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A Practical Guide for Transitioning from Classical Immunosuppressants to Dupilumab in Atopic Dermatitis

Running Head: Transitioning immunosuppressant to dupilumab in AD

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Abstract:

The treatment of moderate-severe atopic dermatitis (AD) has traditionally relied upon the off-label use of systemic immunosuppressants such as cyclosporine (CsA), methotrexate (MTX), and mycophenolate mofetil (MMF). However, significant side effects may arise due to the less-targeted nature of these immunosuppressant and therefore chronic usage is limited. AD patients taking immunosuppressants are candidates for dupilumab treatment for its desirable efficacy and favorable side effect profile. However, there exists a gap in clinical knowledge on how to transition patients from immunosuppressants to dupilumab. Herein we provide a practical recommendation on tapering of immunosuppressants that complements the onset of dupilumab's clinical effects.

Key Words:

- Atopic Dermatitis
- Dupilumab
- Immunosuppressants
- Transition

Conflicts of Interest:

Vivian Shi is a stock shareholder of Dermveda, has served as an advisor for Sanofi

Genzyme/Regeneron, AbbVie, Novartis, Sun Pharma, Pfizer, Menlo Therapeutics, Burt's Bees,

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Peter Lio has served as an investigator, speaker, advisory board member, and consultant for

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declare.

Atopic dermatitis (AD) is a chronic relapsing inflammatory dermatosis characterized by intense pruritus and rash. Its etiology is complex and influenced by an interplay of genetics, environmental triggers, epidermal barrier dysfunction and imbalanced regulation of the immune system [1]. Immunologically, AD is driven by a skewed T-helper 2 cell response and their cytokines, including IL-4 and IL-13 [2].

Historically, the treatment of moderate-severe AD refractory to topical treatment has relied upon the off-label use of systemic immunosuppressants [3]. These steroid-sparing agents include cyclosporine (CsA), methotrexate (MTX), and mycophenolate mofetil (MMF). They act as broad suppressants of the immune system and their less-targeted nature limits chronic usage as significant adverse effects may arise. Dupilumab is a biologic drug that antagonizes the IL-4 α receptor and blocks the actions of both IL-4 and IL-13 cytokines [4]. Since its approval in 2017, it has remained the only FDA approved systemic treatment for moderate-severe AD aside from prednisone. Many patients who are candidates for dupilumab therapy have had suboptimal response with immunosuppressants. For this cohort, the goal is to strategically transition from the classic immunosuppressants to dupilumab while minimizing the risk of an AD exacerbation. However, the Phase 3 pivotal trials that confirmed dupilumab's efficacy and safety profile required a 4-week washout period for any systemic immunosuppressants prior to starting study interventions. In practice, patients with moderate-severe AD typically are taking immunosuppressants and do not undergo a washout period upon dupilumab initiation. This paper aims to fill the knowledge gap in clinical practice, of how to optimally discontinue immunosuppressants once patients begin taking dupilumab. Herein we propose an approach to tapering immunosuppressants that capitalizes on the growing therapeutic effect of dupilumab during the first 12 weeks of treatment with the biologic. This method assumes that additive

effects exist between the original medication and accumulating dupilumab dose that can be exploited during the transitional period to minimize the chance of AD flare.

Dupilumab Initiation and Clinical Efficacy

The approved dosing of dupilumab in adults consists of a 600 mg subcutaneous loading dose followed by maintenance doses of 300 mg every other week [5]. Dupilumab has a favorable safety profile with conjunctivitis, nasopharyngitis, upper respiratory infection, and injection site reactions most commonly reported. Patients taking dupilumab do not require baseline or maintenance serological testing [5]. In the two phase III pivotal trials (SOLO1 and SOLO2) involving adults with moderate-severe AD, steady-state concentration of dupilumab is achieved by week 16 of treatment [5]. Both Eczema Area and Severity Index (EASI) and Pruritus Numerical Rating Scale (Pruritus NRS) scores demonstrate a steady decrease, nadiring as early as week 12 and reaching steady state by week 16 [6].

Transition Approaches

There is a paucity of literature in AD discussing how to taper immunosuppressants. Most of our knowledge on transition from immunosuppressants to biologics is gleaned from expert opinion in treating psoriasis [7]. Since dupilumab requires 12 weeks to reach its maximum clinical benefit, discontinuing systemic immunosuppressants soon after dupilumab initiation carries the risk of AD exacerbation. We propose that a rational way to optimize transition from classic immunosuppressant to biologic is to continue taking the immunosuppressant while tapering the dose to match the increasing clinical efficacy of dupilumab. There are no known interactions between Dupilumab and MTX, CSA, and MMF, making the risk of concurrent administration safe to our knowledge. Tracking percentage changes in EASI and pruritus NRS is a reasonable

way to estimate the clinical effect of dupilumab relative to its maximum peak effect and may identify when tapering should proceed. Simpson et al. numerically reported the maximum percentage decreases in EASI and pruritus NRS in SOLO1 and SOLO2, and presented graphs depicting the decreases in these scores over time. From this data we are able to extrapolate that dupilumab achieves 50%, 75%, 87.5%, and 90% of its peak clinical efficacy at weeks 3, 5, 8, and 12 of treatment, respectively [6].

Beginning at week three of therapy, the systemic immunosuppressant dose may be halved at each of these time points. This proposed tapering schedule purposefully lags to account for dupilumab's delayed effects and minimize risk of AD flare (Figure 1). It also serves as a simplified schedule for patients that changes doses on the same day of the week to avoid confusion. The above recommendations are made with two assumptions: 1) halving the dosage of traditional steroid-sparing agents will result in halving the effect of the drug and 2) maximum clinical effect of CsA, MTX, or MMF has been achieved prior to initiation of dupilumab.

Cyclosporine Taper

CsA inhibits calcineurin's action in T-cells, preventing the appropriate transcription of IL-2 and stunting T-cell proliferation [8]. The recommended dosing regimen for AD is initiated at 2.5 mg/kg/day with increases every 2-4 weeks to a maximum dosage is 5mg/kg/day until the desired clinical effect is achieved [9]. CsA use is associated with hypertension and blood pressure should be taken at baseline and monitored closely through treatment. Nephrotoxicity typically occurs at doses exceeding those required in the treatment of AD. Nonetheless, serum creatinine and blood urea nitrogen should be taken at baseline and monitored. While CsA provides rapid clinical improvement within two weeks of initiation, its pharmacodynamics upon

discontinuation are largely unknown [10]. Limited literature on CsA tapering in AD warns of high risk of disease relapse with abrupt withdrawal, even if remission has been achieved [11].

For psoriasis patients, an overlap period of 2-8 weeks is recommended during the transition from CsA to a TNF α antagonist or ustekinumab [12]. Outside of transition to biologic, experts recommend tapering CsA after clinical goal is achieved as opposed to stopping abruptly [13]. In the treatment of erythrodermic psoriasis, CsA should be tapered slowly to prevent exacerbation by decreasing 0.5mg/kg/day every 2 weeks [14]. We propose that the tapering schedule for CsA can proceed more quickly than 0.5mg/kg/day when dupilumab is started simultaneously because of dupilumab's high efficacy in reducing AD burden [6]. CsA dose should remain unchanged until dupilumab reaches 50% of its maximum clinical effect at week three. Over the first 12 weeks of dupilumab treatment, the CsA dose is halved three times before discontinuation (Table 1). Patients' blood pressure should be monitored for elevation until CsA is fully discontinued.

Methotrexate Taper

MTX is a metabolite that inhibits dihydrofolate reductase. It prevents proliferation of lymphocytes by preventing DNA replication, and is cytotoxic via increased release of adenosine [15]. For AD patients, MTX is started at 10mg/week and dosed between 10-25mg weekly [16]. It is administered concomitantly with a folate supplement of 1mg daily to decrease nausea and prevent megaloblastic anemia [17]. Pancytopenia, hepatotoxicity, and renal toxicity can occur at even low dosages. Complete blood count, and liver and renal function serologies should be obtained at baseline and monitored regularly during MTX treatment [18]. Female patients starting MTX should have a baseline negative pregnancy test and be counseled on contraception.

In psoriasis treatment, MTX has additive clinical effects with the TNF α antagonist etanercept [19] and phosphodiesterase inhibitor apremilast [20], and overlap with biologics during transition has been shown to be safe [12]. We recommend the same tapering schedule for MTX as for CsA (Table 1). MTX is more difficult than CsA to dose at exactly 25% and 12.5% of dose because it is commonly available only as 2.5 mg tablets. If medication is unavailable in the exact dosage on the tapering schedule, we recommend rounding the dosage upwards to ensure therapeutic coverage. Routine laboratory monitoring to assess for toxicities should continue until the patient is no longer taking MTX. We also recommend continuation of folate supplementation at the initial dosage, as differing folate dosages does not affect incidence of toxicity [17].

Mycophenolate Mofetil (MMF) Taper

Mycophenolate Mofetil (MMF) inhibits inosine monophosphate dehydrogenase in *de novo* purine synthesis, specifically affecting B and T cells as they lack purine recycling mechanisms [21]. The recommended MMF dosing for adults with AD is 1000 mg twice daily [22]. MMF use is most commonly associated with vomiting, diarrhea or leukopenia at the beginning of treatment. Neutropenia or gastrointestinal bleeding can occur with MMF use at near maximum recommended dose of 3g daily [3]. These adverse events are rare, and routine laboratory measurements are generally not required during MMF treatment. MMF is a known teratogen, thus a negative pregnancy test should be obtained in female patients of childbearing potential and they should be counseled on contraception before initiation [23].

Relevant literature on MMF discontinuation and tapering is rarer than for CsA and MTX, perhaps because MMF is not used as frequently in psoriasis treatment. In dermatology, apart from the treatment of AD, MMF is most often used to treat blistering disorders. While we have

not been able to locate any recommendations for safe MMF discontinuation or tapering in treatment of dermatological disease, there is evidence that MMF has been safely and successfully used as an adjunct to rituximab treatment of pemphigus vulgaris [24]. There is a paucity of literature on MMF taper in dermatologic conditions. We propose that a similar tapering schedule for MTX and CsA can be used for MMF. However, in the case of MMF the 25% and 12.5% dosages are exceedingly low; 250mg once or twice daily dosage would not be expected to have appreciable effect. Thus we recommend halving the dosage to 500 twice daily and then discontinuing MMF after the second maintenance dose of dupilumab (Table 1)

In cases where patient non-adherence is a concern, a simplified, more rapid taper could be considered, albeit one that may carry a higher chance for a disease exacerbation. The immunosuppressant could be kept at the same dose upon dupilumab initiation, halving the dose after the second dupilumab injection (2 weeks), and discontinuing once the third dose of dupilumab is given (week 4), when approximately 75% of the dupilumab clinical effect has been noted.

Conclusion

As we enter a new era of AD treatment, a large number of highly targeted therapeutic options are currently under investigation, including biologics that target other cytokines and intracellular mediators involved in the pathogenesis of AD [25]. Protocols for treating partial and nondurable responders [26], transitioning from immunosuppressants to biologics, and from biologic to biologic will become increasingly more pertinent: all with the common goal of maximum clinical benefit while minimizing AD flare and side effects. The above proposal for transitioning from immunosuppressant to dupilumab treatment is the first step in defining best practice. The

pharmacokinetics of immunosuppressant during taper and the resulting pharmacodynamics effects deserve further investigation as we prepare for monumental changes in AD therapeutic landscape.

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Week	Dupilumab Dosing	% of maximum clinical effect of dupilumab	% dosage of Immunosuppressant	Example dosage of Cyclosporin A	Example dosage of Methotrexate	Example dosage of Mycophenolate Mofetil
0	Loading Dose	0	100%	100mg BID	25mg weekly	1000 mg BID
3	After maintenance dose 1	50	50%	50 mg BID	12.5 mg weekly	500 mg BID
5	After maintenance dose 2	75	25%	25 mg BID	7.5 mg weekly	250 mg BID
8	Maintenance dose 3	87.5	12.5%	25 mg 1x daily	5 mg weekly	250 mg 1x daily
12	Maintenance dose 5	90-100%	0%	—————	—————	—————

Table 1. Recommended dosages of systemic immunosuppressants during the 12-week transition to dupilumab.

Figure 1. The proposed taper schedule for immunosuppressants mirrors the changes in dupilumab clinical indices scores.

