



Management Recommendations for Dupilumab Partial and Non-durable Responders in Atopic Dermatitis

Aleksi J. Hendricks¹ · Peter A. Lio^{2,3} · Vivian Y. Shi⁴

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Abstract

As the first targeted systemic agent for the treatment of moderate to severe atopic dermatitis (AD), dupilumab represents a novel therapeutic opportunity for both patients and providers. However, a subset of patients receiving dupilumab are either partial responders who exhibit some improvement in Investigator's Global Assessment score but not sufficient to meet the primary endpoint, or are non-durable responders who achieve therapeutic endpoint with subsequent partial loss of efficacy. We propose a therapeutic algorithm for the management of dupilumab partial responders and non-durable responders that involves maximizing topical therapy, seeking alternative diagnoses, and using dupilumab in conjunction with traditional systemic immunosuppressive agents. With a number of targeted agents for AD in the drug development pipeline, we encourage patients who do not have an adequate response to dupilumab to remain patient and optimistic as the arsenal of AD treatment modalities continues to expand.

Key Points

Atopic dermatitis patients who improve but do not reach therapeutic endpoint after 16 weeks of dupilumab treatment can be considered partial responders or non-durable responders. In these subsets of patients, additional therapeutic considerations are warranted.

Management approaches involve exclusion of new diagnoses, maximization of topical therapy, phototherapy, increasing dupilumab dose or frequency, and addition of traditional immunosuppressive agents.

Cyclosporine, mycophenolate mofetil or methotrexate can be strategically added to an existing dupilumab regimen.

1 Introduction

Dupilumab is the first and only currently approved targeted systemic medication for the treatment of moderate to severe atopic dermatitis (AD) in adults. It is a fully human monoclonal antibody that inhibits interleukin (IL)-4 and IL-13 signaling via binding to the IL4-receptor- α subunit, which is common to both IL-4 and IL-13 receptors [1].

For treatment of AD, the FDA-approved dupilumab regimen is a loading dose of 600 mg subcutaneously followed by 300 mg every 2 weeks. In phase III trials, 36–38% of participants achieved primary endpoint at 16 weeks, defined as an Investigator's Global Assessment (IGA) score of 0 (clear) or 1 (almost clear), with at least a 2-point reduction in IGA from baseline [2]. In this discussion, the therapeutic endpoint of 2-point IGA reduction from dupilumab pivotal trials is utilized to define response versus non-response. However, additional patient-reported measures such as reduction in pruritus (as measured by the pruritus numerical rating scale) and improvement in quality of life (as measured by the Dermatology Life Quality Index) are important to consider when assessing a patient's response to dupilumab.

Despite its efficacy, there remains a subset of AD patients who fail to achieve the therapeutic endpoint after 16 weeks. These patients can be categorized as (1) non-responders (NR) with little or no improvement, (2) partial responders (PR) who exhibit some improvement in IGA but not

✉ Vivian Y. Shi
vshi@email.arizona.edu

¹ College of Medicine, University of Arizona, Tucson, AZ, USA

² Department of Dermatology, Northwestern University Feinberg School of Medicine, Chicago, IL, USA

³ Medical Dermatology Associates of Chicago, Chicago, IL, USA

⁴ Division of Dermatology, Department of Medicine, University of Arizona, 7165 N Pima Canyon Drive, Tucson, AZ 85718, USA

sufficient to meet the primary endpoint, or (3) non-durable responders (NDR) who achieve therapeutic endpoint with subsequent partial loss of efficacy. Herein we aim to discuss our management algorithm for AD patients who are dupilumab NR, PR, and NDR, which includes seeking additional diagnoses and combining dupilumab with traditional systemic immunosuppressive agents.

2 Management Strategies

For NR after 16 weeks of dupilumab treatment, it seems very unlikely that an effect will be seen with additional time. Thus, for most patients in this group, it is reasonable to discontinue dupilumab. For such patients, it is important to consider other potential diagnoses (listed in Fig. 1) and consider off-label use of alternative systemic agents.

We propose a second therapeutic ladder for adult AD patients on dupilumab who are PR or NDR (Fig. 1). These designations should be made only after 16 weeks of treatment, and patients should remain on dupilumab. For both groups, general considerations for add-on treatment should include maximizing the pillars of AD care, with diligent moisturization, routine bleach baths, and topical anti-inflammatory agents including corticosteroids, calcineurin inhibitors, and PDE4 inhibitors. Addition of phototherapy should also be considered.

2.1 Potential Causes of Non-durable Response

For NDR, clinical considerations should include an acute AD flare, drug tolerance, or development of a secondary diagnosis. The lack of sustained response may indicate ‘biologic fatigue’ due to drug tolerance via development of anti-drug antibodies, although there is currently no commercially available test to assess for antibody presence. Additional diagnoses to consider include allergic contact dermatitis, airborne contact dermatitis, urticaria, drug reaction, secondary infection, scabies infestation, and cutaneous T cell lymphoma. Common forms of secondary infection or microbial overgrowth such as impetigo, inflamed molluscum, and tinea versicolor should be ruled out or treated as applicable. More rare infectious etiologies may include eczema herpeticum and secondary infection with coxsackie virus, so called ‘eczema coxsackium’ [3, 4]. In patients with head and neck dermatitis, development of periorificial dermatitis, seborrheic dermatitis, and steroid-induced rosacea are prudent clinical considerations. For pediatric patients, consider mastocytosis and miliaria as potential alternative diagnoses. Practitioners should evaluate for dupilumab-related exacerbation in the form of a paradoxical head and neck reaction [5] and for other drug-related cutaneous conditions.

2.2 Management of Partial Responders and Non-durable Responders

In PR and NDR, the addition of another systemic agent should be considered until alternative targeted therapies become approved. Except in the case of suspected paradoxical drug reaction, all patients should continue at least the FDA-approved dupilumab dosing regimen to minimize the likelihood of developing anti-drug antibodies.

The first consideration in managing PR and NDR patients is modifying dupilumab frequency or dose. For patients reporting flares between administrations, consider increasing injection frequency to weekly dosing. Although the proportion of patients achieving therapeutic endpoint in dupilumab phase III trials was similar for 300-mg weekly (36–37%) and 300-mg every-other-week dosing (36–38%) [2], based on our experience, a subset of AD patients do gain additional benefit from weekly dosing. In patients with higher BMI or more severe disease at baseline, it may be useful to increase the dose per injection, but little is known about the safety and efficacy of such doses. Despite potential therapeutic benefits, higher injection dose or frequency involves insurance coverage considerations with requirements for prior authorization and additional documentation, which may complicate and delay treatment.

If escalation of dupilumab dose or frequency is not immediately available, the next step could involve adding a traditional systemic immunosuppressive agent such as cyclosporine, mycophenolate mofetil, or methotrexate (Table 1). In patients already receiving dupilumab, we recommend beginning traditional immunosuppressives at a quarter of the dose used in a biologic-naïve patient and increasing as needed to half of the dose used in a biologic-naïve patient. Alternatively, these agents can be started at half of the dose used in a biologic-naïve patient and decreased to the lowest possible dose for maintenance. While not FDA-approved for the treatment of AD and not formally studied together, to our knowledge there is no absolute contraindication for the concurrent use of dupilumab with an immunosuppressant. As inflammatory cytokines have been found to affect formation of cytochrome P450 (CYP450) enzymes, there is theoretical justification for monitoring of CYP450 substrates (such as cyclosporine) in patients on dupilumab. However, a recent drug–drug interaction study found no clinically relevant effects of dupilumab on the pharmacokinetics of CYP450 substrates [6, 7].

Cyclosporine tends to provide the most rapid response, but should be used cautiously under close surveillance due to nephrotoxicity and hypertension associated with its long-term use [8]. In a retrospective analysis of serum creatinine levels in 150 AD patients treated with cyclosporine, long-term therapy was not associated with a clinically relevant

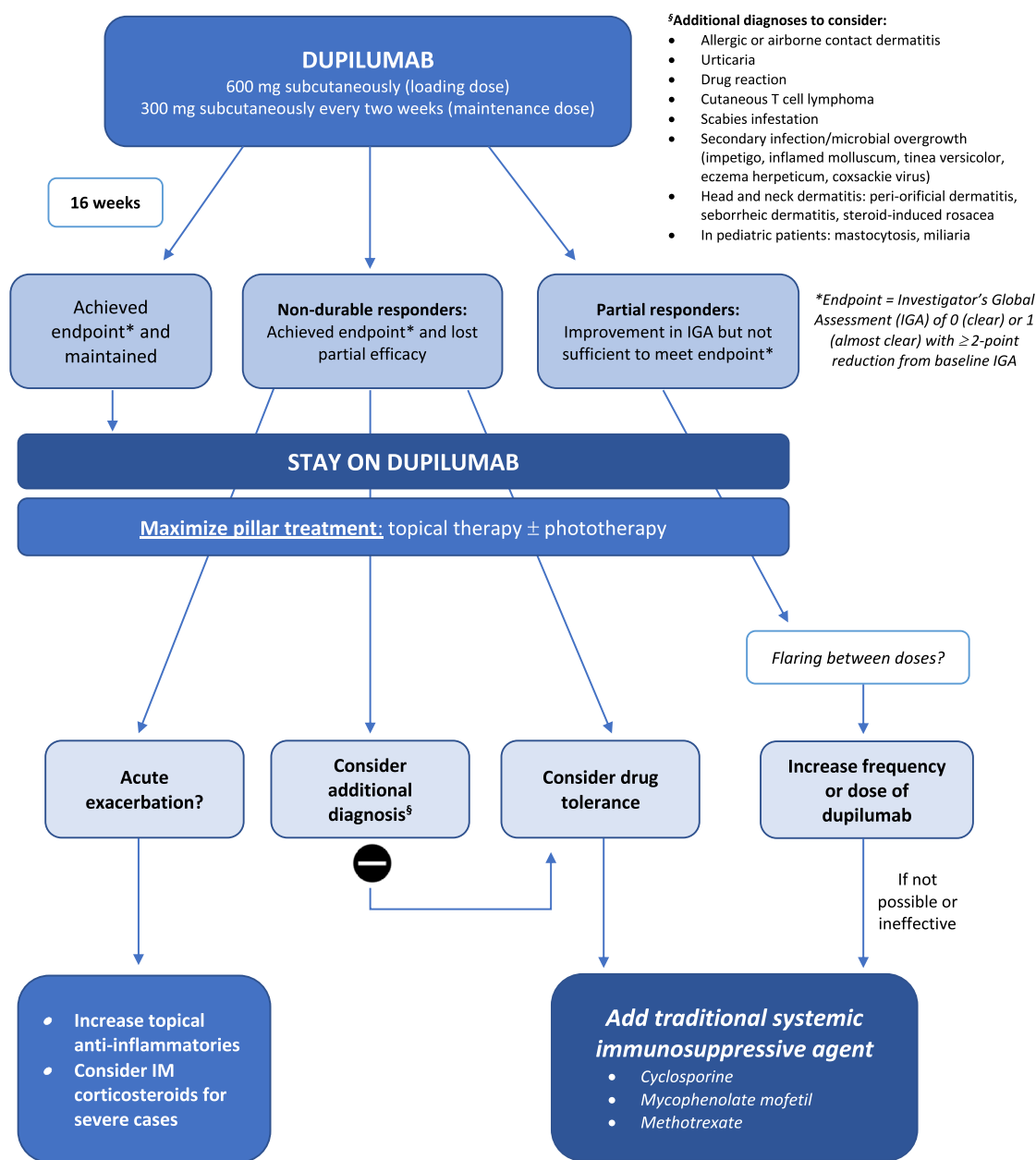


Fig. 1 Management algorithm for dupilumab partial and non-durable responders. *IM* intramuscular

increase in serum creatinine. Twenty-two patients experienced a >30% increase in serum creatinine, although not clinically symptomatic. These patients were found to be significantly older than those with a <30% rise in serum creatinine (41.4 vs 33.8 years of age, $p=0.01$) [9]. Therefore, cyclosporine should be avoided or used with extreme caution and routine laboratory monitoring in older patients, those with underlying renal disease or taking other nephrotoxic agents, patients with poorly controlled or uncontrolled hypertension, and those with electrolyte abnormalities. Cyclosporine can be initiated at 0.5–0.75 mg/kg (a quarter

of the 2–3 mg/kg/day dose used in biologic-naïve patients) divided into twice daily administration with subsequent dose increase as needed. An alternative approach is starting cyclosporine at a higher dose of 1–1.5 mg/kg (half of the 2–3 mg/kg/day dose used in biologic-naïve patients) to control disease activity, and decreasing as tolerated. Once satisfactory improvement is achieved, cyclosporine should be tapered to the lowest possible dose that maintains an adequate clinical response or reduced from daily to weekend-only dosing. Oral cyclosporine weekend dosing at up to 5 mg/kg on Saturday and Sunday as maintenance therapy

Table 1 Proposed dosing for traditional systemic immunosuppressives in dupilumab partial and non-durable responders

Medication	Initial dose	Dose escalation and maintenance	Considerations
Cyclosporine	0.5–0.75 mg/kg ^a divided BID and titrate up to 5 mg/kg divided BID as needed OR 1–1.5 mg/kg ^b divided BID and titrate down	Maintenance with lowest dose that provides satisfactory clinical response OR Decrease from daily to weekend-only dosing (up to 5 mg/kg on Saturdays and Sundays)	Avoid/use with caution in patients with renal disease or hypertension
Mycophenolate mofetil	250 mg BID OR 500 mg BID	Increase by 250 mg every other week as needed (up to 1500 mg BID) OR Decrease as tolerated	
Methotrexate	5 mg weekly PO or SQ OR 10 mg weekly PO or SQ	Increase up to 20 mg weekly OR Decrease as tolerated	IM or SQ have higher bioavailability and less hepatotoxicity than PO Avoid/use with caution in patients with liver disease

BID twice daily, *IM* intramuscular, *PO* oral, *SQ* subcutaneous

^aQuarter of dose used in biologic-naïve patients

^bHalf of dose used in biologic-naïve patients

is relatively safe and has demonstrated success in treatment of AD and psoriasis refractory to topical agents [10–12].

Additional options for systemic immunosuppressive therapy include mycophenolate mofetil and methotrexate. Mycophenolate mofetil can be initiated at 250 mg twice daily with dose escalation by 250 mg every other week as needed, up to 1500 mg twice daily. Methotrexate can be started at 5 mg weekly and increased up to 20 mg weekly in adults, but should be avoided or used with caution in patients with existing liver disease [13]. Alternatively, mycophenolate mofetil or methotrexate may be initiated at a higher dose (500 mg twice daily for mycophenolate mofetil; 10 mg weekly for methotrexate) and tapered down as tolerated. Providers may prefer this approach in cases of more severe or widespread AD when rapid clinical improvement is paramount. Compared with oral administration, subcutaneous or intramuscular methotrexate administration has less first-pass metabolism, improved tolerability with fewer gastrointestinal side effects, and decreased hepatotoxicity [14, 15]. Methotrexate for injection is most commonly available as a 25-mg/mL solution, such that 0.1 mL of solution is equivalent to a 2.5-mg oral tablet [13]. While subcutaneous methotrexate can be self-administered, intramuscular injection requires in-office administration by qualified medical personnel.

If initiation of traditional nonsteroidal systemic immunosuppressives is not possible due to patient preference or comorbidities and an intervention for acute AD exacerbation is required, systemic corticosteroids could be used when absolutely necessary. Intramuscular administration is favored

over oral administration due to slower release, decreased side effects of agitation, hyperglycemia, and hypertension, and less potential for rebound flaring [16, 17]. Although not commonly recommended, low-dose oral prednisone may be used as a last resort at 5–10 mg daily and slowly tapered over a few months to minimize the risk of rebound AD flares. Practitioners must be mindful of the widespread side effects of systemic steroid therapy, with special attention given to gastrointestinal ulcer and osteoporosis prophylaxis. Upon discontinuation of systemic steroids, rebound flaring and symptoms of steroid withdrawal (weakness, fatigue, decreased appetite, abdominal pain, nausea, vomiting, and diarrhea) may occur despite tapering [18].

3 Conclusion

The addition of dupilumab to the AD treatment armamentarium has been a promising development for both AD patients and dermatologists. However, supplemental management strategies are necessary for patients who are PR or NDR to dupilumab. We present additional management approaches for patients who do not achieve the therapeutic endpoint after 16 weeks of dupilumab treatment. Critical components of this management algorithm include continuing dupilumab administration to prevent disease exacerbation and development of drug tolerance, thorough evaluation for potential additional dermatologic diagnoses, and strategic selection of traditional systemic immunosuppressive agents for refractory disease. Although a 2-point reduction in IGA is used as

the metric to distinguish responders from non- and partial responders in this discussion and in dupilumab pivotal trials, evaluation of treatment response should also encompass improvement in pruritus and quality of life. While IGA assessment is relatively simple, it is by no means a comprehensive evaluation tool, and clinicians should determine the adequacy of treatment response on a patient-to-patient basis utilizing IGA as a high-level guide.

We encourage patients, caregivers, and providers to continue to be diligent in their AD treatment regimens and remain hopeful and patient until additional targeted therapies become available. With many new biologics and small molecules in the drug development pipeline [19], we will soon be equipped with a greater selection of targeted systemic treatment options for AD management. Once safety and efficacy data has been established and additional agents are brought to market, patients who experience partial or non-durable responses to dupilumab can begin combination therapy or transition to new targeted therapies. Ongoing partnership between physicians, patients, and their caregivers will help to bridge the gap to new systemic therapeutic options for the heterogeneous population of AD patients. Together, we maintain hopeful optimism that we are entering the renaissance era of AD treatment, with unprecedented breakthroughs on the horizon.

Compliance with Ethical Standards

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