2018

Is Dupilumab A Safe And Effective Treatment For Patients With Moderate-To-Severe Atopic Dermatitis?

Alanna M. Viken
Philadelphia College of Osteopathic Medicine

Is Dupilumab A Safe And Effective Treatment For Patients With Moderate-To-Severe Atopic Dermatitis?

Alanna M. Viken, PA-S

A SELECTIVE EVIDENCE BASED MEDICINE REVIEW

In Partial Fulfillment of the Requirements For

The Degree of Master of Science

In

Health Sciences – Physician Assistant

Department of Physician Assistant Studies

Philadelphia College of Osteopathic Medicine

Philadelphia, Pennsylvania

December 15, 2017

Abstract

Objective: The objective of this selective EBM review is to determine whether or not dupilumab is a safe and effective treatment for patients with moderate-to-severe atopic dermatitis

Study Design: Review of three randomized, double blind, placebo control trials between 2014-2016.

Data Sources: Three randomized, double blind, placebo controlled trials were found via EBSCOHost and PubMed.

Outcomes Measured: In all three randomized controlled trials, outcomes measured includes the IGA score. Moderate-to-severe atopic dermatitis is a 3 or 4 on the IGA scale, respectively, while the goal was to get patients to a 0-1 on the IGA scale (indicating clear or almost clear disease state).

Results: Three double-blind, randomized controlled clinical trials evaluated the use of dupilumab 300mg SQ weekly vs. placebo in patients with moderate-to-severe atopic dermatitis. The study done by Beck, et al. showed that 40% of patients improved on an IGA scale from 3-4 to 0-1 compared to 7% in the control group. Simpson, et al. reported that 37% of patients improved to an IGA score of 0-1 compared to 10% in the control group. Thaçi, et al. had 33% of patients in that clinical trial with an IGA score of 0-1 compared to 2% in the control group.

Conclusions: Review of these articles suggests that dupilumab is beneficial in treating patients with moderate-to-severe atopic dermatitis whom failed topical intervention. Long term use of dupilumab needs to be evaluated more thoroughly in long term trials. Concomitant use of dupilumab with topical glucocorticoids also prompts further evaluation in improved patient outcomes.

Key Words: dupilumab, atopic dermatitis

Introduction

Atopic dermatitis is a chronic, relapsing, inflammatory skin disease that is characterized by an up-regulation of type 2 immune responses, impaired skin barrier, and increased *Staphylococcus aureus* colonization.[5] Patients with moderate-to-severe atopic dermatitis can experience intense pruritus, sleep deprivation due to the persistent pruritus, anxiety, and depression relating to their symptoms.[5] These symptoms ultimately lead to a poor quality of life, which stems from the large amount of surface area skin lesions of moderate-to-severe atopic dermatitis can cover.[5] Typically, patients will have exploited topical treatments and have gained little benefit due to the severity of the disease. Systemic treatment options have substantial side effects, such as cyclosporin, thus the need for a safe, long term systemic treatment.[7] This paper evaluates three randomized controlled trials (RCTs) comparing the efficacy of dupilumab as monotherapy vs. placebo in treating moderate-to-severe atopic dermatitis.

Atopic dermatitis affects 3-10% of adults and up to 20% of children.[7] Patients' quality of life declines with moderate-to-severe disease.[7] Adults with moderate-to-severe atopic dermatitis were surveyed via the 2013 National Health and Wellness Survey indicating that $27,164 is spent annually per patient in the treatment of atopic dermatitis and comorbidities.[3] Comorbidities include hypertension, nasal allergies/hay fever, asthma, arthritis, and high cholesterol.[3] This survey included emergency room visits, health care provider visit costs, and hospitalization costs.[3] In adults with mild atopic dermatitis, $21,624 is spent annually, while adults without atopic dermatitis spend $14,619 annually.[3] The survey indicates that adults with moderate-to-severe atopic dermatitis see their provider 7-10 times annually, while they may see necessity for an emergency room visit or hospitalization once yearly.[3]

Similarly to other atopic disorders, Th2 cytokines are prominent in atopic dermatitis, while Th1-mediated and Th22-mediated processes might have an association with the pathogenesis of atopic dermatitis.[7] There have been clinical trials showing IL-4 and IL-13 are key Th2 cytokines that drive atopic diseases such as asthma and chronic sinusitis with nasal polyposis.[7] When IL-4 and IL-13 are blocked, patients have shown significant improvements in their disease states.[7]

Methods used to treat atopic dermatitis include topical glucocorticoids, systemic glucocorticoids, emollients, and calcineurin inhibitors such as tacrolimus.[2] Cyclosporine is an approved systemic treatment for atopic dermatitis in some countries, but has been associated with a marked rebound effect after discontinuation of treatment along with systemic glucocorticoids.[7] There is no systemic immunomodulator approved for the treatment of atopic dermatitis.[7]

The above treatments are currently used in the treatment of atopic dermatitis however, they don't exhibit a lasting or significant effect on adults with moderate-to-severe atopic dermatitis.[7] Due to the mechanism of action of dupilumab in blocking the signaling of IL-4 and IL-13 on asthma patients with moderate-to-severe disease and the similarity in patients with asthma and atopic dermatitis, it has shown effectiveness in moderate-to-severe atopic dermatitis.[7]

Objective

The objective in this systematic review is to determine whether dupilumab is a safe and effective treatment for patients with moderate-to-severe atopic dermatitis.

Methods

Criteria used in the collection of the studies includes adults 18 years or older with moderate-to-severe atopic dermatitis that isn't adequately controlled with topical intervention.

The intervention was dupilumab 300mg subcutaneous injection weekly compared to placebo. The studies evaluated patients based on the IGA scale, a 5-point scale numbered 0-4. 0 indicated clear while 4 indicated severe disease. Types of studies included three randomized, double blind, placebo controlled clinical trials.

All articles were published in the English language in peer reviewed journals and chosen based on patient oriented evidence that matters (POEMs) and the relevance to the clinical question. Studies were found via PubMed and EBSCOHost utilizing key words such as "dupilumab" and "atopic dermatitis". Inclusion criteria involved studies published within the last fifteen years that were randomized, double blind, placebo controlled clinical trials. Exclusion criteria included patients under 18 years of age, prior treatment with dupilumab, and severe comorbidities.

All studies presented dichotomous data, which enabled the calculation of the control event rate (CER), experimental event rate (EER), relative benefit increase (RBI), absolute benefit increase (ABI), and number needed to treat (NNT), relative risk increase (RRI), absolute risk increase (ARI), and number needed to harm (NNH). P values determined significance.

Table 1: Demographics and Characteristics of Included Studies.

Study	Type	# Pts	Age (yrs)	Inclusion Criteria	Exclusion Criteria	W/D	Interventions
Beck[2]	RCT	109 Placebo: 54 Dupilumab: 55	18+	Adults with moderate-to-severe atopic dermatitis not adequately controlled by topical treatment.	Less than 18 years of age, patients who had adequately controlled atopic dermatitis	4	Dupilumab 300mg SQ

Simpson[5]	RCT	671 Placebo: 224 Dupilumab weekly: 223	18+	Moderate-to-severe atopic dermatitis, IGA score of 3 or 4, topical treatment providing inadequate control or was medically inadvisable, chronic atopic dermatitis for 3 years	Less than 18 years of age, patients who didn't qualify via the IGA score of length of time for dx of atopic dermatitis, patients who had adequately controlled atopic dermatitis	6	Dupilumab 300mg SQ
Thaçi[7]	RCT	380 Placebo: 61 Dupilumab: 63	18+	Chronic atopic dermatitis for 3 years, IGA score of 3, atopic dermatitis involvement of 10% or more of BSA, patients with a poor response to topical treatments	Previous treatment with dupilumab, active acute or chronic infections, use of topical treatments for atopic dermatitis within 1 week of baseline, systemic immunosuppressive or immunomodulating drugs within 4 weeks of baseline, significant comorbidities or laboratory abnormalities	30	Dupilumab 300mg SQ

Outcomes Measured

Outcomes measured were in a static fashion with the Investigator's Global Assessment (IGA) score. It is a 5 point scale ranging from 0-4. 0 indicates clear, 1 indicates almost clear, 2 indicates mild disease, 3 indicates moderate disease, 4 indicates severe disease. The IGA score is based on consultation from a physician. The physician observes if the patient has erythema,

oozing, crusting, scaling, and other symptoms of atopic dermatitis and applies the IGA score accordingly.

Results

All three randomized controlled trials were evaluating the effectiveness and safety of dupilumab vs. placebo on adults over the age of 18 with moderate-to-severe atopic dermatitis that was inadequately controlled by other interventions. Patients could never have previously used dupilumab, had comorbidities, or had adequately controlled atopic dermatitis to participate. Comparisons included dupilumab 300mg subcutaneously weekly vs. a placebo. Each study contained dichotomous data to calculate RBI, ABI, NNT, RRI, ARI, and NNH. There was no mention of clinical trial setting, nor compliance with intervention.

The study by Beck et al contained 109 patients diagnosed with moderate-to-severe atopic dermatitis that correlated with an IGA score of 3 or 4, respectively. Patients were randomized into a placebo group (n=54) and a dupilumab group (n=55). Patients in the placebo group received a subcutaneous injection weekly of placebo, while patients in the dupilumab group received a weekly subcutaneous injection of 300mg.[2] All parties were kept blind throughout the 12-week monotherapy trial.[2] 4 out of 109 patients withdrew for various reasons.[2] 1 patient withdrew from the dupilumab group due to an adverse reaction and 3 patients withdrew from the placebo group in the 12-week trial due to adverse reactions.[2] After the trial, there were 54 patients in the dupilumab group and 51 patients in the placebo group.[2]

The study by Beck at al utilized the IGA score to determine the severity of the patients' disease before treatment, on day 29, and after the 12-week trial in both the placebo group and the dupilumab group. All patients in both groups had an IGA score of 3 or 4.[2] At day 29, 2 (4%) patients in the placebo group had an IGA score of 0 or 1 while in the dupilumab group 10 (18%)

patients had an IGA score of 0 or 1.[2] When the trial ended, 4 (7%) patients in the placebo group recorded an IGA score of 0 or 1 and in the dupilumab group, 22 (40%) recorded an IGA score of 0 or 1.[2] These results contain statistical significance (p value <0.001 and a CI of 95%) in patients whom achieved symptom reduction and an IGA score of 0 or 1.[2] The NNT was calculated to be 4, indicating that 4 patients needed to be treated in order to have a favorable outcome.[2] ABI and RBI were also calculated (Table 2).

Simpson et al had a study containing 671 patients with 447 of those patients being evaluated in this systematic review. Patients must have a diagnosis of moderate-to-severe atopic dermatitis or an IGA score of 3-4, respectively.[5] Patients were randomized into a placebo group (n=224) and a dupilumab group (n=223) where the placebo group received a subcutaneous injection weekly and the dupilumab group received a 300mg subcutaneous injection of dupilumab weekly.[5] All parties were kept blind in the 16-week monotherapy trial.[5] 4 patients withdrew in the dupilumab group and 2 patients withdrew in the placebo group due to adverse reactions.[5] At the end of the trial, 218 patients in the dupilumab group and 222 patients in the placebo group remained.[5]

The IGA score was used to determine the severity of the patients' disease states in Simpson et al before the clinical trial began, and then again after 16 weeks of treatment. Initially, all patients had an IGA score or 3-4.[5] After 16 weeks of dupilumab monotherapy, 83 (37%) patients reported an IGA score of 0 or 1 while the placebo group had 23 (10%) patients reported with an IGA score of 0 or 1.[5] These results were statistically significant (p value <0.001) and the calculated NNT value was 4, indicating that in 4 people treated with dupilumab, 1 patient had a favorable outcome.[5] ABI and RBI were also calculated (Table 2).

The clinical trial by Thaçi et al utilized 380 patients diagnosed with moderate-to-severe atopic dermatitis that correlated with an IGA score of 3-4, respectively, 124 of which are evaluated in this systematic review. Patients were randomized into a placebo group (n=61) and a dupilumab group (n=63).[7] Each group received a weekly subcutaneous injection with the dupilumab group receiving a 300mg injection of dupilumab instead of placebo.[7] All parties were kept blind in the 16-week clinical trial.[7] 19 patients from the placebo group withdrew from the study and 11 patients from the dupilumab group withdrew from the study due to adverse reactions, lack of efficacy, lost to follow up, withdrawal by patient, or physician decision.[7] At the end of the trial, 52 patients remained in the dupilumab group and 42 remained in the placebo group.[7]

Thaçi et al utilized the IGA score to determine the severity of patients' atopic dermatitis before the trial began and after the 16-week trial concluded. All patients had an IGA score of 3-4 indicating moderate-to-severe atopic dermatitis when starting the dupilumab or placebo monotherapy.[7] After 16 weeks of monotherapy, 23 (33%) patients in the dupilumab group achieved an IGA score of 0 or 1, indicating clear or almost clear, while 1 (2%) patient in the placebo group achieved an IGA score or 0 or 1.[7] These results were statistically significant (p value <0.0001).[7] The confidence interval was 95% and ranged from 21.95-46.34 likely indicating a small sample size.[7] NNT was calculated to be 4, meaning that for 4 people treated with dupilumab, 1 person has a favorable outcome.[7] ARI and RRI were calculated (Table 2).

Adverse reactions were reported in all three clinical trials. Most commonly seen adverse reactions include: nasopharyngitis, headache, injection site reactions, exacerbations of atopic dermatitis, herpes simplex, conjunctivitis, and upper respiratory infection.[2,5,7] Beck et al reported adverse reactions in 76% of patients in the dupilumab group and in 80% of patients in the

placebo group. Simpson et al reported adverse reactions in 69% of patients in the dupilumab group and 65% of patients in the placebo group. Thaçi et al reported 84% of patients in the dupilumab group and 80% of patients in the placebo group experienced adverse reactions. The RRI, ARI, and NNH were calculated as well (Table 3). The results of the calculations for adverse events signify that patients treated with dupilumab have a 5-6% higher risk of experiencing an adverse event when compared to placebo. The number needed to harm (NNH) indicates the number of patients that are treated with dupilumab to see one adverse reaction.

Table 2: Analysis of outcomes in treatment with dupilumab.

Name of Study	Relative Benefit Increase (RBI)	Absolute Benefit Increase (ABI)	Number Needed to Treat (NNT)
Beck et al	470%	33%	4
Simpson et al	270%	27%	4
Thaçi et al	155%	31%	4

Table 3: Analysis of adverse reactions in treatment with dupilumab.

Name of Study	Relative Risk Increase (RRI)	Absolute Risk Increase (ARI)	Number Needed to Harm (NNH)
Beck et al	5%	4%	25
Simpson et al	6%	4%	25
Thaçi et al	5%	4%	25

Discussion

Atopic dermatitis is a chronic, systemic disease thought to be provoked mainly through Th2 mediated pathways.[8] IL-4 and IL-13 are humoral mediated cytokines that contribute to the disease and are also the cytokines that dupilumab inhibits.[8] Evidence also shows an increase in eosinophils, mast cells, and basophils in those with atopic dermatitis.[8] Their mechanism of action is not fully understood however, they may play a role in skin protection.[8] There is evidence that atopic dermatitis is associated with Th22, Th17, Th1, and epithelial dysfunction, all of which

contribute to disease severity and/or progression.[8] Dupilumab works against atopic dermatitis by inhibiting IL-4 and IL-13 cytokines, effectively reducing the severity of the disease states. Dupilumab can cause patients to experience nasopharyngitis, headache, injection site reactions, exacerbations of atopic dermatitis, herpes simplex, conjunctivitis, and upper respiratory infection.[2,5,7] Patients should report to their provider any history of eye problems, asthma, plans to become pregnant, or plans to receive a live vaccine prior to starting dupilumab.[6] There are no black box warnings reported for this drug, nor studies indicating teratogenicity.[6]

The articles only evaluated adults with atopic dermatitis, although children have a higher risk of developing atopic dermatitis. However, there are no biologic drugs approved for the treatment of atopic dermatitis. Systemic drugs used in children and adults to treat atopic dermatitis both have marked side effects and questionable safety for long term use, thus the need to evaluate dupilumab in adults. Dupilumab is FDA approved as of March 28, 2017.[4] The FDA approved the use of dupilumab either as monotherapy or in conjunction with topical therapies in the treatment of atopic dermatitis.[4] The expected annual cost of dupilumab will be $37,000, which is aligned with other biologic treatment costs for psoriasis.[1] For insurance to cover costs of this drug, there will need to be extra steps for providers and patients.[9] Patients will need to fail topical treatment options, have a prior authorization initiated by their health care provider, and must have a diagnosis of moderate-to-severe atopic dermatitis.[9]

An obvious limitation to all three studies was the age of the sample size. Children were not evaluated in treatment of atopic dermatitis with dupilumab, only adults over the age of 18. There is evidence that most children with atopic dermatitis grow out of the disease by adulthood, but it is estimated that 25% or more of those children with atopic dermatitis will have persistent disease into adulthood. Other limitations to this study include the lack of consistent use of

glucocorticoids with dupilumab. This combination of drugs could prove useful in full management of atopic dermatitis. The lengths of the trials could be much longer, evaluating full treatment of patients in a 12 month timespan rather than a 3-4 month timespan.

Conclusion

There is good evidence to suggest that dupilumab is a successful treatment for patients with moderate-to-severe atopic dermatitis whom have failed topical interventions. All three randomized controlled trials came to a similar conclusion that for every 4 patients treated with dupilumab, 1 patient will have the desired outcome. However, it is worth noting that this has potential to be further improved with concomitant use of topical glucocorticoids. Clinical trials with a combination of dupilumab and topical glucocorticoids should be conducted to evaluate the possibility of improved treatment outcomes with combination therapy.

It is also worth noting that dupilumab is an IL-4 and IL-13 antagonist from the Th2 medicated pathways. As previously mentioned, Th22, Th17, and Th1 mediated pathways also have precedence in atopic dermatitis. Further evaluation of systemic drugs that affect these associated pathways should be prompted to compare treatment effectiveness with the different pathways.

Evaluation also needs to be done in patients under the age of 18 with moderate-to-severe atopic dermatitis whom failed topical interventions. There is evidence to suggest that pediatric-based atopic dermatitis occurs with a different mechanism of action than adulthood atopic dermatitis. Therefore, this prompts evaluation on the disease state of childhood atopic dermatitis. Reviewing these RCTs has shown improved treatment options for patients with atopic dermatitis and provides an invitation for further research into the disease state itself as well as treatment options.

References

1. Anderson J. New drug Dupixent is poised for broad coverage despite high price. *AIS Health*. https://aishealth.com/archive/ndbn042117-03. Published April 21, 2017. Accessed November 10, 2017.
2. Beck LA, Thaçi D, Hamilton JD, et al. Dupilumab treatment in adults with moderate-to-severe atopic dermatitis. *New Engl J Med*. 2014;371(2):130-139.
3. Eckert L, Gupta S, Amand C, et al. The burden of atopic dermatitis in US adults: Health care resource utilization data from the 2013 National Health and Wellness Survery. *Journal of the American Academy of Dermatology*. October 2017. doi:10.106/jaad.2017.08.002.
4. FDA approves new eczema drug Dupixent. *US Food and Drug Administration Home Page*. https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm549078.htm. Published March 28, 2017. Accessed November 10, 2017.
5. Simpson EL, Bieber T, Guttman-Yassky E, et al. Two phase 3 trials of dupilumab versus placebo in atopic dermatitis. *New Engl J Med*. 2016;375(24):2335-2348.
6. Take action with dupixent (dupilumab). https://www.dupixent.com/. Accessed December 10, 2017.
7. Thaçi D, Simpson EL, Beck LA, et al. Efficacy and safety of dupilumab in adults with moderate-to-severe atopic dermatitis inadequately controlled by topical treatments: A randomised, placebo-controlled, dose-ranging phase 2b trial. *Lancet*. 2016;387(10013):40-52.
8. Werfel T, Allam J-P, Biedermann T, et al. Cellular and molecular immunologic mechanisms in patients with atopic dermatitis. *Journal of Allergy and Clinical Immunology*. 2016;138(2):336-349. doi:10.1016/j.jaci.2016.06.010.

9. Will new atopic dermatitis drugs be covered by insurance? *National Eczema Association*. https://nationaleczema.org/insurance-for-atopic-dermatitis-drugs/. Published September 11, 2017. Accessed November 10, 2017.