12-2016

Does Adalimumab Effectively Treat Moderate to Severe Chronic Plaque Psoriasis in Adults?

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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 Science – Physician Assistant

Department of Physician Assistant Studies
Philadelphia College of Osteopathic Medicine
Philadelphia, Pennsylvania

December 16, 2016

ABSTRACT

OBJECTIVE: The objective of this EBM review is to determine whether or not "Does adalimumab effectively treat moderate to severe chronic plaque psoriasis in adults?"

STUDY DESIGN: This review is based on two randomized controlled trials and one retrospective study. The studies compared the efficacy of adalimumab in reducing the body surface area affected by plaque psoriasis.

DATA SOURCES: All articles used in this review are peer reviewed journals, published in English, and found using PubMed and Ebscohost.

OUTCOMES MEASURED: For all studies, the effectiveness of adalimumab on moderate to severe plaque psoriasis was evaluated using Psoriasis Area Severity Index (PASI) and Physician's Global Assessment of hand and/or feet (hfPGA).

RESULTS: All studies concluded that adalimumab used as monotherapy, or in combination with topical calciptriol/betamethasone proved to be effective in treating moderate to severe chronic plaque psoriasis.

CONCLUSIONS: ADA + C/B resulted in more rapid improvement during the first four weeks of treatment vs. ADA monotherapy. There was no statistical difference in the PASI 75 response at week 16 but there was statistical significance in the PASI 90 response. Regardless of patient demographics at baseline, ADA proved to be effective. All treatment regimens were well tolerated.

KEY WORDS: Adalimumab, psoriasis, biological therapy

INTRODUCTION

Psoriasis is a chronic, relapsing, inflammatory skin condition that varies in severity and body surface area (BSA) affected. It can manifest from a few localized lesions to complete body coverage. Furthermore it can primarily involve the hands, feet, fingernails and toenails[1.] The plaque type of psoriasis is the most common, although several clinical variants of psoriasis are documented. The pathophysiology of plaque psoriasis is suggested to be immune with pathology occurring in both the epidermal and dermal layers of the skin[1.] It is characterized by sharply defined red plaques covered with silvery scales. It is often asymptomatic, but itching may occur and can be severe[2.] Plaque psoriasis occurs worldwide, and its prevalence varies with race, geography and environmental factors such as sun exposure, trauma, smoking and alcohol consumption. However, family history has had the largest affect on predicting disease occurrence[2.]

To Physician Assistants who practice in general medicine and dermatologic specialties, it is a common condition seen affecting 1-3% of the population in the United States[1, 2.] Furthermore, plaque psoriasis treatment estimates an annual cost of $11,029 and $26,708 for patients treated with conventional systemic agents and biologics respectively[3.] There is not an exact estimate available for the amount of health care visits per year for the treatment of plaque psoriasis, but the annual treatment cost across the United States is estimated at $11 billion dollars[3.]

Plaque psoriasis is a well-known and studied pathology; however, as stated previously, the exact pathophysiology is only suggested to be immune mediated. The exact cause remains a focal point of research. Psoriasis impacts patients both physically and psychologically. Patients report a reduction in physical and mental function

comparable to that seen in diseases such as cancer, arthritis, heart disease and depression leading to marked impairment in quality of life[4.] The inflammatory process of psoriasis is linked to a variety of comorbidities such as arthritis, cardiovascular complications, malignancies, depression, anxiety, and obesity[2, 4.] Psoriatic arthritis is a chronic inflammatory arthropathy often associated with psoriasis affecting between 20% and 30% of patients with psoriasis[4.] One recent population based cohort study confirmed that patients with psoriasis are at an increased risk of myocardial infarction and stroke with an increase of 6.2% in the 10 year risk rate compared to the normal population[4.] Additionally, psoriasis patients are an increased risk to melanoma and non-melanoma skin cancers. The co-morbidities of psoriasis not only impact the patient's daily life in the short term but prolonged disease may result in cumulative impairment of many facets of life including financial status, professional careers, and reduced life expectancy[4.]

There are a variety of therapeutic options available in the treatment of psoriasis and are chosen according to the extent of BSA affected, and the presence of other findings such as associated arthritis. In limited disease affecting less than 10% BSA, high to ultra-high potency topical corticosteroids (Clobetasol, Betamethasone) are the mainstay of treatment. The addition of a Vitamin D analog such as calcitriol ointment may be indicated in limited disease. In moderate disease affecting 10-30% of BSA, patients are frequently treated with UV phototherapy. Systemic agents such as methotrexate and cyclosporine may be indicated as well. Established systemic therapies are typically indicated if the disease is severe or refractory to topical treatment[1, 2,4.] Applicable to this review, tumor necrosis factor (TNF) inhibitors such as adalimumab

(ADA) has been approved in the United States for moderate to severe chronic plaque psoriasis.

The method proposed and studied by this particular review is treatment with subcutaneous ADA. The injectable TNF inhibitor is used as mono-therapy in hopes that inhibiting a major inflammatory mediator will improve the erythematous, scaly, itchy lesions and BSA affected by moderate to severe chronic plaque psoriasis.

OBJECTIVE

The objective of this EBM review is to determine whether or not ADA effectively treats moderate to severe chronic plaque psoriasis in adults.

METHODS

Two double blind, randomized, placebo control trials, and one retrospective study were included in this EBM review. The studies were selected based on several criteria including population, interventions used, comparison groups, and outcomes measured. In all three studies, the population studied were patients 18 years of age or older with a history of moderate to severe plaque psoriasis with a baseline Psoriasis Area Severity Index (PASI) greater than or equal to 10 or a baseline of at least 3 on the Physician's Global Assessment of hand and/or feet (hfPGA).

For all reviewed studies, the intervention applied was 40 mg of subcutaneous ADA administered every two weeks. All three studies compared the effects of ADA to the placebo with the outcomes measured based on the reduction of baseline PASI and hfPGA scores, and adverse drug reactions in regards to patient safety during trials.

Articles were researched by the author of this review via Ebscohost, and PubMed databases and were selected based on their relevance to the clinical question. The

outcome measured included patient oriented evidence that matters (POEMS). All three articles were written in the English language between 2010 and 2013, and published as peer reviewed journals. Key words entered in the databases included “adalimumab”, “psoriasis”, “treatment outcomes”, and “biological therapy”.

The studies selected for this EBM review included the following inclusion criteria: all studies were a form of primary research (RCTs, retrospective studies, cohort studies etc.), all included POEMS, and all evaluated the efficacy of ADA on moderate to severe chronic plaque psoriasis as an outcome measure. The exclusion criteria included patients under the age of 18 years, those with mild disease (PASI < 3), nail psoriasis, and patients who had psoriasis on the hands and feet only. If a patient had lesions on the hands and feet, evidence of psoriatic disease had to identify in at least one other cutaneous region to be included in this study.

Poulin et al.[1] excluded all patients who have been previously treated with ADA, and Thaci et al.[5] excluded patients who had been treated with ADA or calcipotriol/betamethasone (C/B) two weeks prior to baseline study visits. Furthermore, patients were excluded if treated with systemic or topical corticosteroids within 4 weeks and 2 weeks respectively. The statistics used in these three trials included Control Event Rate (CER), Experimental Event Rate (EER), p-value, Numbers Needed to Treat (NNT), Relative Benefit Increase (RBI), and Absolute Benefit Increase (ABI).

Table 1: Demographics and Characteristics of Included Studies

Study	Type	#Pts	Age (yrs)	Inclusion Criteria	Exclusion Criteria	W/D	Interventions
Poulin[1]	Double blind RCT	72	18+	Adult (18+) men and women	-Pts <18 y/o. -Pts with nail psoriasis. Previous tx	9	ADA 40mg SQ every 2 weeks

				with MSPP for at least 6 months and a baseline score of 3 on hfPGA.	with ADA. Palmoplantar pustulosis or other active skin infection.		
Thaci[4]	Double blind RCT	730	18+	-chronic plaque psoriasis for at least 6 months. PASI >10 and >10% BSA affected. -Failure therapy with another biologic or systemic	Prior ADA tx, topical C/B therapy 2 wks prior to baseline study. Tx with systemic or topical steroid 4 and 2 wks prior, systemic disease that could alter tx (TB, CA, HCV)	0	ADA 80 mg week 0, 40mg every other week from week 1-15
Sanchez[5]	Retrospective study	84	18+	PASI >3, psoriatic arthritis, nail psoriasis.	PASI <3 if tx prior with topical drugs	0	ADA 40 mg SQ every 2 weeks.

OUTCOMES MEASURED

All three studies evaluated the effects of patient baseline characteristics on efficacy of ADA treatment of chronic cutaneous plaque psoriasis. In Poulin et al.[1,] patients with moderate to severe plaque psoriasis of the hands and feet with at least one other cutaneous lesion were randomized 2:1 to ADA or placebo during the 16 week, double blind period. The primary endpoint was percentage of patients achieving an hfPGA of clear/almost clear at week 16. In the 16 week randomized, vehicle controlled

study conducted by Thaci et al.[5], patients were randomized in a 1:1 ratio to receive ADA with calcipotroil hydrate plus betamethasone dipropionate topical ointment (C/B) or an identically supplied and formulated drug-free vehicle. The primary goal was 75% improvement from baseline in the PASI at the conclusion of the study. Sanchez-Regana et al.[6] performed a retrospective study on 84 patients with moderate-severe chronic psoriasis between January 2006 and January 2009. The primary endpoint of the retrospective study was to evaluate the patients who achieved 75% improvement in PASI using ADA compared to classical treatment at 24 weeks.

RESULTS

All studies were performed using the methods outlined above. In the study conducted by Poulin et al.[1], 72 patients were analyzed. 49 patients received ADA and 23 received placebo. Due to investigator non-compliance at one study center, all 9 patients at that center were excluded from all analysis. Post hoc analyses reported in this study included age, gender, weight, disease distribution and disease duration. A significantly greater percentage of ADA treated patients achieved an hfPGA score of clear/almost clear at week 16 compared to patients treated with placebo ($P = 0.014$) outlined in Table 2. The study concluded that effectiveness of ADA treatment was similar in all age groups and gender. However, patients who weighed less than 88 kg had a significant clinically greater hfPGA response (38.1%) compared to patients greater than 88 kg (25.0%) [1.] Interestingly, patients treated with ADA demonstrated improvement in both shorter and longer duration psoriasis but patients with longer duration disease (>4.7 years) showed a better hfPGA response (40%) compared to shorter duration patients (20.8%) [1.]

Table 2: Efficacy of ADA on Hand and Foot Psoriasis with Evidence of Cutaneous Disease

		Relative benefit increase (RBI)	Absolute benefit increase (ABI)	Number needed to treat (NNT)
Proportion of patients having symptom improvement with placebo (CER)	Proportion of patients having symptom improvement with ADA (EER)	$\frac{\text{EER- CER}}{\text{CER}}$	EER - CER	1/ABI
(4.3%) 0.043	(30.6%) 0.306	6.11	0.263	4
			P = 0.014	

In the Thaci et al.[5] study, a total of 730 patients participated with 366 patients receiving ADA + C/B and 364 patients receiving ADA + vehicle. Initially, PASI responses were higher in the combination therapy (40.7%) compared to ADA mono-therapy (32.4%) after four weeks (P = 0.021) [5.] After week 4, the trend was towards higher response rates with ADA mono-therapy, with no statistical difference in the PASI 75 response at week 16 (64.8% for ADA + C/B, 70.9% for ADA, P = 0.086) [5.] Interestingly, at week 16, patients receiving ADA as mono-therapy achieved PASI responses of 90% improvement (50%) compared to ADA + C/B (38%, P =0.002) [5.] Table 3 summarizes the efficacy of the Thaci et al.[5] study in patients who achieved PASI 90.

Table 3: Efficacy of ADA with Topical C/B compared to ADA mono-therapy

		Relative benefit increase (RBI)	Absolute benefit increase (ABI)	Number needed to treat (NNT)
CER	EER	$\frac{\text{EER- CER}}{\text{CER}}$	EER - CER	1/ABI
(38.8%) 0.388	(50%) 0.50	0.289	0.112	9

	p-value = 0.002

In the Sanchez-Regana et al.[6] study, 84 patients with moderate to severe psoriasis where reviewed in retrospective form. They concluded that the rate of response to treatment in patients with cutaneous disease achieved a PASI 75 with ADA therapy (80%) compared classical treatment (53.1%) at 24 weeks (P = 0.01). Table 4 summarizes the effectiveness of ADA compared to classical treatment of plaque psoriasis.

Table 4: Efficacy of ADA Therapy for Moderate-Severe Plaque Psoriasis

		Relative benefit increase (RBI)	**Absolute benefit increase (ABI)**	**Number needed to treat (NNT)**
CER	EER	$\frac{\text{EER- CER}}{\text{CER}}$	EER - CER	1/ABI
(53.1%) 0.531	(80%) 0.80	0.51	0.269	4
			P < 0.01	

DISCUSSION

The Poulin et al.[1] study demonstrated that patient demographics and disease characteristic such disease duration did not effect the efficacy of ADA for the treatment of moderate to severe plaque psoriasis. All patients demonstrated improved responses following ADA therapy, but greater response to treatment was seen in patients that had longer disease duration and lighter body weight. The NNT is calculated to determine the number of patients that needed to receive ADA in order to benefit one patient. Only 4 patients needed to be treated to have one with symptom improvement compared to

control. The major limitation of this study was patient sample size. In the Thaci et al.[5] study, greater efficacy at week 16 was not significant with the combination of ADA and topical C/B compared to ADA mono-therapy. However, since there was statically significant improvement at week 4 using the ADA combination therapy, this suggests that combination therapy may be useful when a rapid response is warranted. Alternatively, both therapies were effective in achieving a PASI 75, but ADA monotherapy was superior in attaining PASI >75 when compared to combination therapy. The author of this review elected to use data representing a PASI 90 due to its statistical significance (P = 0.002) compared to PASI 75 data (P = 0.086). Thaci et al. identified that patient non compliance may have impacted their study findings. The Sanchez-Regana et al.[6] retrospective study found that biological therapy (adalimumab, infliximab etc.) were most effective in treating both cutaneous and nail psoriasis especially in moderate to severe disease. Furthermore, biologic therapy was effective in treating associated comorbidities such has psoriatic arthritis. The major limitation to the Sanchez-Regana et al. study was that it was a retrospective study.

CONCLUSION

Psoriasis has a negative impact on patient quality of life due to its visibility and associated comorbidities. Based on this EBM review, it can be concluded that ADA is effective in treating moderate to severe chronic plaque psoriasis in adults. All three studies noted that treatment regimens were well tolerated with minimal adverse reactions. Additionally the Thaci et al. study concluded that adjunctive topical therapy with a TNF inhibitor can be a safe and effective treatment option in patients who have moderate to severe plaque psoriasis. Future studies may be warranted to investigate the effects of

using a TNF inhibitor to treat the associated comorbidities of psoriasis such as psoriatic arthritis, malignancies, and heart disease. Although ADA was deemed safe in the research conducted for this review, adverse effects related to long-term application of ADA beyond 16 weeks may warrant investigation due to the drugs ability to eliminate an important inflammatory marker of our innate immune system.

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