (≥65 years) and adults with the previously mentioned comorbidities. We surveyed IEC members on their preferred systemic medications for each patient population.

Results: We identified 25 studies on the use of systemic medications in special populations of adults with AD. Although IEC members preferred dupilumab as the first-line systemic agent across all special populations, many could not identify viable third-line systemic therapy options for some populations.

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Conclusions: Data on systemic therapy for AD for older adults and adults with comorbidities are limited. Although IEC members' access to systemic therapies differs geographically, expert opinion suggests that dupilumab is preferred for those patients.

Abbreviations: AD atopic dermatitis, IEC International Eczema Council

CAPSULE SUMMARY

-Randomized clinical trials (RCTs) for atopic dermatitis often exclude older patients or patients with significant comorbidities, and safety data for these special patient populations are limited

-Our survey of clinical practice patterns indicates that dupilumab is the preferred treatment across all special patient population

For patients with moderate-to-severe atopic dermatitis (AD) refractory to topical therapy, systemic treatment is often indicated.¹ Currently available on-label or off-label, systemic medications include methotrexate, cyclosporine, azathioprine, mycophenolate, and dupilumab. Systemic corticosteroids are commonly used, although it is recommended that their long-term use should be avoided in patients with AD.^{2,3} The choice of which systemic therapy to choose is complex and must factor in effectiveness, safety, cost, availability and patient-specific factors, such as age, comorbidities, drug-drug interactions, and patient preference.¹

Randomized clinical trials and network meta-analyses can be helpful for patients and clinicians to understand the relative efficacy and safety of treatments,^{4,5} but the populations included in randomized clinical trials (RCTs) for AD are often limited. In a systematic review, a third of AD systemic therapy trials had explicit upper age limits, and 70% had other exclusion criteria that would preferentially exclude older adults.⁶ The trials in that systematic review also commonly excluded people with liver disease, renal disease, viral hepatitis, HIV, or a history of malignancy.⁶ Observational data can help fill some of those gaps, but a systematic review of observational studies found only 2 small studies on the safety of systemic therapy for older adults with AD.⁷

To help guide clinical decision making for adults with AD in special populations, we conducted a scoping review of the literature and a survey of International Eczema Council (IEC) members. The aim of the scoping review was to identify literature on the use of systemic therapy for adult AD with comorbid liver disease, renal disease, viral hepatitis B and C, HIV, and a history of malignancy. The aim of the survey was to describe practice patterns of clinicians with expertise in AD.

MATERIALS AND METHODS

Scoping Review

We conducted the scoping review according to the methodological framework of Arksey and O'Malley⁸ and reported results in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis extension for Scoping Review (Supplemental Table S1, <http://links.lww.com/DER/A97>).⁹ We registered a protocol on Open Science Framework (<https://osf.io/j96s4>).

We searched MEDLINE via Ovid, Embase via Ovid, and Web of Science from inception to September 14, 2020, using a search strategy developed with the assistance of a research librarian (Supplemental Tables S2–S4, <http://links.lww.com/DER/A97>, respectively). We also manually searched citations of potentially relevant review articles for additional studies not included in our electronic searches.

Two investigators (pairs of M.L., R.M., J.Y., M.C.) screened titles, abstracts, and full texts independently and in duplicate. When necessary, discrepancies were resolved by consulting a senior author (A.M.D.). We included observational studies and case reports reporting on the use of cyclosporine, methotrexate, azathioprine, mycophenolate, systemic corticosteroids, and dupilumab for AD in individuals with HIV, viral hepatitis B or C, liver disease, renal disease, or a history of malignancy.

The following elements were abstracted in duplicate from each full-text article meeting our inclusion criteria using a standardized form: study characteristics (author, year, study design, country, participant source, funding), participant characteristics (total sample size, mean age, number and proportion of participants with HIV, liver disease and type, renal disease and type, history of malignancy and type), treatment, adverse, and efficacy outcomes (if reported).

We performed a qualitative content analysis of included articles, and study characteristics were synthesized in a descriptive summary. We produced an evidence map categorizing patients based on treatment and condition.

The IEC Survey

The IEC is a global nonprofit organization consisting of councilors and associates from 24 countries with research and clinical expertise in AD (<http://www.eczemacouncil.org/>). An electronic questionnaire was developed by IEC members (A.M.D., C.F., J.T., K.K., R.B., A.N.) and sent using SurveyMonkey on September 1, 2020, to all 103 IEC councilors and associates, of which 66 responded.

As anchoring questions, participants were asked about their approach to systemic treatment of a 30-year-old patient with AD for whom childbearing is not an important consideration. Participants were then asked about their approach to systemic treatment of AD among adults in special patient populations, including those with significant liver disease, kidney impairment, history of malignancy, HIV infection, or chronic hepatitis B or C infection. The questionnaire consisted of a 2-part question for each patient population: (1) which systemic agent would you consider prescribing for the patient population, out of azathioprine, corticosteroids, cyclosporine, dupilumab, methotrexate, mycophenolate, or none of these, and (ii) rank the systemic treatments you would consider for the patient population by your preferred first-, second-, and third-line

systemic treatments (Supplemental Table S5 for full questionnaire, <http://links.lww.com/DER/A97>).

Reminders were sent at 2, 3, and 4 weeks, and responses were accepted for 5 weeks following the date that the questionnaire was sent. We calculated the proportion of respondents selecting each medication for each question across all survey participants and then separately in subgroups of IEC members practicing in Europe and North America.

RESULTS

Scoping Review

A total of 9688 records were retrieved from our literature search, and after the removal of 1992 duplicates, 7696 records were assessed based on titles and abstracts (Fig. 1). Full texts of 571 records were assessed, of which 25 met our eligibility criteria.^{10–34} Eleven studies were conducted in Europe, 10 in the United States, 2 studies in Asia, 1 in Australia, and 1 study in Mexico. Figure 2 summarizes the number of participants reported by included studies within each special population group, coded by treatment type. Most studies were published in 2019 (6 studies) or 2020 (11 studies). Two studies were published in 2017, and the remaining 6 studies were published in 2009 or prior.

Eight studies (6 case reports, 2 case series) included 9 AD participants with HIV/acquired immunodeficiency syndrome.^{11–15,17,33,34} Seven of these studies examined dupilumab treatment; 6 included adult patients with well-controlled HIV infections or under antiretroviral therapy, who experienced improvement under dupilumab treatment.^{11,13–15} Two of these studies reported no adverse effects on the patients' HIV disease after 15 months¹⁵ and 4 months¹⁴ of

dupilumab treatment, and both reported undetectable viral loads (CD4 counts of 860 cells/ μL ¹⁴ and 668 cells/ μL ¹⁵). One study examining dupilumab included a patient with poorly controlled HIV infection (viral load, 276 copies/mL; CD4 count, 77 cells/ μL) who reported improvements in self-reported itch intensity.¹⁷ One study examined cyclosporine treatment in an adolescent with perinatal transmission of HIV, resulting in complete clearance of skin lesions.¹²

Three studies included 3 cases with hepatitis C,^{12,14,21} and 2 studies included 3 cases with hepatitis B.^{18,22} Two patients treated with dupilumab were adults with a history of hepatitis C,^{14,21} and 1 adolescent patient with perinatal transmission of hepatitis C was treated with 12 months of cyclosporine and observed a reduction of hepatitis C virus RNA and alanine aminotransferase levels during the first phase of cyclosporine treatment.¹² Ly et al²² examined 2 adult patients with chronic, well-controlled hepatitis B infections showing improvement with 20 months of dupilumab treatment, and Campione et al¹⁸ examined an adult patient with hepatitis B treated with 6 months of cyclosporine treatment and reported that liver function and hepatitis markers did not change with treatment.

Other liver diseases, including hepatosplenomegaly and acute liver failure due to Wilson disease, were reported in 11 participants across 5 studies (3 case reports, 2 cohorts).^{19,25,27,29,32} Three studies examined treatment with oral corticosteroids,^{19,27,32} with one of these studies also treating with 11 months of azathioprine after 1 month of oral prednisone.²⁷ Two studies examined treatment with dupilumab,^{25,29} with one of these studies (Bosma et al²⁵) reporting a patient with renal insufficiency and liver function abnormalities, who was treated with dupilumab.²⁵

In addition to the study by Bosma et al,²⁵ 5 additional studies (2 case reports, 3 cohorts) reported a total of 13 participants with renal

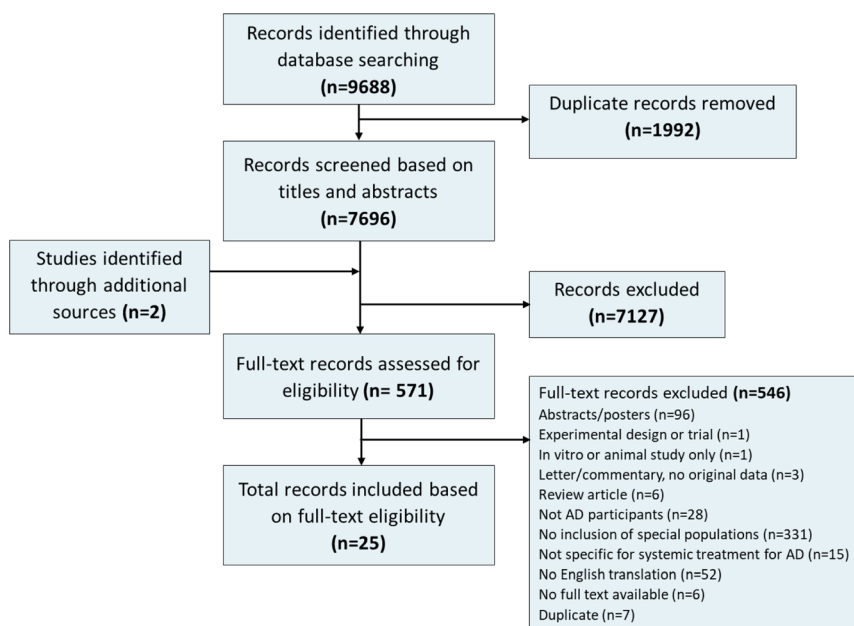


Figure 1. Study selection for the scoping review on the treatment of AD in people with HIV, viral hepatitis B or C, liver disease, renal disease, or a history of malignancy.

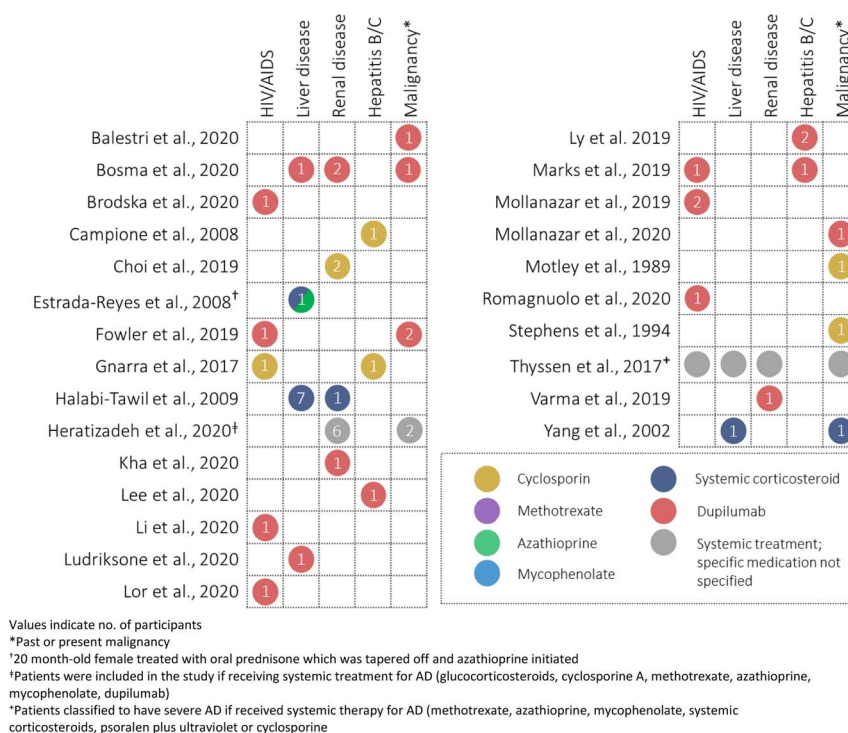


Figure 2. Evidence map of the studies on systemic therapy of AD in people with HIV, viral hepatitis B or C, liver disease, renal disease, or a history of malignancy.

disease, including hydronephrosis, renal insufficiency, and end-stage renal disease.^{19,20,25,26,28,31} Three studies examined dupilumab treatment,^{20,25,31} 1 study used cyclosporine treatment,²⁶ 1 study examined systemic corticosteroid treatment,¹⁹ and 1 study did not specify the systemic treatment used.²⁸ Choi et al²⁶ examined treatment with cyclosporin and reported that 1 patient with chronic kidney disease and 1 patient with end-stage renal failure on dialysis at the start of study, out of 92 patients in total. Varma et al³¹ presented a case report of a 22-month-old patient with a history of hydronephrosis who received 4 weeks of dupilumab. Kha et al²⁰ presented a case report of a man with end-stage renal disease after kidney transplantation treated with 8 months of dupilumab. Halabi-Tawil et al¹⁹ reported 1 participant with membranous glomerulonephritis treated with systemic corticosteroids. Heratizadeh et al²⁸ reported 6 patients (of 612) with comorbid renal insufficiency receiving systemic treatment (specific treatments received not specified).

Eight studies (4 case reports, 2 case series, 2 cohorts)^{10,11,16,24,25,28,30,32} included 3 participants with active malignancy, 1 participant who passed away because of complications of Hodgkin lymphoma, and 6 participants with past malignancy, including a history of breast cancer,¹⁰ skin cancer,²⁸ and adenocarcinoma of the prostate.²⁴ Three case reports presented 3 patients with lymphoma, examining treatment with dupilumab,¹⁶ intermittent oral corticosteroids,³² and cyclosporine.³⁰ After 3 months of dupilumab treatment, Mollanazar et al¹⁶ noted a slight improvement in cutaneous T-cell lymphoma-specific laboratory values. Motley et al³⁰ reported a stable condition in their T-cell lymphoma patient after 8 months of cyclosporine

treatment. Bosma et al²⁵ included 1 patient with active low-grade bladder cancer receiving dupilumab.

The IEC Survey

Sixty six of the 103 IEC councilors and associates (participation rate, 64.1%) responded to the survey. Respondents were from institutions in Africa (n = 1), Asia (n = 9), Australia (n = 1), Europe (n = 31), North America (n = 23), and South America (n = 1).

Across all special populations, dupilumab was the most common systemic treatment that respondents would consider prescribing (Supplemental Fig. S1 and Supplemental Table S6, <http://links.lww.com/DER/A97>) and was the systemic treatment most frequently selected as the preferred first-line agent for all patient populations (Table 1; Supplemental Table S7, <http://links.lww.com/DER/A97>). This was consistent in subgroup analyses limited to IEC members practicing in Europe and North America, respectively (Supplemental Figs. S2–S3 and Supplemental Tables S8, S9, <http://links.lww.com/DER/A97>).

For older adults with AD, most respondents considered treatment with dupilumab (86.3%) and methotrexate (65.2%; Supplemental Fig. S1B, <http://links.lww.com/DER/A97>), which were also the most common preferred first- and second-line agents for older adults. Mycophenolate was the most common preferred third-line agent among older adults (23.3%).

For patients with significant liver disease, dupilumab (84.8%) was the treatment most frequently considered, followed by

TABLE 1. Summary of the IEC Members' Ranked Preferred Systemic Treatments for the Treatment of Adults With AD in Special Patient Populations

Most Commonly Preferred First-, Second-, and Third-Line Systemic Treatments for Patients Who Are Candidates for Systemic Therapy and Who:	First-LINE	Second-Line	Third-Line
Are 30 y old for whom childbearing is not an important consideration	Dupilumab (46.2%)	Cyclosporine (32.8%) Dupilumab (32.8%)	Methotrexate (33.3%)
Are older (≥65 y)	Dupilumab (53.2%)	Dupilumab (25.8%) Methotrexate (25.8%)	Mycophenolate (23.3%)
Have significant liver disease (excluding viral hepatitises B and C)	Dupilumab (76.7%)	Cyclosporine (48.1%)	None of these (27.9%)
Have significant kidney impairment	Dupilumab (76.3%)	Mycophenolate (25.5%)	None of these (33.3%)
Have a history of malignancy (other than KC/NMSC) presumed cured for <5 y	Dupilumab (73.7%)	Methotrexate (39.1%)	None of these (65.2%)
Have a history of malignancy (other than KC/NMSC) presumed cured for ≥5 y	Dupilumab (65.0%)	Methotrexate (28.1%)	None of these (24.4%)
Have an HIV infection	Dupilumab (67.3%)	Methotrexate (25.6%)	None of these (41.2%)
Have a chronic hepatitis B and/or C viral infection	Dupilumab (75.9%)	Corticosteroids (37.1%)	None of these (57.1%)

Complete results for each special population and medication are given in Table E6.

KC/NMSC, keratinocyte carcinoma or non-melanoma skin cancer.

cyclosporine (37.9%; Supplemental Fig. S1B, <http://links.lww.com/DER/A97>). Dupilumab (76.7%) and cyclosporine (48.1%) received the highest number of responses for preferred first- and second-line therapy, respectively. Notably, the most frequently selected third-line treatment was none of the listed systemic treatments.

Respondents most frequently considered prescribing dupilumab (87.9%), methotrexate (34.8%), and mycophenolate (31.8%) for patients with significant kidney impairment (Supplemental Fig. S1D, <http://links.lww.com/DER/A97>). Dupilumab (76.3%) and mycophenolate (25.5%) were most commonly selected as preferred first- and second-line agents, respectively, for patients with significant kidney impairment.

For patients with a history of malignancy cured for less than 5 years and cured for 5 or more years, dupilumab (85.8%, 86.4%) and methotrexate (40.9%, 53.0%) were most frequently considered (Supplemental Figs. S1E, F, <http://links.lww.com/DER/A97>) and were the most frequent preferred first- and second-line treatments, respectively. None of the listed systemic treatments were most commonly selected for preferred third-line treatment. Results were similar for patients with HIV (Supplemental Fig. S1G, <http://links.lww.com/DER/A97>).

Most respondents would consider treatment with dupilumab for patients with chronic hepatitis B and/or C viral infection (Supplemental Fig. S1H, <http://links.lww.com/DER/A97>). However, 10 respondents (15.2%) indicated that none of the listed systemic treatments would be considered for this patient group. Dupilumab (75.9%) and cyclosporine (37.1%) were most commonly selected as the preferred first- and second-line treatment, but more than half of the respondents (57.1%) indicated that none of the listed systemic treatments were preferred third-line treatment.

DISCUSSION

In our scoping review of observational studies and case reports, we found limited evidence to guide systemic treatment decisions for older adults with AD and comorbid liver disease, renal disease,

viral hepatitises B and C, HIV, or a history of malignancy. Our previous systematic reviews of RCTs and observational studies also found limited evidence for the treatment of older adults with systemic therapy.^{6,7}

Ideally, all treatment decisions should be made on robust evidence applicable to the person with AD being treated. In the absence of such evidence, though, understanding expert practice patterns can be helpful. The results of our survey of IEC councilors and associates indicate that for all special populations under study, dupilumab would be the first-line systemic agent. Although cyclosporine was the most common second-line agent recommended for a hypothetical younger adult without comorbidities and for patients with liver disease, respondents tended to avoid it for patients with renal disease, viral hepatitises B and C, HIV, or a history of malignancy. This is similar to expert recommendations made in a recent review on treating psoriasis in special populations, which recommended against both cyclosporine and methotrexate for patients with chronic viral infections (hepatitis B, hepatitis C, and HIV).³⁵ For patients with a history of malignancy, respondents favored methotrexate as a second-line agent.

Mycophenolate was the most commonly recommended third-line treatment for older adults, but the most common response for third-line treatment in the other special populations was “none of these.” This points to the current paucity of safe and effective treatments for severe AD, with dupilumab as the only targeted agent approved in most jurisdictions. Methotrexate, cyclosporine, azathioprine, and mycophenolate are all effective options, but their use is limited in AD patients with comorbidities due to: (1) their broad-spectrum immunomodulatory activity; (2) other potential toxicities, such as hepatotoxicity for methotrexate, azathioprine, and mycophenolate, and renal toxicity for cyclosporine; and (3) the lack of approval in moderate-to-severe AD for methotrexate, azathioprine, and mycophenolate.

Conclusions from our scoping review are limited by the low level of evidence from case reports and the limited number of observational

studies included. Several reports also lacked sufficient detail on duration and safety of treatment. Our scoping review and survey are limited by their inclusion of only medications currently in widespread use. Many new systemic medications are being investigated for AD, but “real-world” data from observational studies are not yet available for them, and most IEC members do not have experience with these agents outside of clinical trial settings. Future work could replicate our studies, updated to include new medications, such as abrocitinib, baricitinib, upadacitinib, and tralokinumab. Access to different systemic medications differs geographically, so some IEC members' responses are likely influenced by local access.

As more biologic and other targeted agents are approved, there will be more options to use for older patients and those with comorbidities. Ideally, clinical trial inclusion criteria can be broadened to include such patients, but in the absence of that, high-quality observational data are needed. Ongoing AD registries will be instrumental in providing data on the safety of both new and older systemic agents for special populations of adults with AD, and observational studies should specifically aim to include older patients and those with comorbidities.

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