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Is Apremilast (Otezla) Effective in Reducing Pruritus in Adults over 18 Years Old with Plaque Psoriasis?

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A SELECTIVE EVIDENCE BASED MEDICINE REVIEW

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ABSTRACT

OBJECTIVE: The objective of this selective EBM review is to determine whether or not apremilast (Otezla) is effective in reducing pruritus in adults over 18 years old with plaque psoriasis

STUDY DESIGN: This review is based on three randomized controlled trials (RCTs) published in 2012, and 2015.

DATA SOURCES: Three randomized controlled trials comparing the effectiveness of apremilast to a placebo in reducing pruritus in adults over 18 years old with plaque psoriasis, found using PubMed.

OUTCOMES MEASURED: The outcome studied was improvement of the psoriatic plaques based on reduction in pruritus measured by the Pruritus Visual Analogue Scale (VAS) score and Psoriasis Area and Severity Index (PASI) score.

RESULTS: Papp et al. (2012) showed a significant reduction in pruritus while using 30 mg of apremilast BID ($p<0.0004$). The study by Papp et al. (2015) showed that apremilast resulted in a significantly greater improvement compared to placebo, in reducing pruritus ($p<0.0001$). The study by Paul et al. displayed significant improvements in pruritus when compared to the placebo ($p<0.001$)

CONCLUSIONS: Results of all three studies demonstrate that 30mg of apremilist BID is effective in reducing pruritus in adults with plaque psoriasis. Each study showed improvement of pruritus with minimal side effects.

KEYWORDS: Psoriasis, apremilast, otezla

INTRODUCTION

Psoriasis is an immune-mediated dermatologic disease that presents most commonly as plaque psoriasis.[1] Plaque psoriasis is characterized by thick, pruritic, silvery scales most commonly on the extensor surfaces of the body and the scalp.[2] This paper evaluates three randomized controlled trials (RCTs) comparing the efficacy of apremilast (Otezla) in reducing pruritus in adults over 18 years old with plaque psoriasis to a placebo.

Plaque psoriasis is relevant to patients and the physician assistant profession due to its prevalence and cost to the patients. Psoriasis affects 2% of the world's population. It appears to have a genetic link, as 40% of patients with the condition have a family history of the disorder in first-degree relatives.[3] About 40% of those with the condition can eventually develop psoriatic arthritis.[4] Studies have estimated that the annual expenses of psoriasis can be as high as $25,796 per person.[5] It is also thought that about $135 billion is spent annually in the United States for psoriasis.[5] Approximately 2 million health visits per year occur due to this condition.[4]

The exact cause of psoriasis is unknown, however, it is believed that it is due to hyperproliferation of cells, the immune system, and a genetic link. T-cells begin to attack healthy skin and there also is rapid cell turnover within a few days causing cells to rise and pile on the surface of the skin. There are several presentations such as plaque, inverse, guttate, pustular, and arthritic psoriasis. Plaque psoriasis most commonly presents as sharply defined, erythematous margins with a thick silvery scale that is often pruritic and can range from 1-10 cm in diameter.[3]

Treatment depends on the type, location, and severity of the disease, however, avoiding excessive drying and keeping the area hydrated is essential in all cases.[2] Topical glucocorticoid

steroids, vitamin D analogs, retinoids (methotrexate), or UV light therapy are commonly used treatment choices.

The alternative treatment proposed and studied by this particular review is management with apremilast. Apremilast specifically inhibits PDE4, which is an enzyme that is found in the inflammatory cells and is important in the process of inflammation.[6] When apremilast blocks the PDE4 enzyme, it down-regulates the inflammatory response. Apremilast can be offered as effective treatment with an acceptable safety and tolerability profile and improved convenience compared to current treatment choices.

OBJECTIVE

The objective of this selective EBM review is to determine whether or not apremilast is effective in reducing pruritus in adults over 18 years old with plaque psoriasis.

METHODS

All three studies used in this review required patients that were 18 years or older with moderate to severe plaque psoriasis. The intervention was the implementation of apremilast (Otezla) 30 mg taken twice daily. Comparisons were made between subjects who received the apremiliast to a group receiving a placebo. The specific outcome measured was the improvement of the psoriatic plaques based on the severity of plaques and the reduction in pruritus measured by the Pruritus Visual Analogue Scale (VAS) score and The Psoriasis Area and Severity Index (PASI) score. All three studies were randomized controlled trials (RCTs).

Keywords used when searching for articles consisted of: psoriasis, apremilast, and Otezla. All of the articles were published in English peer-reviewed journals. The articles chosen were researched by the author and obtained through PubMed. The articles were selected based on the type of studies, the relevance to the clinical question being asked, and that the outcomes

of the studies mattered to the patients (were POEMS). Inclusion criteria for selecting these articles included randomized controlled trials that directly benefited the patient and patients that have plaque psoriasis. Exclusion criteria included patients under 18 years old. The statistics that were utilized and reported included: *p*-value, relative benefit increase (RBI), absolute benefit increase (ABI), numbers needed to treat (NNT), relative risk increase (RRI), absolute risk increase (ARI), and numbers needed to harm (NNH). Table 1 displays the demographics and characteristics of the included studies.

Table 1- Demographics & Characteristics of Included Studies

Study	Type	# pts	Age	Inclusion Criteria	Exclusion Criteria	W/D	Intervention
Papp, 2012[6]	RCT	352	≥18 yo	Pts ≥18 yo with moderate to severe plaque psoriasis for 6 months or longer and were candidates for phototherapy or systemic therapy	Pts with hx of or present significant disease, including TB, or HIV infection; had positive screening test for hepatitis B/C; were pregnant or breastfeeding; used topical therapy within 2 wks or phototherapy /systemic within 4 wks	18	Apremilast (Otezla) 10, 20, 30mg BID vs. placebo group
Papp, 2015[7]	RCT, double -blind	844	≥18 yo	Pts ≥18 yo with chronic plaque psoriasis and were candidates for phototherapy or systemic therapy	Other significant or major uncontrolled disease, significant infection, active or hx of incomplete tx of TB, use of active topical agents for psoriasis within 2 weeks, and prolonged sun or UV exposure	53	Apremilast (Otezla) 30 mg BID vs. placebo group
Paul, 2015[8]	RCT, double -blind	411	≥18 yo	Adults aged ≥18 yo with chronic plaque psoriasis for ≥12 months	Significant cardiac, pulmonary, or immunological disease; active TB or hx of incomplete tx of TB, prolonged sun/UV exposure, use of biologics within 12-24 wks, conventional systemic treatments within 4 wks or active topical treatments within 2 weeks	37	Apremilast (Otezla) 30 mg BID vs. placebo group

OUTCOMES MEASURED

The outcomes measured in each of the studies focused on pruritus and the severity of the lesion, both, of which are important to the patient. In all three studies, the Visual Analog Scale (VAS) measured the change in pruritus over time. The Psoriasis Area and Severity Index (PASI) score measured the severity of the lesions. When PASI-75 is achieved, this means that there was a 75% decrease from the baseline score. These scores encompass how much area of the skin is involved and how severe the lesions are. A decrease in severity and the overall area that is affected by psoriasis influences pruritus.[8]

RESULTS

The results were presented in dichotomous form in all three randomized controlled trials (RCTs) that were analyzed. Paul et al. & Papp et al. (2015) were also double blinded studies. All three studies assessed the effectiveness of apremilast (Otezla) 30 mg twice daily in the treatment for reducing pruritus in adults 18 years and older with plaque psoriasis. All three of the studies used a placebo group as the comparative group and randomized the patient population.

Papp et al. (2012), randomized patients to take either 10mg, 20mg, 30mg of apremilast or the placebo for a total of 24 weeks. However, for this review the 30mg vs. the placebo group will be focused on. There were a total of 88 patients receiving the placebo and 88 receiving 30mg of apremilast twice daily and both groups were the same at baseline. The apremilast 30mg was shown to provide rapid relief in pruritus during the initial 2 weeks, and was maintained throughout the entire 24 weeks, when compared to the placebo group. Patients were evaluated at 16 and 24 weeks to assess any improvements. At week 16 the pruritus visual analog scale (VAS) scores were significantly lower with apremilast 30mg ($p<0.004$) compared to the placebo group. At 24 weeks, the mean percentage change from the baseline VAS scores was -41.5 (51.1) in

those taking the apremilast. The PASI-75 at week 16 was achieved in 6% of patients taking the placebo and 41% of patients receiving 30mg of apremilast twice daily. The relative benefit increase (RBI) was calculated to be 5.38% and the absolute benefit increase (ABI) was 35%. This study determined that the number needed to treat (NNT) was 3 patients and the *p*-value was <0.0001.

Papp et al. (2015), randomized 844 patients, 282 to receive the placebo and 562 to receive apremilast. After 16 weeks, approximately a 50% decrease in pruritus severity was noted in those receiving apremilast. The change in VAS score for the apremilast population was -31.5 (32.43) and for the placebo group it was -7.3 (27.08). The VAS score was steady and showed minimal change at 32 weeks. There were 33% of apremilast patients who achieved PASI-75 compared to 5.3% of placebo patients. (95% CI 23.1-32.5% for difference between apremilast and placebo of 27% *p*-value<0.0001). At 32 weeks, patients who originally started on apremilast at baseline were randomized to either stay on apremilast or switch to the placebo. Those that were randomized to stay on apremilast, 61% had PASI-75 response at the end of the study at 52 weeks and 75.3% had 70% or more improvement in PASI score from baseline. The population who started to receive the placebo at 32 weeks, 83.1% lost PASI-75 response. The RBI was shown to be 5.25% and the ABI was 27.8%. NNT was determined to be 4 for those receiving 30mg of apremilast.

In the study by Paul et al., the placebo group of 137 patients was compared to 274 patients who received apremilast 30mg twice daily. Mean improvements from baseline in pruritus and skin discomfort VAS score were significantly greater with apremilast (-33.5) vs. placebo (-12.2) (*p*-value <0.001), with a decrease in approximately 50% from baseline in the severity of pruritus and skin discomfort at week 16. At the conclusion of the study, 52 weeks, the

VAS score showed minimal, if any change from week 16. Analyzing PASI- 75 at week 16, demonstrated that it was achieved in 28.8% of the apremilast patients compared to 5.8% of those in the placebo group. Also at week 16, placebo patients switched to receive apremilast. At week 32, those achieving PASI-50 were re-randomized to either start the placebo or continue with the apremilast. Most of the patients re-randomized to apremilast at week 32 had a PASI-50 response at the end of the study (80%). The RBI was shown to be 3.97% and the ABI was 23%. NNT was determined to be 5 for PASI-75. Table 2 displays the analysis of effectiveness of apremilast in reducing pruritus in plaque psoriasis for all three randomized controlled trials.

Table 2. Analysis of effectiveness of apremilast in reducing pruritus in plaque psoriasis

Study	Placebo	Apremilast	RBI	ABI	NNT	*p*-value/CI
Papp (2012)	6%	41%	5.83%	35%	3	<0.0001/95%
Papp (2015)	5.3%	33%	5.25%	27.8%	4	<0.0001/ 95%
Paul (2015)	5.8%	28.8%	3.97%	23%	5	<0.001

Treatment effects were analyzed and measured by assessing the adverse effects associated with taking apremilast. One of the most common adverse effects experienced in all three studies was that of diarrhea. Most cases of diarrhea were mild to moderate and usually resolved within 1 month. Table 3 shows the percentage of patients whom had diarrhea and the numbers needed to harm (NNH) for the selected studies.

Table 3: Adverse Effects that result in NNH for the selected studies

Study	Placebo	Apremilast	RRI	ARI	NNH
Papp (2012)	5%	14%	1.8%	9%	12
Papp (2015)	7.1%	18.8%	1.65%	11.7%	9
Paul (2015)	5.9%	15.8%	1.69%	10%	10

DISCUSSION

Since plaque psoriasis affects so many people, it is imperative to discuss the efficacy, safety, and realistic application of apremilast as treatment. Apremilast is an oral medication that

is slowly titrated from 10mg in the morning (can be taken on an empty stomach) on Day 1, to eventually 30mg twice daily on day 6.[9] Contraindications include hypersensitivity to apremilast or any ingredient used to create it. In regards to safety, neuropsychiatric effects such as depression and suicide ideation have been reported, thus it is advised to use precaution in patients who have a past medical history of depression. Unexplained weight loss has been seen as well and apremilast should be discontinued if significant weight loss occurs. It is also advised to use with caution in those with renal impairment and dosage reduction is recommended.[10] Apremilast is considered to be a category C medication and has risks and unknowns during pregnancy.

Current pricing in the US is $3,103.46 for 60 tablets of 30mg (1 month's supply).[10] There is currently no generic for this medication. Apremilast is delivered by a specialty pharmacy, that may need to receive prior authorization from the patient's insurance company before they send the prescription.[9] Apremilast is not only used in plaque psoriasis, but is also being prescribed as medical therapy for psoriatic arthritis.

All three RCTs showed limitations within their study. Papp et al. (2012) only had 24 weeks worth of data to analyze, while Papp et al. (2015) and Paul et al. had 52 weeks. All three studies lacked long term data on efficacy and safety. The studies also enrolled a number of obese, white men, thus the results may not be generalizable to a diverse population, other races, non-plaque psoriasis, or other co-morbidities.

CONCLUSION

The three selected studies for this systematic review demonstrated that apremilast (Otezla) is effective in reducing pruritus in adults over 18 years old suffering from plaque psoriasis. The positive changes in patients' VAS score and the amount of patients achieving

PASI-75 when taking 30mg of apremilast twice daily, demonstrates that it is a very useful therapeutic intervention for medical providers to consider when an adult patient is complaining of pruritus due to plaque psoriasis. It is also important to remember that the side effect profile was low in all three studies and that most symptoms resolved within 1 month, thus most patients tolerated the medication and continued with treatment. While evidence provided in these studies supports the use of apremilast 30 mg BID to reduce pruritus, further suggestions to improve studies would be to research the efficacy in patients with a more diverse background, and not limited to obese, white men. The duration of treatment was also short term, thus warranting additional studies to evaluate the long-term effects of apremilast on plaque psoriasis symptom improvement.

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