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Is Monotherapy Treatment of Etanercept Effective Against Plaque Psoriasis?

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Abstract

Objective: The objective of this systematic review is to determine whether or not monotherapy treatment of etanercept is effective against plaque psoriasis.

Study Design: Review of three English language primary randomized controlled trials published 2007-2008.

Data Sources: Randomized, controlled clinical trials comparing etanercept to a control group were found using OVID, MEDLINE, and Cochrane database.

Outcome Measured: Disease improvement and Adverse Effects (headache). Disease improvement was measured using the Physician's Global Assessment (0=clear, 5=severe) and the Psoriasis Area and Severity Index (0 = no disease, 72 = maximal disease). Adverse effects (headache) were measured using the Common Toxicity Criteria of the National Cancer Institute.

Results: Three randomized controlled trials were included in this review. Etanercept 50 mg QW (van de Kerkhof et al) demonstrated greater efficacy than 50 mg BIW (Tyring et al and Moore et al) when etanercept was shown to improve plaque psoriasis. Although the incidence of adverse effects was not frequent, headache was more commonly experienced in the etanercept group than the control group.

Conclusion: The results of the randomized controlled trials reviewed demonstrated that etanercept 50 mg QW was more effective than 50 mg BIW in improving plaque psoriasis. This should continue to be used as the starting dose in the treatment of plaque psoriasis. The relative low incidence of adverse effects encourages its use in treating plaque psoriasis. Further studies should be done accounting for patient compliance in administering the drug.

Key Words: Plaque Psoriasis, Etanercept, Enbrel

Introduction

Plaque psoriasis is the most common type of psoriasis, affecting approximately 1-5% of the population in the United States.[1] It commonly affects individuals from 16-22 years and again from 57-60 years. Plaque psoriasis is a papulosquamous disease defined by erythematous plaques with a silvery scales. These patches typically involve the extensor surfaces (elbows and knees), lower back, scalp, and nails.[2] The impact of psoriasis on patient's lives is substantial, including potential inability to work, discrimination, financial burden, and depression.[1] Cost for patients to treat plaque psoriasis varies depending on disease severity. Topical treatments range from $9 to $354. Biologic therapies range from $8,400 to $22,112. The cost of etanercept is $20,700 (60 doses) for one year of continuous treatment.[3]

Treatment of plaque psoriasis focuses on the improvement of the plaques not the disappearance of them due to its chronic nature. The most effective treatment initially is the combination of steroids and calcipotriene, a vitamin D derivative. However steroids must be used intermittently due to their side effects. If the psoriasis is limited to the scalp, first line management is antidandruff shampoo. If patients do not respond to these treatments or have plaques that cover more than 20% of their body surface area, then light and systemic therapy is recommended. Light therapy involves UVB phototherapy and ultraviolet A (UVA) photochemotherapy. Systemic medications include retinoids, methotrexate, cyclosporine, hydroxyurea, and immunomodulator drugs (i.e. etanercept).[3]

Plaque psoriasis is a T cell- mediated autoimmune disorder. Plaques occur due to T cells attacking healthy skin cells by mistake. The process begins when an environmental factor induces T cells to produce cytokines. Cytokines stimulate keratinocyte proliferation and

production of antigenic adhesion molecules in the dermal blood vessels. These molecules further stimulate T cells to produce cytokines, keeping the cycle going.[3]

As described above, plaque psoriasis is an immune-mediated dermatologic condition. It has often been associated with increased levels of TNF, a proinflammatory cytokine, concluding that a TNF inhibitor would be most effective in treating plaque psoriasis.[1] Etanercept is a soluble TNF receptor that has be approved by the FDA for treatment of various inflammatory disorders, including moderate to severe rheumatoid arthritis (RA), psoriatic arthritis, ankylosing spondylitis, and moderate to severe plaque psoriasis.[1]

Objective

The objective of this systematic review was to determine whether or not "Is monotherapy treatment of etanercept effective against plaque psoriasis?". Recent studies have suggested that etanercept may be safer and more effective than other drugs currently being used.

Methods

All three trials used met the following criteria. Participants had to be age > 18 years of age with stable, active psoriasis covering ≥ 10% of body surface area. The intervention used was subcutaneous injections of etanercept. The treatment group receiving etanercept injections were compared to those receiving a control treatment. Outcomes measured were the reduction in disease severity and adverse effects (headache), which are patient oriented evidence that matters (POEM). The types of studies used were the randomized controlled trials.

Tyring et al randomly assigned patients to receive subcutaneous injections of placebo or 50 mg of etanercept BIW for first 12 weeks. After the 12 weeks, all continuing patients received 50 mg etanercept BIW in an open-label fashion. Patients were trained on giving the injections at home.[4] Moore et al had two groups, continuous and interrupted therapy that were randomly

assigned. During the first 12 weeks, all patients received 50 mg twice weekly. The continuous group received 50 mg QW for an additional 12 weeks. At week 12, responders in the interrupted group discontinued therapy and upon relapse reinitiated treatment.[5] Van de Kerkhof et al assigned patients to receive subcutaneous injections of placebo or 50 mg etanercept QW for 12 weeks, in this double blind phase study. After 12 weeks, all patients entered an open-label phase until 24 weeks.[1]

Key words used in the literature search were plaque psoriasis, Etanercept, and Enbrel. All articles were published in the English language in peer review journals after the year of 2005. Literature searches occurred via OVID and Medline using Cochrane databases. Articles were selected based on importance of outcomes to the patient (POEMS). Studies that were included were those that were randomized, controlled and based on patient oriented outcome. Those excluded were studies that included patients under the age of 18 and body surface index $\leq 10\%$. Statistics utilized in these studies was p-values, relative risk reduction (RRR), absolute risk reduction (ARR), numbers needed to treat (NNT), and numbers needed to harm (NNH).

Outcomes measures were those of patient oriented evidence that matters. Disease improvement was measured using the Physician's Global Assessment (0 = clear, 5 = severe); and Psoriasis Area and Severity Index (0 = no disease, 72 = maximal disease). Adverse effects (headache) were measured using the Common Toxicity Criteria of the National Cancer Institute. Table 1 demonstrates the demographics included in the studies.

Table 1: Characteristics of Studies Included for Analysis of Etanercept in the Treatment Of Plaque Psoriasis

Study	Type	# Pts	Age (yrs)	Inclusion Criteria	Exclusion Criteria	W/D	Interventions
Tyring, 2007 (4)	Randomized, double blind, controlled	618	Mean age = 45.6	-At least 18 years of age -Active, stable plaque psoriasis involving ≥ 10% of the body surface area (BSA) -Minimum PASI score of 10 -Received at least 1 previous phototherapy or systemic therapy or was a candidate -Adequate hematologic, renal, and hepatic function	-History of psychiatric disease that would interfere -Skin conditions other than psoriasis that would interfere -Had active gestate, erythrodermic, and pustular psoriasis screening -Can not have received psoriasis therapy or PUVA for 4 weeks before, corticosteroids 2 weeks before, or immunomodulators any time	154	- Efficacy of 50 mg of Etanercept BIW for 12 weeks vs. Placebo - Safety of 50 mg of Etanercept BIW for 12 weeks vs. Placebo
Moore, 2007 (5)	Randomized, open-label	2546	Mean age = 45.4	-Pts 18 years or older with stable, active plaque psoriasis involving ≥ 10% BSA	-Any grade 3 or 4 adverse event or infection within 28 days before screening, or between screening and study drug initiation -Other skin conditions that would interfere -PUVA, oral retinoids, alefacept, or anthralin within 14 days of drug initiation -Prior exposure to TNF inhibitor -History of TB	345	-Interrupted therapy of etanercept 50 mg BIW (over 24 weeks) vs. Continuous therapy of 50 mg BIW (over 24 weeks) - Safety of interrupted therapy of etanercept 50 mg BIW vs. continuous therapy of 50 mg BIW
Van de Kirchhoff, 2008 (1)	Randomized, double blind, controlled	142	31-58	-Adult with stable plaque psoriasis involving ≥ 10% BSA -Minimum PASI score of 10 -Failed to respond to at least one systemic of phototherapy	-Pts with active guttate, erythrodermic or pustular psoriasis -Pts with serious infection within 1 month of study or BMI greater than 38 -Pts that received a TNF inhibitor -No PUVA within 1 month, no corticosteroids within 2 weeks	20	- Safety of Etanercept 50 mg QW vs. Placebo -Efficacy of Etanercept 50 mg QW vs. Placebo

Results

The results were presented in dichotomous form in all three studies that were analyzed. Tyring et al demonstrated 51.1% in the etanercept group and 51.6% in the placebo group achieved a 75% improvement (PASI 75) in their plaque psoriasis. The test is statistically significant ($P < 0.001$). The relative benefit increase (RBI) was calculated to be -0.001 and the absolute benefit increase (ABI) was -0.01. This study determined that the number needed to treat (NNT) was -100 for the treatment of etanercept 50 mg BIW (Table 2).

Moore et al. showed that 59.5% of participants in the etanercept group and 71.0% of those in the control group showed a response in their PGA score. The test was seen to be statistically significant ($P < 0.0001$). The absolute benefit increase was shown to be -0.115 and the relative benefit increase was -0.162. NNT was determined to be -9 for those receiving 50 mg QW (Table 2).

Van de Kerkhof et al. demonstrated that 71.1% of those in the etanercept group and 44.4% of those in the control group had a 75% improvement (PASI 75) in their plaque psoriasis. The test was statistically significant ($p < 0.0001$). The RBI was calculated to be 0.60 and the ABI was shown to be 0.266. NNT for the study was found to be 4 patients at a dose of 50 mg QW (Table 2).

Table 2: Efficacy of Etanercept on Improving Plaque Psoriasis

Study	Responders in the Etanercept group	Responders in the control group	P-value	RBI	ABI	NNT
Tyring (2007)	155/304 (51.1%)	148/287 (51.6%)	P < 0.001	-0.001	-0.01	-100*
Moore (2007)	758/1274 (59.5%)	903/1272 (71.0%)	P < 0.0001	-0.162	-0.115	-9*
Van de Kerkhof (2008)	64/90 (71.1%)	16/36 (44.4%)	P < 0.0001	0.60	0.266	4

RBI = Relative Benefit Increase ABI = Absolute Benefit Increase NNT = Numbers Needed to Treat

**Since outcome measured was improvement of plaque psoriasis, the negative value for NNT indicates that for every 100/9 participants who took etanercept, there was one fewer who would have improvement in plaque psoriasis than in the group of participants taking the placebo.*

There appears to be an inverse relationship related to the dosage of etanercept received and the numbers needed to treat. Studies that received 50 mg BIW (Tyring et al and Moore et al) demonstrated negative values, as opposed to those receiving 50 mg QW who exhibited positive values.

One of the most common treatment emergent adverse effects experienced in all three studies was that of headache. Headaches were typically mild and resolved in a day. Headache was reported in 5.8%, 6.0%, and 13.5% of patients in the etanercept group for the studies Tyring et al, Moore et al, and van de Kerkhof et al respectively (Table 3).[1,4,5] Headaches were typically more common in the etanercept group than the control group. This was not seen in Tyring et al, which demonstrated a numbers needed to harm (NNH) as a negative value.

Table 3: Incidences of Headache in Etanercept and Control groups

Study	Incidences of headache in Etanercept group	Incidences of headache in control group	P-value	RRI	ARI	NNH
Tyring (2007)	9.2/158.0 (5.8%)	36.4/418.8 (8.7%)	NR	-0.747	-0.272	-4*
Moore (2007)	76/1274 (6.0%)	61/1272 (4.8%)	NR	0.25	0.012	83
Van de Kerkhof (2008)	13/66 (13.5%)	1/46 (2.2%)	$P \leq 0.05$	5.14	0.113	8

RRI = Relative Risk Increase ARI = Absolute Risk Increase NNH = Numbers Need to Harm

*Outcome measured was incidence of headache, so this negative value means that for every 4 participants, one more participant will report the adverse effect of headache than if they received etanercept.

Discussion

The Randomized Controlled Trials on the study of the efficacy and safety of etanercept on treatment of plaque psoriasis demonstrated that 50 mg twice weekly (Tyring et al and Moore et al) was not as effective as 50 mg once weekly (van de Kerkhof et al). Taking a closer look at the study of Moore et al, we see that the control group consisted of those patients receiving continuous therapy versus the experimental group, which received interrupted therapy. This signified that although continuous therapy was more effective, that treatment of etanercept could be stopped and restarted and patients would still see improvement. The treatment of 50 mg QW was shown to be highly efficacious and is currently the recommended starting dose for etanercept in the treatment of plaque psoriasis.

Etanercept was generally well tolerated by participants, showing the drug to be safe in the treatment of plaque psoriasis. One of the most common adverse effects was that of headache, affecting the etanercept group more often. However, similar frequency of headache was seen

between the etanercept groups and the control groups. This suggests that headache may not have been related to drug use.

Conclusion

Etanercept, a TNF inhibitor, was shown to be effective and safe in the treatment of plaque psoriasis. While the results were not overwhelming convincing, it was demonstrated that the current recommended starting dose of 50 mg QW showed greater improvement. We can also conclude that etanercept was effective when administered continuously or after discontinuation and re-treatment. Although greater benefit was seen with continuous treatment, patients can re-initiate treatment and expect similar response and without increased safety risk.[5] Overall, etanercept demonstrated low numbers of treatment emergent adverse effects indicating it to be a relatively safe and tolerable drug. Examining the methods used, limitations of the studies suggest that lack of high response seen may be due to noncompliance with etanercept administration or psoriasis-specific factors that decrease TNF dependency of the disease in patients treated with TNF antagonists.[1] Future studies should eliminate noncompliance ad well as identify the psoriasis-specific factors that could affect the outcome. Etanercept should continue to be used at 50 mg QW effectively and safely as statistically significantly demonstrated by these three studies.

References

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