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Is Tildrakizumab Monotherapy Effective In Treating Moderate To Severe Plaque Psoriasis?

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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
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ABSTRACT

Objective: The objective of this selective EBM review is to determine whether or not tildrakizumab monotherapy is effective in treating moderate to severe plaque psoriasis.

Study Design: Systemic review of three randomized placebo controlled clinical trials published in 2015 and 2017.

Data Sources: Three randomized controlled trials published in peer-reviewed journals comparing the effects of IV or subcutaneous tildrakizumab to a visually matched placebo for the treatment of moderate to severe plaque psoriasis. Data sources were found using the PubMed database.

Outcomes Measured: The reduction of psoriatic lesions following treatment was measured using the Psoriasis Area and Severity Index 75 (PASI 75) through visual evaluation of patients by investigators.

Results: All three studies demonstrated a reduction in psoriatic lesions with the use of tildrakizumab. PASI 75 measured at week 12 or 16 showed an approximate 60% absolute benefit increase with tildrakizumab versus visually matched placebo. This resulted in a NNT of 2 for all studies.

Conclusions: All three studies illustrated that tildrakizumab is effective as monotherapy for moderate to severe plaque psoriasis in adults. While this is true, study sample sizes were relatively small and patient demographics were not representative to the general population. Further studies are needed to compare tildrakizumab to other biological medications that are more widely used.

Keywords: tildrakizumab, psoriasis

INTRODUCTION

Psoriasis is a chronic, inflammatory, hyper-proliferative dermatologic condition that is caused by genetic and/or environmental irritants.¹ There are many different forms of psoriasis with plaque psoriasis being the most prevalent, affecting about 90% of psoriasis patients.² Plaque psoriasis is characterized by well-demarcated, erythematous plaques with a white-silvery scale. The lesions predominately occur on the scalp, elbows, knees, palms, soles, and nails. Depending on the location and extent of the disease, psoriasis may make it difficult for a patient to perform daily tasks or may lead to insecurities regarding their physical appearance.

In addition to the evident rash and scaling of psoriasis, the condition may also impart a financial burden on the patient due to the cost of medications and office visits. While there has not been an estimate released in the recent years, a small US study performed in 2013 with 3,000 participants found that patients with moderate to severe psoriasis and/or psoriatic arthritis spent approximately \$20,000 annually on pharmaceutical and associated medical costs.³ Another study released in 2008 estimated that the annual economic burden of psoriasis in the US was \$11.25 billion.⁴ Little is known of the medical utilization for psoriasis, but a study published in 1996 estimated an average of 1.5 million visits to physician per year for psoriasis.⁵ Psoriasis is believed to affect approximately 2% of the world's population and occurs in most racial groups, affecting males and females equally.² The prevalence and detrimental effects of psoriasis on patients make it necessary for providers to understand the condition and properly treat it.

While the exact cause of psoriasis is unknown, it is known that there is a strong genetic component, and that environmental and behavioral factors play a role. It is also known that psoriasis is a complex immune-mediated inflammatory disorder which causes alterations in both

the adaptive and innate immune systems. These immune cascades lead to the release of cytokines and ultimately keratinocyte hyperplasia in affected areas.

Conventional treatments for the local skin thickening caused by psoriasis include emollients, topical glucocorticoids, vitamin D analogs, topical retinoids, tar shampoo, and anthralin. Phototherapy (UV, NB-UVB) may also be used when topical agents are not sufficient. Severe psoriasis may require the use of systemic medications such as methotrexate, oral retinoids, biologics, or immunosuppressants.

The above treatments are all effective in the treatment of psoriasis. However, each patient reacts differently to medications and the biologic tildrakizumab may prove to be more effective or have less side effects than other options for certain patients. Tildrakizumab is a monoclonal antibody that binds to the IL-23p19 subunit which eventually pairs with the IL-12p40 subunit.⁶ Both of these subunits are overexpressed in psoriasis and together form the heterodimeric cytokine IL-23.⁶ By targeting both subunits, and ultimately more of IL-23, researchers are hoping to more effectively treat psoriasis patients.⁶

OBJECTIVE

The objective of this selective EBM review is to determine whether or not tildrakizumab monotherapy is effective in treating moderate to severe plaque psoriasis.

METHODS

All studies included in this selective EBM review were written in English and published in peer-reviewed journals obtained from PubMed. The keywords used to search these articles included “psoriasis” and “tildrakizumab”. Studies were selected by this author based on their relevance to the clinical question and their inclusion of patient-oriented evidence that matters (POEMs). The inclusion criteria used for this review were randomized clinical trials (RCTs)

published after 2008 that discussed the efficacy of tildrakizumab as monotherapy for adults with plaque psoriasis and evaluated the POEM of interest. Exclusion criteria included studies prior to 2008, studies with subjects under 18 years of age, studies that evaluated tildrakizumab's efficacy with other therapies, and studies that did not assess the POEM of interest.

Three placebo-controlled RCTs with specific populations, interventions, comparisons, and outcomes were selected. All studies focused on adult patients over the age of 18 with moderate to severe plaque psoriasis. The intervention with tildrakizumab through subcutaneous or IV was administered and compared to a visually matched placebo. These results were measured using the Psoriasis Area and Severity Index 75 (PASI 75) to objectively record the reduction of psoriatic lesions following the intervention. PASI is an internationally utilized scale to rate the severity of psoriasis through its distribution, redness, thickness, and scale. PASI 75 is when a 75% reduction of psoriasis is seen in an individual from the beginning to the end of the time period of the trial.

Demographics and characteristics of included studies are outline in Table 1. The statistical significance of the outcomes measured were determined using relative benefit increase (RBI), absolute benefit increase (ABI), numbers needed to treat (NNT), number needed to harm (NNH), and p-value. Outcomes were considered statistically significant if the p-value was \leq to 0.05.

OUTCOMES MEASURED

All three studies measured the reduction of psoriatic lesions using the Psoriasis Area and Severity Index 75 (PASI 75). This was done by investigators who visually evaluated each patient and objectively determined if 75% or more of the psoriasis lesions had cleared from baseline

after a given time period. These findings were compared to placebo at named time periods for the respective studies.

TABLE 1: Demographics and characteristics of included studies

Study	Type	#Pts	Age (yrs)	Inclusion	Exclusion	W/D	Interventions
Kopp, 2015 (1)	RCT	77	18-65	-Healthy adult ≥ 18 -Stable diagnosis -BSA $\geq 10\%$ and PASI ≥ 12 -On therapy: BSA $\geq 10\%$ and PASI ≥ 10	-Recent psoriasis tx: topicals in week, phototherapy in 4 weeks, monoclonal antibodies in 3 months -Contraindications for biologic use - All subjects were otherwise healthy (see Methods of study for details)	12	-Safety -Efficacy of IV tildrakizumab at 10 mg kg ⁻¹
Papp, 2015 (2)	RCT	355	18-82	-Healthy adult ≥ 18 -Diagnosis of psoriasis > 6 months - BSA $\geq 10\%$ and PASI ≥ 12 -PGA of moderate, marked, or severe at baseline	-Contraindication for biologic use -Recent abx, concurrent steroids, any cancer -Prior use ≥ 2 TNF- α without efficacy -Uncontrolled arrhythmias, HTN, DM, or cardiac revascularization within 6 months of screening	16	-Subcutaneous injection of tildrakizumab at 100 mg
Reich, 2017 (3)	RCT	772	18-82	-Healthy adult ≥ 18 with mod/severe psoriasis - BSA $\geq 10\%$ and PASI ≥ 12 - PGA ≥ 3 -Not pregnant and abstain from sex or coverage with contraception	-Contraindication for biologic use -Recent abx -Live vaccination within 1 month -HIV, Hep B/C -Prior malignancy excluding minor skin or CIS of cervix s/p treatment -Admission for cardiovascular event, illness, or surgery within 6 months -Uncontrolled HTN, DM -Prior use of tildrakizumab or IL 23/17 inhibitors or etanercept	28	-Subcutaneous injection of tildrakizumab at 100 mg

RESULTS

Kopp et al.⁶ conducted a 3-part, rising dosage, double-blind, phase I RCT to evaluate the clinical activity, pharmacokinetics, safety, and efficacy of tildrakizumab in subjects with moderate to severe plaque psoriasis. In part 1, patients were randomized to receive IV placebo, or IV tildrakizumab at 0.1, 0.5, 3, 10 mg kg⁻¹ on days 0, 56, and 84. IV medication/placebo were administered over 1 hour. In part 2, after favorable outcomes and limited side effects were seen during part 1, the lower dosages were eliminated and subjects were randomized to receive IV placebo, IV tildrakizumab 3 or 10 mg kg⁻¹ on days 1, 28 and 36. Part 3 was added to explore the efficacy seen at lower dosages during part 1. Data were dichotomous with subjects reaching PASI 75 or not. All subjects were followed with intention to treat analysis with the exception of 3 subjects who did not return after enrollment.

A total of 77 subjects enrolled with 65 subjects completing the study. Two subjects discontinued due to side effects, one on 10 mg tildrakizumab due to convulsions, and the other on placebo due to arthralgia and worsening psoriasis. Another 7 subjects withdrew consent. Regarding safety and tolerability, 81% of subjects reported no adverse event. The most common complaints were headache, upper respiratory tract infection, cough, and nasopharyngitis. There were 11 serious side effects reported by 8 subjects, with convulsions being the only one deemed possibly related to tildrakizumab.

Endpoint efficacy of treatment was evaluated on week 16 using PASI 75 scores. The maximum dosage of this phase 1 trial was analyzed. The PASI 75 response at week 16 was 60% with IV tildrakizumab 10 mg kg⁻¹, compared to 0.0% in the placebo group. This resulted in an ABI of 60%, and a NNT of 2. None of the subjects receiving placebo reached PASI 75, therefore RBI was zero. The mean percentage change in baseline PASI 75 extrapolated from Figure 1 in

the article was approximately 80% for tildrakizumab 10 mg at week 16 for parts 1 and 3 combined.⁶ No p-value was provided. While the article states, “The mean and 95% confidence interval (95% CI) was provided for each treatment group as well as the difference between tildrakizumab and placebo...” no such confidence interval was found.

Papp et al.⁷ conducted a 3-part, double-blinded, parallel-group, dose-finding phase IIb RCT to evaluate safety and efficacy of subcutaneous (SQ) tildrakizumab on adult patients with moderate-severe plaque psoriasis. This study was conducted from November 2010 to June 2012 in 64 sites in the US, Canada, Japan, and Europe. In part 1, subjects were randomized to receive SQ tildrakizumab (5, 25, 100, 200 mg), or placebo on day 0 and week 4. Subjects in part 1 were evaluated on week 16. In part 2, all subjects were then re-randomized based on responder status. They were then either given their current dosage or had their dosage of tildrakizumab increased to 100 mg or 200 mg. Intervention was administered every 12 weeks until week 52. In part 3, patients were no longer receiving intervention, but were instead followed for lasting efficacy until week 72. Considering the preferential re-randomization and lack of a direct control in part 2, only part 1 of the study was evaluated in this review. Data was dichotomous with subjects reaching PASI 75 at week 16 or not. All subjects were followed with intention to treat analysis after a single dose, termed in the article as the “full analysis set”. Subjects who discontinued due to lack of efficacy, or used prohibited medication were considered to have not met PASI 75 at week 16. Subjects who discontinued for other reasons were analyzed at their last recorded PASI value.

A total of 355 subjects were enrolled and randomized, with 353 analyzed in part 1 as 2 subjects were randomized but did not receive treatment. Of the 353, 6 subjects discontinued due to side effects and 1 subject died. Regarding safety and tolerability in part 1, 65% of subjects

reported at least one side effect. The incidence of side effects was similar in all experimental arms including placebo. The most common complaints were headache and nasopharyngitis. Hypertension was the only dose related side effect affecting 9 out of the 308 subjects receiving tildrakizumab compared to the 0 out of 45 subjects receiving placebo. The reporting of serious side effects included 4 subjects in part 1, 14 subjects in part 2, and 5 subjects in part 3. Of these serious side effects, the ones that may have been caused by tildrakizumab included: bacterial arthritis, lymphedema, melanoma, stroke, epiglottitis, and infection of the knee. A 63 year-old gentleman with a history of alcohol abuse died of unknown causes during part 1 of the study. He was dosed at 100 mg tildrakizumab. Autopsy was inconclusive, but a blood alcohol level of 0.275% was noted.

Endpoint efficacy of treatment was evaluated on week 16 using PASI 75 scores. The PASI 75 response at week 16 was 66% for SQ tildrakizumab 100 mg. The PASI 75 for placebo was 4%. This resulted in an RBI of 15.5, an ABI of 62%, and a NNT of 2. A p-value ≤ 0.001 was reported for each tildrakizumab dose vs. placebo. No associated confidence interval was provided.

Reich et al.⁸ conducted three-part, double-blind, parallel, phase 3 RCTs to compare SQ tildrakizumab to placebo or etanercept in adult patients with mild to moderate plaque psoriasis. reSURFACE1 was performed between December 2012 to October 2015 at 118 sites in the US, Australia, Canada, and Japan. In part 1, subjects of both trials were randomized to receive tildrakizumab (100 mg, 200 mg) or placebo on week 0 and week 4. After evaluation at week 12, subjects participating in part 2 were re-randomized to receive treatment every 12 weeks, with all subjects previously on placebo receiving active medication. In part 3, responders and partial responders to tildrakizumab were re-randomized at week 28 to receive treatment every 12 weeks

until week 64. Data was dichotomous with subjects reaching PASI 75 at week 12 or not. All subjects were followed with a full-analysis-set, which included all randomized subjects who received at least one dosage of intervention.

A total of 977 subjects were screened and 772 subjects were randomized into reSURFACE1, with subjects discontinuing part 1 due to the following: 5 side effects, 5 lost to follow-up, 1 lack of efficacy, 4 physicians decision, 1 progressive disease, 1 pregnancy, 2 protocol violations, and 8 participant withdrawals. Regarding safety and tolerability, the most common complaints were nasopharyngitis, URTI, and erythema of injection site. Severe side effects of infections, malignancies, and cardiovascular events were infrequent and similar across all arms of the study.

Endpoint efficacy was evaluated on week 12 using PASI 75 scores. For reSURFACE1, the PASI 75 response was 64% with tildrakizumab 100 mg, compared to 6% in the placebo group. This resulted in an RBI of 9.67, an ABI of 58%, and an NNT of 2. In this trial, the tildrakizumab arm had a significantly higher proportion of subjects who achieved a PASI 75 at week 12 than compared to the placebo group with a $p < 0.0001$. The 95% CI from placebo was 51.0-64.1.

TABLE 2: Treatment effects of tildrakizumab for each RCT

Author	Treatment	RBI	ABI	NNT	P-value	95% CI
Kopp et al.	IV tildrakizumab 10 mg/kg	0	60%	2	--	--
Papp et al.	SQ tildrakizumab 100 mg	15.5	62%	2	≤ 0.001	--
Reich et al.	SQ tildrakizumab 100 mg	9.67	58%	2	< 0.0001	51.0-64.1

DISCUSSION

This systematic review is limited as it only evaluates the results from early trials of tildrakizumab research. In addition, PASI 75 efficacy was evaluated at early endpoints of week 12 and 16 so long-term efficacy and possible tolerance is not demonstrated. The biggest limitations of Kopp et al.⁶ phase 1 study was its small number of subjects and suboptimal dosing. The maximum dosing evaluated was IV tildrakizumab 10 mg because safety and tolerability of the new drug was a concern. With only 77 participants, and most of them being white males, the study does not fully evaluate tildrakizumab's effect on the general population. Of concern, no confidence interval or p-value was provided, reducing the ability to determine precision of the provided data. While this does raise some suspicion, the data itself is supportive of even suboptimal dosage of tildrakizumab 10 mg making a positive effect on psoriasis patients with a NNT of 2.

Papp et al.⁷ had a larger sample size of 353 randomized patients. Most of the subjects were white (82%) and male (76%), raising concern for tildrakizumab's effect on a more diverse population. Although a confidence interval was not reported, a statistically significant p-value ≤ 0.001 was reported and supports the efficacy of tildrakizumab 100 mg with a NNT of 2. In general, this study illustrates the dose-dependent efficacy of tildrakizumab and its tolerability. Reich et al.⁸ provided a little more diversity in reSURFACE1 with a representation of Asians, but still lacks gender and more extensive racial inclusion. The reSURFACE trial encompassed a bigger sample size, provided a statistically significant p-value < 0.0001 , and had a relatively narrow 95% confidence interval compared to placebo. This supports tildrakizumab's efficacy as monotherapy.

In all three studies, re-randomization was done through different parts of the trials and should be taken into consideration when making comparisons. Direct comparisons of these three studies cannot easily be made as different modes of administration were used (IV, SQ), different dosage of medication was used, and efficacy was measured at different time periods (week 12, week 16). Tildrakizumab's efficacy was only evaluated after 12-16 weeks of treatment, further research is needed to determine long term side effects and efficacy, the possibility of tolerance or diminished effect, and efficacy in genders and ethnicities. Research is also needed to compare tildrakizumab to leading therapies that are already on the market. Combination therapy with tildrakizumab and other therapies may also prove to be beneficial to patients. Despite these differences and limitations all three double-blind, RCTs reported a NNT of 2 and showed a statistically significant reduction of psoriatic plaques with the use of tildrakizumab.

CONCLUSION

All three studies illustrate that tildrakizumab is effective as monotherapy in adults with moderate to severe plaque psoriasis. While no new trials have been performed, additional evaluations of the above trials have been performed. The reSURFACE trials were extended to evaluate patient tolerance and efficacy after two years, with positive results.⁹ In addition, a retrospective analysis of patients with psoriasis of the genitalia reported improvement in their quality of life and personal relationships after treatment with tildrakizumab.¹⁰ Tildrakizumab has only recently been approved for commercial use, but as it is more widely used in the outpatient setting, more population inclusive information is likely to be reported. Further research is needed to directly compare the efficacy of tildrakizumab to other well-established biologics and therapies. Research regarding efficacy and adjunctive therapies with tildrakizumab is important as many patients have tried many medications, including biologics and still have refractory

psoriasis. With efficacious results in trials, tildrakizumab may be able to provide long awaited relief to someone who has been fighting psoriasis for many years. Although there are still unknowns regarding the medication, tildrakizumab is already proving to be life changing for several patients.

REFERENCES

1. Papadakis MA, McPhee SJ. *Current Medical Diagnosis & Treatment*. 57th ed. New York, NY: McGraw-Hill Education; 2018.
2. Kelly-Sell M, Gudjonsson JE. *Therapy for Severe Psoriasis*. Philadelphia: Elsevier; 2017. <https://www-clinicalkey-com.ezproxy.pcom.edu/#!/content/book/3-s2.0-B9780323447973120018>. Accessed September 29, 2018.
3. Lee S, Xie L, Wang Y, et al. Evaluating the effect of treatment persistence on the economic burden of moderate to severe psoriasis and/or psoriatic arthritis patients in the U.S. department of defense population. *J Manag Care Spec Pharm*. 2018 Jul;24(7):654-663. doi: 10.18553/jmcp.2018.24.7.654
4. Fowler JF, Duh MS, Rovba L, et al. The impact of psoriasis on health care costs and patient work loss. *J Am Acad Dermatol*. 2008;59(5):772-780. doi: <https://doi.org/10.1067/mjd.2002.119669>
5. Stern RS. Utilization of outpatient care for psoriasis. *J Am Acad Dermatol*. 1996;35(4):543-545. doi: [https://doi.org/10.1016/S0190-9622\(96\)90676-3](https://doi.org/10.1016/S0190-9622(96)90676-3)
6. T, Riedl E, Bangert C, et al. Clinical improvement in psoriasis with specific targeting of interleukin-23. *Nat Int J Sci*. 2015;1(1):222-226. doi: <https://doi.org/10.1038/nature14175>
7. Papp K, Thaci D, Reich K, et al. Tildrakizumab (MK-3222), an anti-interleukin-23p19 monoclonal antibody, improves psoriasis in a phase IIb randomized placebo-controlled trial. *Br J Dermatol*. 2015;173(4):930-939. doi: <https://doi.org/10.1111/bjd.13932>
8. Reich K, Papp K, Blauvelt A, et al. Tildrakizumab versus placebo or etanercept for chronic plaque psoriasis (reSURFACE 1 and reSURFACE 2): results from two randomised controlled, phase 3 trials. *Lancet*. 2017;390(10091):276-288. doi: [https://doi.org/10.1016/S0140-6736\(17\)31279-5](https://doi.org/10.1016/S0140-6736(17)31279-5)
9. Safety and tolerability of tildrakizumab, an anti-interleukin-23p19 monoclonal antibody, in patients with chronic plaque psoriasis over two years of treatment: results from long-term extensions of two phase III clinical studies (reSURFACE 1 and reSURFACE 2). *J Am Acad Dermatol*. 2018;79 (3, Supplement 1):AB251. doi: <https://doi.org/10.1016/J.JAAD.2018.05.998>
10. Effect of tildrakizumab on personal relationships in patients with moderate-to-severe chronic plaque psoriasis. *J Am Acad Dermatol*. 2018;79:AB116. doi: <https://doi.org/10.1016/J.JAAD.2018.05.493>