

Review of Systemic Treatment Options for Adult Atopic Dermatitis

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Journal of Cutaneous Medicine and Surgery
1-9

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DOI: 10.1177/1203475416670364

jcms.sagepub.com



Abstract

Background: Atopic dermatitis (AD) is a chronic, pruritic inflammatory skin disease resulting from defects in skin barrier and aberrant immune responses. AD significantly affects the quality of life. Not all patients respond to topical therapies, and often systemic therapy is required to control the disease.

Objective: To review the treatment options for adult AD patients including those options for patients who do not respond adequately or have contraindications to oral systemic therapy.

Methods: A working group of clinicians with experience managing AD was convened to review the current literature on treatment options for adult AD patients. This review is based on the best available evidence from a published systematic review and an additional literature search.

Results: Current treatments for AD are reviewed, including options for adult AD patients who do not respond or have contraindications to current systemic therapies. A new approach with targeted therapies is reviewed based on best available evidence.

Conclusion: Many AD patients respond satisfactorily to topical or systemic treatments, but for those patients who do not respond or have contraindications, new biologic agents appear to be promising therapies.

Keywords

atopic dermatitis, systemic therapy, adults, biologics, IL-4, IL-13, dupilumab

Background

Atopic dermatitis (AD) is a chronic, pruritic inflammatory skin disease that affects both children and adults and severely affects quality of life (QOL).¹⁻⁴ Increasing knowledge of the immunopathogenesis of AD has promoted research on new therapeutic targets.³ Although many patients respond satisfactorily to topical anti-inflammatory agents, about 10% require systemic treatments to achieve adequate control of their illness.⁵ For AD patients who do not respond or have contraindications to available systemic treatment, biological treatments are proposed as an alternative.^{3,5}

Method

A working group of clinicians experienced in treating AD was convened to review the literature on treatment options for adult AD patients, including those options for patients who do not respond adequately or have contraindications to systemic therapy. For instance, cyclosporine therapy is contraindicated in conditions such as hypertension and renal insufficiency.⁵ The following clinical question on systemic and biologic

treatment for AD patients was discussed by the working group: What is the positioning of the different systemic treatments for AD? The discussion followed a detailed summary

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Figure 1. Neck, chin, and face.



Figure 2. Back.

of the papers and a published systematic review performed by Roekevisch et al. (2013).⁵ References published more recently were introduced by various authors. New references were reviewed as extensions to the most recent literature review.

Impact of AD

AD is a debilitating relapsing, pruritic inflammatory skin disease that occurs in 20% of children and perhaps as many as 10% of adults.^{1,2,6} This complex immunological disease often begins in childhood, with approximately 60% of patients developing AD prior to the age of 1 year and 90% by the age of 5 years.⁷ The literature suggests that up to 10% may develop AD as adults.^{2,6,7} The early onset of AD may be the first clinical manifestation of atopic disease that includes food allergy, allergic rhinitis, and asthma.⁸ The diagnosis of AD remains clinical, because there is currently no reliable biomarker that can distinguish it from other inflammatory conditions.^{7,9} AD presents with pruritus, erythema, scaling, edema, excoriations/erosions, oozing, crusting, and lichenification (Figures 1-3).^{7,9}



Figure 3. Wrists and hand.

AD is associated with significant morbidity as well as physical, psychological, and economical QOL impairment.^{4,10-24} Intense pruritus frequently leads to significant sleep disturbances as well as irritability and reduced performance at school and work in both those affected with AD and their caregivers.²⁵ Even in remission, AD can have long-term behavioral and neurocognitive effects. QOL may be further reduced because of the social stigma of the visible skin condition.¹²

Topical Treatment and Phototherapy

Emollients are the cornerstone of AD treatment and maintenance as they restore and preserve skin barrier integrity and are often used in combination with prescription therapy.^{26,27} Topical corticosteroids (TCS) have proven to be efficacious and safe in more than 110 different randomized controlled trials (RCTs), although their use is limited by potential side effects and steroid phobia.^{26,27} Topical calcineurin inhibitors (TCIs) inhibit calcineurin-dependent T-cell activation, blocking the production of proinflammatory cytokines and mediators involved in the pathogenesis of AD.^{28,29} These agents have been shown to be as effective as low- to mid-potency topical steroids, without compromising the epidermal barrier, and they can be used safely on the entire body including eyelids and in flexural areas.²⁸ Most common adverse events include transient burning, stinging, and pruritus early in administration.²⁹ The potential skin cancer and lymphomas risk when using TCIs is not supported with conclusive evidence.²⁹ Continued use of either TCS (1-2 times/wk) or TCI (2-3 times/wk) after disease stabilization, to previously involved skin, is recommended to reduce subsequent flares or relapses.³⁰ Phototherapy can be used as monotherapy or in combination with emollients and topical agents; however, the availability of this treatment is often limited.³¹ Another challenge of managing AD is adherence to application of topical therapy, and reasons for nonadherence should be addressed as part of the treatment regimen.³²

Systemic Treatments

There are many therapeutic possibilities to temporarily control signs and symptoms of AD, but none are able to cure the disease.²⁷ Most flares can be controlled with TCS or TCIs, but refractory AD may require the addition of a systemic treatment.⁵ Systemic immunomodulating medications may be used off-label for the subset of patients in whom optimized topical regimens and/or phototherapy do not adequately control the disease.^{27,31,32} A published systematic review on the efficacy and safety of systemic treatments for AD⁵ reviewed 34 RCTs on 12 different systemic treatments in a total of 1653 AD patients. In addition to the published review, we included additional recent publications on biologic agents,³³⁻⁴⁶ the rationale for their use,⁴⁷⁻⁶⁰ and publications on oral systemic agents.⁶¹⁻⁷⁹ Cyclosporine is recommended as first-line treatment for short-term use, azathioprine is second-line, and methotrexate third-line.⁵ These treatment options and their benefits, drawbacks, and contraindications are reviewed in Table 1.⁶¹⁻⁷⁹ Recommendations were not given for mycophenolate, montelukast, intravenous immunoglobulins, and systemic glucocorticoids because of limited available evidence. Roekvisch and coauthors⁵ concluded that strong recommendations are possible only for the short-term use of cyclosporine and that there were methodological limitations in most trials, preventing a meta-analysis and evidence-based conclusions.⁵

Biologics for AD Treatment

There are currently no biologic agents indicated for treatment of AD. Many oral therapeutic choices are available to AD patients; however, some patients face issues, such as primary failure of treatment response, intolerance to treatment, or loss of treatment response. Further limitations in the use of systemic therapies may be comorbidities precluding use of some agents, potential end-organ toxicities, and immunogenicity to monoclonal antibodies. Therefore, there is a major need for new effective agents.³ Current therapies for refractory AD fail to modulate the precise pathways integral to disease initiation and pathogenesis. Biologic agents systemically modulate inflammatory pathways associated with disease pathogenesis. Using monoclonal antibodies may enable more effective and less toxic treatment compared with systemic therapy.³

To explore this further, the literature was reviewed on the role of biologics as a new treatment option in AD. The largest and high-quality double-blind randomized studies (5 RCTs, N = 586) were found for dupilumab^{33,34} followed by a parallel-group double-blind RCT (N = 43) for mepolizumab³⁵ and a phase 2 RCT (N = 33) for ustekinumab.⁴⁶ The other treatment modalities were supported by open-label studies or case series (Table 2).³⁵⁻⁴⁵

Dupilumab

In acute and chronic skin lesions of AD patients, interleukin (IL)-4 and IL-13 are significantly elevated and patients have

increased numbers of CD4- and CD8-positive cells that release IL-4 and IL-13.^{7,47} These Th2 cytokines,⁴⁸⁻⁵² their common receptor IL-4R α ,^{53,54} and the downstream transcription factor signal transducer and activator of transcription (STAT) 6⁵⁵ play a role in AD development. High levels of IL-4 and IL-13 have been shown to act as inhibitors of epidermal differentiation and antimicrobial peptides contributing to the phenotype of AD⁵⁶⁻⁵⁸ (Figure 4). Since IL-4 and IL-13 signal through a common receptor, interfering in this pathway could be efficacious in treating AD patients.⁵⁹ Dupilumab is a monoclonal antibody that blocks both IL-4 and IL-13 signaling through IL-4R α .⁶⁰ Two early-phase studies (NCT01259323, NCT01385657) that included transcriptomic analyses of pretreatment and posttreatment skin biopsy specimens from patients with moderate-to-severe AD treated weekly with 150 or 300 mg of dupilumab or placebo showed rapid improvement of the AD molecular signature.^{33,60} The mean percentage change in eczema area severity index (EASI) scores in the parent study (n = 67) was consistent with that of the substudy (n = 18) and suggests that IL-4 and IL-13 drive a complex, TH2-centered inflammatory axis in patients with AD.⁶⁰ Weekly treatment with dupilumab monotherapy for 12 weeks reduced AD severity (by EASI score) by 74.0% compared with 23.3% with the placebo ($P < 0.001$).³³ Patients in the dupilumab group demonstrated a 60% reduction in body surface area affected and 40% of patients achieved AD clearance (investigators global assessment score of 0 or 1) at day 85 ($P < 0.001$).³³ Patients treated with dupilumab noted a significant decrease ($P < 0.001$) in pruritus scores and demonstrated numerically fewer skin infections (0.05 infections per patient) than those in the placebo group (0.20 infections per patient); however, statistical significance was not reported.³³

A phase 2b dose-ranging RCT also showed superior efficacy of dupilumab (300 mg every week, 300 mg every 2 weeks, 200 mg every 2 weeks, 300 mg every 4 weeks, 100 mg every 4 weeks) to placebo at all dosing levels (NCT01859988).³⁴ The least-squares mean percentage improvement in EASI score was -74% (300 mg every week), -68% (300 mg every 2 weeks), -65% (200 mg every 2 weeks), -64% (300 mg every 4 weeks), and -45% (100 mg every 4 weeks) compared with -18% (placebo; $P < .0001$ for all comparisons).³⁴ There was also marked improvement in the patient-reported outcome of pruritus as measured by the pruritus numeric rating scale (NRS) score, with a significant reduction as early as week 1. The peak weekly improvement in pruritus NRS appeared to be dose dependent. At week 16, all dupilumab dose regimens, except for 100 mg every 4 weeks, resulted in least-squares mean percentage reductions in pruritus ranging from 33% to 47% ($P < .0001$ vs placebo), with the greatest improvement reported for doses of 300 mg every week or every 2 weeks. There were no significant safety concerns noted for those patients who received dupilumab.³⁴

Three new phase 3 trials are currently ongoing in adults as well as trials in the pediatric population (NCT02407756).

Table 1. Systemic treatment options benefits and drawbacks.

Drug	Benefits		Drawbacks	
Mode of Action and Recommendation	Clinical Efficacy	Quality of Life	Side Effects	Contraindications
Cyclosporine: Inhibits Th1 and Th2 cells as well as dendritic cells Recommendation: First-line treatment for use of up to a year ⁵ Based on moderate- to high-quality large studies showing efficacy and safety for short-term use ⁵	Four placebo-controlled RCTs ⁶¹⁻⁶⁴ showed between 53% and 95% improvement after 10 d to 8 wk in different clinical scores Six head-to-head RCTs showed cyclosporine was superior to prednisolone, ⁶⁷ IVIG, ⁶⁸ UVAB, ⁶⁹ and similarly effective to EC-MPS ⁷⁰ and tacrolimus ointment, ⁷¹ and old versus new formulation ⁷² Three RCTs on dosing ^{65,73,74} showed higher dosages (5 mg/kg per day) had a more rapid response and superior efficacy	Significant improvement in QOL reported in patients taking cyclosporine ^{65,66}	Nausea, headache, paresthesia, renal impairment, hypertension, sequelae of chronic immunosuppression	Renal impairment, uncontrolled hypertension, malignancies
Azathioprine: Purine analog antagonizes purine metabolism, inhibiting synthesis of DNA; its use in AD is off-label Recommendation: Second-line treatment ⁵ Based on moderate-quality study efficacy and safety was shown for short- and long-term use (24 wk), including large patient numbers ⁵	Three RCTs ⁷⁵⁻⁷⁷ : 2 placebo-controlled RCTs ^{75,76} and 1 head-to-head RCT versus methotrexate ⁷⁷ At week 12, superior to placebo (mean improvement ^a 26% ⁷⁵ and 37% ⁷⁶) and 39% ⁷⁷ when compared with methotrexate At week 24, for the 16 (84%) patients in the azathioprine group, the mean ^b reduction was 43% ⁷⁷	Itch scores and DLQI improved in patients taking azathioprine compared with placebo ⁷⁶	Not well tolerated because of gastrointestinal disturbances ⁷⁵ Abnormalities in liver enzymes and blood counts, such as lymphocytopenia were noted ⁷⁵⁻⁷⁷	Unknown/low/absent TPMT activity, malignancies, concurrent allopurinol therapy, pregnancy Relative contraindications: Hepatic and renal impairment Caution: In women of childbearing potential
Methotrexate: Folic acid antagonist with anti-inflammatory effects; its use in AD is off-label Recommendation: Third-line treatment ⁵ Based on moderate-quality study efficacy and safety was shown for short- and long-term use (24 wk), including large patient numbers ⁵	1 RCT: At week 12, equally efficacious as azathioprine (mean improvement ^b of 42% ⁷⁷), and at week 24, the mean ^b score was 48% for 18 (95%) patients ⁷⁷ One open-label, dose-ranging prospective trial (N = 12) showed an average improvement ^a of 52% from baseline ⁷⁸ One retrospective review (N = 31) of children and adolescents showed methotrexate was effective or very effective in 75% ⁷⁹	A mean improvement of 26% in QOL ^c was shown ⁷⁷ Significant improvement in QOL, affected body surface area, loss-of-sleep, and itch scores ⁷⁸	Nausea, elevated liver enzymes, and more rarely pancytopenia and hepatic or pulmonary toxicity was reported; serious adverse events were not observed ⁷⁷	Relative contraindications: Liver disease, renal impairment, significant pulmonary disease, blood dyscrasias, active infection, pregnancy, excessive alcohol consumption Caution: In women of childbearing potential

Abbreviations: AD, atopic dermatitis; DLQI, disease-specific health-related quality of life instrument; EC-MPS, enteric-coated mycophenolate sodium; IVIG, intravenous immunoglobulin; QOL, quality of life; RCT, randomized controlled trial; TPMT, thiopurine methyltransferase; UVAB, ultraviolet light A and B.

^aSASSAD = Six Area of the Six Sign Atopic Dermatitis scores.

^bSCORAD = scoring atopic dermatitis.

^cSKINDEX.

Open-label studies evaluating the long-term safety and efficacy of repeat doses of dupilumab in children, adolescents, and adults who had previously participated in dupilumab controlled studies are ongoing (NCT02612454, NCT01949311).

Limitations

This article focuses on adult patients and may differ with the pediatric population, so the consensus cannot be extrapolated to

Table 2. Biologics treatment options benefits and drawbacks.

Drug Tested	Study Design	No. Of Patients	Benefits	Drawbacks
Dupilumab: Fully human monoclonal antibody directed against the alpha subunit of IL-4 and IL-13 receptors	Dose escalation RCT double-blind ³³ randomised, placebo-controlled, dose-ranging phase 2b trial ³⁴	Four studies N = 207 N = 379	A marked and rapid clinical improvement was observed in the dupilumab group ³³ At week 12, in the dupilumab (300 mg) group, 40% scored clear or near-clear versus 7% in the placebo group ($P < .001$). ³³ Pruritus scores decreased 55.7% for dupilumab versus 15.1% ($P < .001$) for placebo. ³³ Dupilumab improved clinical responses in adults with moderate-to-severe atopic dermatitis in a dose-dependent manner. ³⁴	Side-effect profiles were not dose limiting, and there were no significant safety concerns. ^{33,34}
Infliximab: Antagonist against TNF- α ³⁶	Open-label ³⁶	N = 9	Only 2 of the 9 patients experienced longer-term efficacy	Clinical response tends not to be maintained over time, despite an initial good response; risk of infection (rare: TB, hepatitis, common: URTI)
Mepolizumab: Monoclonal antibody to IL-5 that reduces peripheral blood eosinophils ³⁵	Parallel group RCT, double blind ³⁵	N = 43	No clinical improvement; scarce benefits in AD management	Side effects were mild and no different than the placebo group
Omalizumab: Monoclonal antibody that blocks IgE function Limited peer-reviewed evidence	Open-label ⁴³ Four case series ³⁷⁻⁴⁰ 2 RCTs ^{41,42}	N = 21 N = 64 N = 28	No significant differences versus placebo; conflicting data on efficacy; well tolerated	Safe drug; cost may outweigh the therapeutic benefit
Rituximab: Chimeric monoclonal antibody against the B-cell surface marker CD20	Open-label ⁴⁴	N = 6	Results were inconclusive; well tolerated	Lack of data
Ustekinumab: Targets the shared p40 subunit of IL-12/IL-23	Case series ⁴⁵ and phase 2 RCT ⁴⁶	N = 4 ⁴⁵ and N = 33 ⁴⁶	Case series showed promising results and was well tolerated. ⁴⁵ In the RCT, although the ustekinumab group had higher SCORAD50 scores compared with the placebo group at week 16 (primary endpoint), this did not reach statistical significance; a high placebo response was attributed to allowance of concomitant TCS ⁴⁶	Safe medication and no SAEs reported in the phase 2 RCT ⁴⁶

Abbreviations: AD, atopic dermatitis; IgE, immunoglobulin E; IL, interleukin; RCT, randomized controlled trial; SAE, serious adverse event; TB, tuberculosis; TCS, topical corticosteroid; TNF- α , tumor necrosis factor- α ; URTI, upper respiratory tract infection.

the treatment of children. There are few large, randomized, controlled studies on the newer drugs, so conclusions cannot be drawn until more evidence is available. Local practice may differ from some of the countries where the studies were conducted. Finally, the availability of various agents and phototherapy will differ between countries, and this may affect practice patterns.

Conclusions

The impact of AD on patients and families is widespread and severe and correlates with disease severity. Active disease has major psychosocial and financial implications for individuals, their families, health care providers, and society as a whole. Although many AD patients respond satisfactorily to

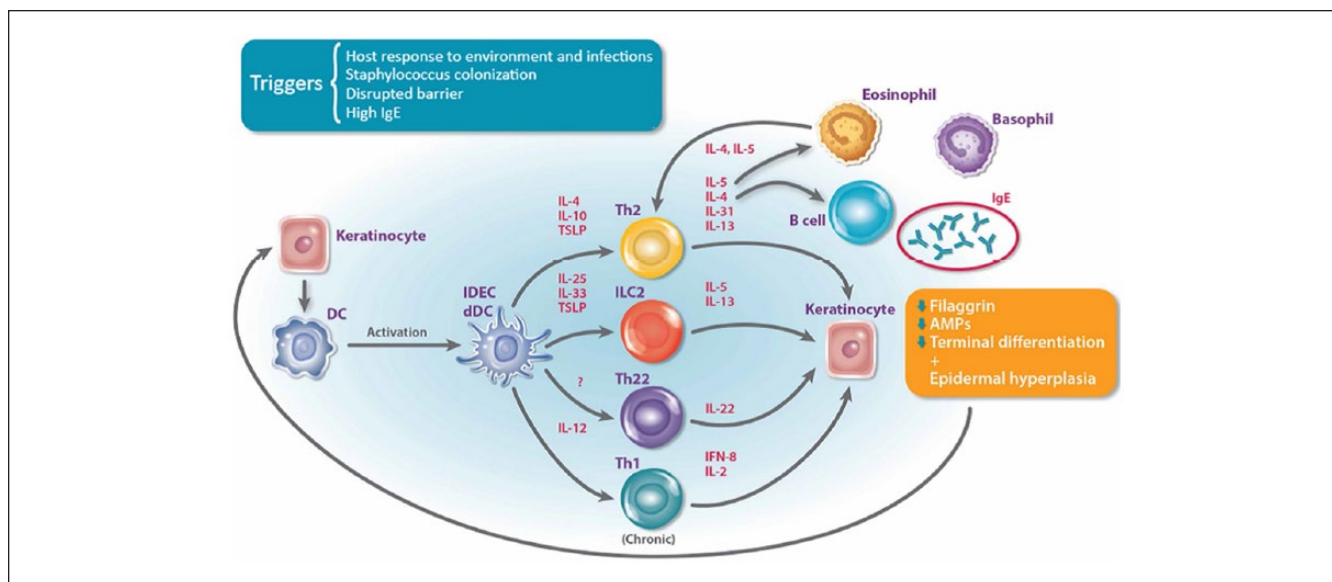


Figure 4. AD pathway. Inflammatory pathway of AD showing the roles of interleukin (IL)–4, IL-13, and B-cell differentiation and class switching. B-cell class switching links to the elevated serum IgE levels characteristic of AD. IL-4 and IL-13 have also been shown to act as inhibitors of epidermal differentiation as well as the production of antimicrobial peptides. AD, atopic dermatitis; AMPs, antimicrobial peptides; DC, dendritic cell; dDC, dermal dendritic cell; IDEC, inflammatory dendritic epidermal cells; IFN, interferon; IgE, immunoglobulin E; IL, interleukin; TSLP, thymic stromal lymphopoietin.

topical treatments, systemic therapy is required for a subset of this population. A systematic review on systemic therapy recommends cyclosporine, azathioprine, and methotrexate for first-, second-, and third-line therapy, respectively. These treatment options may be limited by lack or loss of efficacy, side effects, end-organ toxicity, or contraindications. For those patients who do not respond or have contraindications, biologic agents have been explored, and dupilumab has been shown to be the first biologic agent to show promise.

Declaration of Conflicting Interests

The authors declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: M.G. is an investigator, advisory board member, and consultant for AbbVie, Amgen, Celgene, Janssen, Lilly, Novartis, Pfizer, Regeneron, and Sanofi and investigator for Dermira, GSK, Medimmune, Roche, and UCB. C.W.L. is an investigator and consultant/speaker for Stiefel/GSK, Cypher Pharmaceuticals, Roche Pharmaceuticals, Galderma, La Roche-Posay, Pierre Fabre, Novartis, Janssen, and Valeant. K.P. is an investigator, consultant, and advisory board member for AbbVie, Amgen, Anacor, Astellas, Baxter, Biogen-Idec, Boehringer-Ingelheim, Bristol Myers Squibb, Celgene, Dermira, Eli Lilly, EMD Merck, Galderma, Genentech, GSK, Janssen, Kyowa-Kirin, Leo Pharma, Medimmune, Merck Sharp Dhome, Novartis, Pfizer, Regeneron, Roche, Sanofi, Takeda, and UCB. M.B. is an investigator advisory board member, and consultant for AbbVie, Amgen, Celgene, Eli-Lilly, Janssen, Leo Pharma, Novartis, Pfizer, and UCB. L.G. is a consultant to Galderma, Johnson & Johnson, Leo Pharma, LaRoche Posay, Sanofi, Valeant. Researcher for Galderma, Leo Pharma, La Roche Posay, and Roche and speaker

for Galderma, Johnson & Johnson, Leo Pharma, LaRoche Posay, PremPharm, and Valeant. W.G. is an investigator/advisory board member and/or speaker for AbbVie, Amgen, Celgene, Cipher, Janssen, Lilly, Leo Pharma, Novartis, Pfizer, Roche, Valeant, and Actelion. C.-h.H. is an investigator and/or advisory board member and/or consultant for Celgene, Regeneron, Roche, Medimmune, Janssen, Boehringer-Ingelheim, Eli Lilly, AbbVie, Amgen, Dermira, Galderma, GSK, Leo Pharma, Novartis, and Sanofi. Y.P. is an investigator and advisory board member for Abbvie, Amgen, Celgene, Eli Lilly, Janssen, Leo Pharma, Novartis and investigator for Baxter, Boehringer-Ingelheim, Bristol Myers Squibb, Dermira, Galderma, GSK, Medimmune, Merck, Pfizer, Regeneron, Roche, Takeda, and UCB. G.S. is a consultant for Novartis, Merck, CSL Behring, Shire, Investigator for Novartis, Genentech, DBV Technology, Astra Zeneca, CSL Behring, and Merck. R.V. received grants/research support from Abbvie, Amgen, Centocor, Dermira, Galderma, GSK, Leo, Lilly, Takeda, Novartis, Merck, Pfizer, and Regeneron; speakers bureau/honoraria from Abbvie, Amgen, Janssen, Galderma, GSK, Leo, Lilly, Novartis, Pfizer, Valeant, Actelion, Celgene, Cipher, and Palladin; and consulting fees from Abbvie, Amgen, Janssen, Galderma, GSK, Leo, Lilly, Novartis, Pfizer, Valeant, Actelion, Celgene, Cipher, and Palladin.

Funding

The authors disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: The authors received funding from Sanofi to attend a summary review meeting. Research and writing assistance provided by A. Andriessen, PhD, was funded by Sanofi. The article, tables, and figures were reviewed, edited, and approved by all authors. Funding received from Sanofi for medical writing assistance and participation in a literature review meeting.

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