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Does Adalimumab improve symptoms in patients with moderate to severe Hidradenitis Suppurativa?

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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 "Does Adalimumab improve symptoms in patients with moderate to severe Hidradenitis Suppurativa?"

STUDY DESIGN: A systematic review of three peer-reviewed articles published between 2011 and 2016 which present patient oriented evidence.

DATA SOURCES: Review incorporated analysis of two randomized controlled trials (RCTs) and one open label prospective trial. Studies were selected based upon the relevance to the clinical question, does adalimumab usage improve symptoms in individuals with moderate to severe hidradenitis suppurativa.

OUTCOMES MEASURED: The outcomes measured focused on patient reported reduction in hidradenitis suppurativa symptoms. Two studies analyzed outcomes using patient reported Dermatology Life Quality Index (DLQI) scores, which take into account both physical and psychological disease burden as reported by the patient. The third study evaluated outcomes by analyzing the percentage of participants whom reported at least a 30% reduction in pain scores following adalimumab usage.

RESULTS: The open label trial completed by Sotiriou E, Goussi C, Lallas A, et al. revealed a significant improvement (P= 0.001) in patient reported DLQI scores following adalimumab usage for 24 weeks when compared to their initial DLQI scores. The study completed by Miller I, Lynggaard CD, Lophaven S, et al. failed to show statistically significant improvement in DLQI scores of patients receiving adalimumab compared to those receiving a placebo. The study by Kimball AB, Okun MM, Williams DA, et al. revealed inconsistent results concerning patient reported pain improvement with adalimumab use versus the use of a placebo.

CONCLUSION: Review of the three studies selected revealed inconclusive results. Though the results were inconsistent between studies, the presence of positive results in two of the studies indicates that further investigation of the efficacy of adalimumab use for hidradenitis suppurativa is warranted. Results from the studies analyzed indicate further research should also be carried out to evaluate the efficacy of simultaneous adalimumab and conventional therapeutic usage.

KEY WORDS: Hidradenitis suppurativa, adalimumab

Introduction

Hidradenitis suppurativa (HS) is a dermatologic condition characterized by the formation and recurrence of painful skin nodules, lesions, and sinus tracts that can progress to severe scarring.[1] Patients not only suffer from the visible dermatologic manifestations of HS, but also the subsequent acute and chronic inflammatory states caused by the presence of these abnormalities.[1] HS patients must grapple with its physical effects as well as its psychological effects, which are brought about by the chronic pain patients experience alongside feelings of embarrassment secondary to the visible signs of the disease.[2] These combined physical and psychological sequelae can have a profound effect on the lives of individuals with HS. The fact that HS greatly affects the quality of patients' lives and no gold standard therapeutic regimen has been agreed upon, has led to a multitude of studies evaluating a range of treatment options taking place with the goal of finding a final solution. This review analyzes three studies that attempted to determine whether adalimumab is a potential final solution for HS patients.

HS has an incidence of 11.4 per 100,000 people in the United States.[3] With its severe effects, HS must be a differential considered by healthcare providers across primary care fields as well as dermatologists. HS must also be therapeutically managed by these fields and by general surgery in more severe cases. Apart from the physical effects, studies have also indicated that HS patients suffer monetary effects, spending an average of $5,048 on medications annually, while also incurring greater costs and more frequent visits to the emergency room in comparison to control groups.[4] The latest estimates obtained through analysis of data from 2002 to 2010 indicated that there were about 254,000 health care visits per year addressing HS.[5] Overall,

despite its low prevalence the multispecialty involvement, financial impact, and associated decreases in quality of life make HS a relevant healthcare topic.

The exact cause of HS has not been agreed upon to this point, but the most well supported theory is that HS is the result of chronic follicular occlusion of the folliculopilosebaceous units of the skin.[1] The occlusion of these units leads to their distention as they fill with keratinocytes and potential antigens, and these distended units are thought to be the foundation and cause of the characteristic skin nodules and lesions associated with HS.[1] Subsequent force on the distended units can lead to rupture and dispersal of their contents which in turn lead to an inflammatory response. This inflammatory response leads to the formation of sinus tracts and scarring as well as acute and chronic pain.[1] HS more commonly effects the intertriginous areas of the body due to the persistent friction and pressure at these locations.[1] This increased friction and pressure at intertriginous areas causes a greater number of follicular unit ruptures to occur followed by increased inflammation and scarring compared to other sites.

No "gold standard" therapy has been agreed upon for HS, and this absence of definitive treatment has fueled the testing and usage of many therapies. One of the first forms of management used in HS, as with many disease, is lifestyle changes including weight loss and smoking cessation.[6] Data analysis has revealed obese and current smokers are more likely to develop and experience more severe and progressive HS, so limiting these factors can provide great benefit.[1] The application of antiseptic solutions and antimicrobial lotions at lesion and nodule sites is an early option, though this approach does not halt the formation or recurrence of nodules and lesions.[6] Initial pharmacologic options including topical antibiotics, such as clindamycin, oral antibiotics, and retinoids are used to reduce the chances of infection at active open HS sites and attempt to provide symptom relief.[6] Intra-lesional steroid injection is another

therapeutic measure used to relieve inflammation and attempt to decrease subsequent sinus tract formation and severe scarring.[6] Surgical debridement and excision of active inflammatory lesions and sinus tracts is a late option considered in uncontrolled HS.[1]

The above therapies have provided inconsistent results and varying levels of symptom relief. This inconsistency has led to biologic medications, such as adalimumab, being considered as a treatment option for HS.[6] With the most significant effects of HS being associated with the immune system's inflammatory response to follicular rupture,[1] therapies which can mediate this response have become a focus. Adalimumab, a tumor necrosis factor(TNF) alpha inhibitor medication, is an immunosuppressant.[6] Its administration is intended to lead to a less exaggerated immune and thus inflammatory response to the rupture of the follicular units formed in HS, and these therapeutic effects are thought to lead to a decrease in sinus tract formation, chronic inflammation, and severe scarring associated with HS.[6]

Objective

The objective of this selective evidence based medicine (EBM) review is to determine whether or not "Does Adalimumab improve symptoms in patients with moderate to severe Hidradenitis Suppurativa?"

Methods

The three studies used in this systematic review consisted of two double blind randomized controlled trials and one open label perspective trial. These studies were selected based upon their relevance to the clinical question posed in this review, and their presentation of trial results as patient oriented evidence. The population evaluated in each of the three studies consisted of both men and women over the age of 18 with clinically diagnosed moderate to severe HS.[7,8,9] Two of the studies use the intervention of 40 mg of adalimumab subcutaneously

weekly,[7,9] while the other study had an intervention of 40 mg of adalimumab given subcutaneously once every two weeks.[8] The duration of the studies varied from 12 to 48 weeks. Comparison within the two randomized controlled trials was done by administering visually matched placebos to the control group at the same intervals as the groups receiving adalimumab.[8,9] No comparison group was used in the open label perspective trial.[7] In all studies selected, patient reported changes in HS symptoms were the outcomes measured.

The keywords "hidradenitis suppurativa" and "adalimumab" were used in PubMed to find the studies used within this review. The studies selected were all published in English and appeared in peer reviewed journals. The inclusion criteria used for the selection of studies included being peer reviewed, being published after 2010, and presenting outcomes as patient oriented evidence. Studies presenting non-dichotomous data were analyzed using statistics including: p-values, z-scores, confidence interval (CI), and mean changes from baseline.[7,8] Statistics including number needed to treat (NNT), absolute benefit increase (ABI), and relative benefit increase (RBI) were used for the analysis of the study containing dichotomous data.[9]

Table 1 - Demographics & Characteristics of included studies

Study	Type	# Pt	Age(yrs)	Inclusion Criteria	Exclusion Criteria	W/D	Interventions
Sotiriou[7] (2012)	Prospective open-label clinical trial	15	28-45	18 years of age or older with clinically diagnosed moderate to severe hidradenitis suppurativa. HS must have been present for at least 2 years, and patients have tried and failed at least 3 systemic treatments.	No treatment with biologic medications within in 6 months of the trial start date. Patients could not have chronic or recurrent infection or chronic systemic diseases.	0	80 mg of Adalimumab given at base then one 40 mg injection-weekly for 24 weeks.
Miller[8] (2011)	Double Blind, placebo controlled RCT	21	25-55	Men and women of at least 18 years of age with clinically diagnosed moderate to severe hidradenitis suppurativa. Participants must have	No treatment with biologic medications within 6 months or conventional treatment within 4 weeks. Patients could not have chronic	5	80 mg of Adalimumab given at base followed by a 40 mg injection every other

				had hidradenitis suppurativa for at least 6 months.	or recurrent infection or chronic systemic diseases.		week for 12 weeks.
Kimball[9] (2011-2014)	Double Blind, placebo controlled RCT	633	24-48	18 years or older with clinically diagnosed moderate to severe hidradenitis suppurativa and an inadequate response to oral antibiotic treatment.	Participants could not have taken oral antibiotics within 28 days of baseline in trial 1. No other exclusion criteria were specified.	37	Adalimumab 40 mg given every week for twelve weeks.

Outcomes Measured

The outcomes evaluated in this review are patient oriented outcomes (POEMs) reported within the selected studies. These results were reported by the patients in the respective studies and focused on HS symptom relief brought about by adalimumab usage. The studies by Sotiriou et al. and Miller et al. reported outcomes using patient reported Dermatology Life Quality Index(DLQI) scores. DLQI is a scale with a maximum score of 30 that attempts to quantify the physical pain, impact on daily life, and psychological effects of a dermatological disease experienced by an individual. Outcomes were based upon comparisons of mean DLQI scores at baseline with subsequent scores reported by participants throughout the studies. Outcome evaluation in the study by Kimball et al. consisted of analyzing the percentage of participants who reported at least a 30% reduction in pain and at least a 1-unit reduction from baseline in the pain score as rated on a 0 to 10 scale following the usage of adalimumab.

Result

Sotiriou et al. conducted an open-label perspective study done at Aristotle University in Greece. Of the 20 individuals screened for the study, 15 were selected based upon the inclusion and exclusion criteria seen in Table 1.[7] Qualifying patients were informed of the purpose and design of the study prior to its start, and all participants underwent the intervention being evaluated.[7]

All participants received a subcutaneous dose of 80 mg of adalimumab at baseline, followed by 40 mg doses given weekly for a 24-week period.[7] The DLQI scores of participants were obtained at baseline, after 24 weeks of adalimumab administration, and after an additional 24-week washout period. The mean DLQI scores of all participants were calculated at these intervals and were found to be 15.9, 4.8, and 12.2 respectively.[7] The change in mean DLQI score between these intervals was evaluated to determine the effect of adalimumab use. The change from 15.9 at baseline to 4.8 at the end of the 24-week period of adalimumab usage was found to be significant (Δ= -11.1, P = 0.001, Z = -3.415), indicating a statistically significant improvement in symptoms with adalimumab use.[7] The change in mean DLQI scores from 4.8 at the end of 24 weeks to 12.2 after the washout period was also found to be significant (Δ= 7.4, P= 0.001, Z= -3.423), indicating a significant worsening of symptoms with the cessation of adalimumab.[7] The change from the baseline value of 15.9 to the washout period value of 12.2 was found to be significant (Δ= -3.7, P= 0.005, Z= -2.817), indicating prolonged symptom relief after cessation.[7] Based upon the analysis of change in mean DLQI score in this study adalimumab usage provided a recognizable improvement in HS symptoms, and statistically significant worsening of symptoms was also seen with the discontinuation of adalimumab. This analysis is highlighted in Table 2. No major adverse effects were noted throughout the duration of the study, all participants completed the full therapeutic regimen, and all participants reported at the end of the washout period.[7]

Table 2: Change in Mean DLQI scores following administration of adalimumab and washout period from Sotiriou et al.[7]

	Baseline	End of 24 Weeks	End of 48 Weeks
Mean DLQI Score	15.9	4.8	12.2
Change in Mean DLQI Score from Baseline	-	-11.1(P= 0.001, Z= -3.415)	-3.7 (P= 0.005, Z= -2.817)
Change in Mean DLQI Score from 24 weeks	-	-	+ 7.4 (P= 0.001, Z=-3.423)

Miller et al. conducted a double blind randomized control trial completed at Roskilde Hospital and Gentofte Hospital in Denmark. 21 patients were selected for the trial based upon the same inclusion and exclusion criteria as the Sotiriou et al. study, except pregnant women could also participate in this trial. Computer randomization was used to assign participants to the experimental and control groups at a 2.5:1 ratio, meaning over twice as many participants received adalimumab (15) as opposed to those receiving a placebo (6).[8]

Patients in the experimental group received 80 mg of adalimumab subcutaneously at baseline followed by 40 mg doses given every other week for twelve weeks. Members of the control group were given visually matched placebos at these same intervals.[8] Participants were then followed for an additional 12-week washout period for continued evaluation. Changes in mean DLQI scores were used to measure outcomes in this study, and these values were obtained at baseline, 12 weeks, and 24 weeks.[8] The experimental group mean DLQI scores at these intervals were 16.07, 12.40, and 16.70 respectively, while the control group scores were 8.33, 9.33, and 9.00 respectively. The changes in mean DLQI score for the experimental group were -3.67 from baseline to 12 weeks and 0.53 from baseline to the end of the washout period, compared to changes of 1.00 and 0.67 seen in the control group over these intervals.[8] These scores and differences can be found highlighted in Table 3. Statistical comparison of the changes in mean DLQI scores experiences by the experiment and control groups were used to determine the significance of the study results. Comparison of the changes in mean DLQI scores from baseline to 12 weeks between these two groups revealed a p-value of 0.06, and comparison from baseline to completion of the washout period revealed a p-value of 0.88. These results revealed no significant difference based upon the threshold of $P \leq 0.05$, and thus the trial failed to show

an improvement in HS with adalimumab usage versus a placebo. Based on these results it can be inferred that adalimumab usage did not provide significant symptom relief.

By the conclusion of the study 5 participants had dropped out due to worsening HS symptoms, 3 from the experimental group and 2 from the control group.[8] The study indicates the main adverse effects experienced by participants were mild infection and nonspecific rash.[8] In the case of individuals who dropped out of the study, the last recorded data point for that individual was carried forward and used as the reported value at each subsequent interval.

Table 3: Change in Mean DLQI scores from Miller et al.[8]

	Baseline	End of 12 Weeks	End of 24 Weeks
Mean DLQI Score	Experimental Group: **16.07** (CI: 12.13 to 20.00) Control Group: **8.33** (CI: 4.66 to 12.01)	Experimental Group: **12.40** (CI: 7.79 to 17.09) Control Group: **9.33** (CI: 3.75 to 14.91)	Experimental Group: **16.70** (CI: 12.50 to 20.70) Control Group: **9.00** (CI: 3.61 to 14.39)
Change in Mean DLQI Score from Baseline	-	Experimental Group: **-3.67** (CI: -8.99 to 1.66) Control Group: **1.00** (CI: -1.39 to 3.39)	Experimental Group: **0.53** (CI: -4.66 to 5.73) Control Group: **0.67** (CI: -2.56 to 3.90)
Significance of Mean DLQI Change between Experimental and Control Groups	-	P = 0.06	P = 0.88

Kimball et al. completed two large double-blind randomized controlled trials which took place across 14 different countries at over 200 different sites. Between the two trials a total of 907 people were screened and 633 qualified to participate in the study. The inclusion and exclusion criteria were again similar to those of the Sotiriou et al. study. Although, in this study participants were not required to have failed other treatment regimens prior to entering, and in the second trial patients could continue other antibiotic therapies.[9] In both trials the participants were randomly assigned to the experimental and control groups at a 1:1 ratio.[9]

The study consisted of several phases in which participants were reassigned to various groups and given numerous different interventions. For the purposes of consistently, only the

initial phases of each trial from this study will be evaluated for this systematic review. In both trials the experimental groups were given weekly doses of 40 mg adalimumab subcutaneously, while the control groups were given a visually matched placebo weekly.[9] Outcomes were considered positive if, after 12 weeks of adalimumab use, participants reported a 30% or greater reduction in pain and at least a 1-unit reduction from baseline in pain score as rated on a 0 to 10 scale.[9] This evaluation only included individuals who reported pain scores of 3 or higher at the onset of the study.[9] In the initial trial 27.9% of the experimental group reported qualifying pain reduction compared to 24.8% of the control group (P = 0.63).[9] Analysis of this dichotomous data yields an RBI of 12.5%, an ABI of 3.1%, and an NNT of 33. In the second trial 45.7% of the experimental group versus 20.7% of the control group reported qualifying pain improvement (P= 0.001).[9] This equates to an RBI of 131%, an ABI of 25.9%, and an NNT of 4. The data from the initial trial indicates that for every 33 individuals treated with adalimumab one additional group member will recognize a noticeable benefit in comparison to a group of 33 treated with a placebo, whereas the results from the second trial indicate that an additional benefit would be seen using groups of only 4 individuals. The results of the second trial indicate adalimumab usage is much more efficacious than those of the first. For calculation purposes, no value was entered in the case of participants who withdrew, thus calculations function as if the participants had never been a part of the trials.[9]

Table 4: Change in Pain Score from Kimball et al.[9]

	Experimental Group Qualifying Pain Reduction	Control Group Qualifying Pain Reduction	ABI	RBI	NNT
Trial 1	27.9% (34/122)	24.8%(27/109)	3.1%	12.5%	33
Trial 2	45.7%(48/105)	20.7%(22/111)	25.9%	131%	4

The study indicated that 17 of the initial 307 participants in the first trial and 20 of 448 participants in the second trial failed to complete the full duration of the phase being evaluated.

Reasons for the 37 total withdrawals included adverse effects (9), loss to follow up (6), withdraw of consent (16), and other (6).[9] The most common adverse effect noted during the study was infection.[9] In the first trial 28.3% of the experimental group versus 24.8% of the control group experienced infections, while 25.2% of the experimental group and 32.5% of the control group experiencing infections in the second trial.[9] This data does not appear to show an increased chance of infection with the usage of adalimumab for a 12-week period compared to usage of a placebo, though 12 weeks is a short period when considering adverse effect development.

Discussion

Of the three studies evaluated for this review the study by Sotiriou et al. revealed the most consistent and statistically significant benefits of adalimumab usage, but this trial was also an open label trial in which the participants were informed of the goals of the study beforehand.[7] Prior knowledge that the intervention was being received could have played a role in the positive results reported by the patients. In the Miller et al. study, the large variance in initial mean DLQI scores between the experimental and control groups must be considered as a factor with the potential to effected results.[8] Another variable of note is that the largest study, Kimball et al., was sponsored by a manufacturer of adalimumab.[9] The sponsor was involved in the construction of the study and made aware of all results prior to the publication.[9] The manufacturer's involvement may have led to a preferential set up towards positive results. This study also yielded inconsistent results, with the first trial having a NNT of 33 versus a NNT of 4 found in the second trial.[9] Though, the second trial obtained more promising results the individuals in this trial could continue other conventional therapies while also receiving adalimumab. This difference in parameters between trials can greatly effect results and the ability to attribute positive results solely to the use of adalimumab.

Along with efficacy, the financial feasibility and potential adverse effects of a product must be considered prior to its implementation. A recent study published in 2018 evaluating the costs of conventional therapies compared to adalimumab for HS treatment revealed an average yearly cost of € 8,309.60 for conventional therapies versus €3,264.20 for adalimumab.[10] This indicates that adalimumab usage may be the more cost-effective option, but this study was also partially funded by the adalimumab manufacturer.[10] Concerning safety, though the studies in this review revealed no consistent adverse effects with adalimumab usage, adalimumab is an immunosuppressant with a black box warning for increased chances of developing serious infections as well as lymphoma and other malignancies.[11] Continued evaluation of the adverse effects seen with long term adalimumab use must be analyzed to determine whether the potential benefits outweigh the risks of therapy.

Conclusion

Based upon the above review of three clinical studies it is inconclusive whether adalimumab improves symptoms in individuals with moderate to severe HS. Only one study revealed consistent statistically significant improvement of HS symptoms with adalimumab use.[7] Of the other two studies, one revealed inconsistent result as discussed above[9] and the other failed to show a significant improvement with the use of adalimumab.[8] These inconsistent results may be attributable to the large differences in study designs, but the presence of positive results in some trials indicates that further studies should be done concerning the efficacy of adalimumab use in HS. In future trials, further investigation should be done evaluating whether the use of adalimumab concomitantly with different conventional therapies is more beneficial than the use of single agents alone. The results of the second trial in the final study discussed indicate this may be a more efficacious approach.[9]

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