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**Is Avotermin safe and effective treatment for scar improvement in healthy males and females?**

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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

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## **ABSTRACT**

**OBJECTIVE:** The objective of this selective EBM review is to determine whether or not avotermin is a safe and effective treatment for scar improvement in healthy males and females.

**STUDY DESIGN:** Systemic review of three primary research studies published in the English language, one published in 2010 and the other two in 2011.

**DATA SOURCES:** Two randomized placebo controlled phase II trials and one double blind within patient placebo controlled phase II clinical trial, analyzed and compared the effectiveness in the administration of avotermin against a placebo in the improvement and diminution of scars. All articles were found using Pubmed and Cochrane Library EBM databases.

**OUTCOMES MEASURED:** Each of the studies measured the effectiveness of avotermin to improve appearance and reduce size of scar after surgery procedure. In order to determine reduction of size and improvement of appearance total scar score (ToScar) derived from a visual analogue score (VAS) was used pre and post intervention. So, et al. also used Global scar comparison scale, silicone molds evaluated with PRIMOS scale and histological evaluation of tissue

**RESULTS:** The study by Bush et al reported  $p=0.0031$  and  $p=0.0140$  for avotermin 200ng once or twice respectively at 12 month and 61% of adverse events in experimental group. The study by McCollum et al reported, RR= 6.4, RRR=540%, ARR: 27% NNT= 4 and  $p=0.007$  at 12 month. In addition, RRI=-8%, ARI=-1.3% and NNH=-77. Similar results were obtained in the study by So K et al which reported  $p= 0.04$  at 12 month and RRI=11%, ARI=5% and NNH=20. All studies reported minimal adverse reactions to avotermin in addition to statistical significance in favor of the experimental drug avotermin as an effective treatment for scar improvement.

**CONCLUSIONS:** Based on the congruency of the data analyzed in these trials, avotermin is safe and effective for treatment of scar reduction and improvement which warrants the use of the drug.

**KEY WORDS:** Scar, Avotermin, Transforming growth factor  $\beta_3$

## INTRODUCTION

Scarring is part of the natural biological healing process of tissue repair after injury to the skin that can be caused by a mere accident or surgery.<sup>1</sup> Regardless of the nature of scar, scarring can cause distortion of normal tissue, which can result in psychosocial disturbance associated with aesthetics, distress, and disfigurement that usually impacts negatively an individual's life.<sup>2</sup> This paper appraises two randomized, double blind, within-patient, placebo controlled phase II trials and one randomized phase II clinical trial, which will evaluate and compare the effectiveness in the administration of avotermin against a placebo in the improvement and diminution of scars.

Scarring is relevant to the Physician Assistant profession in regards to patient's physical and psychological wellbeing, prevalence, treatment options, and cost. Patient's own discontent with aesthetic perception of scar can result in "sleep disturbance, anxiety, depression, and disruption of daily activities"<sup>2</sup> in addition to "psychosocial sequelae including development of post-traumatic stress reactions, loss of self-esteem, and stigmatization leading to diminished quality of life."<sup>2</sup> Therefore, eliciting health care provider's interest to find adequate treatment or referrals for proper management of scars in individuals who potentially suffer from secondary somatic and psychological symptoms. It is estimated that each year approximately 100 million individuals acquire scars due to trauma or surgery, resulting in 55 million elective operations and 25 million operations after trauma.<sup>2</sup> There is a wide spectrum of scar types ranging from fine lines to hypertrophic ones. Depending on scar type, treatment may comprise invasive methods involving steroid injections and surgery or conservative methods using compression therapy, topical silicone gel or photodynamic therapy.<sup>3</sup> The exact number of patients undergoing scar

revision surgery within the last few years is not currently available; however according to the American Society of Plastic Surgeons report of 2009, there were 171,237 scar revision procedures done in the United States in that year.<sup>4</sup> Exact annual cost for scar revision surgery is variable and depends on surgeon's fee, hospitals costs, anesthesia fees, and region in the United States in which the surgery is performed at.<sup>5</sup>

Despite all the available invasive and conservative alternative treatments for scar reduction, there is no individual intervention that completely eliminates scars or cause scars to disappear. Recent studies introduced transforming growth factor  $\beta_3$  (TGF- $\beta_3$ ) also known as avotermin as an alternative prophylactic treatment for scarring, due to its vital role in suppression of scar formation, relative safety, efficacy, and tolerability upon administration.

## **OBJECTIVE**

The objective of this selective EBM review is to determine whether or not avotermin is safe and effective treatment for scar improvement in healthy males and females.

## **METHODS**

Articles utilized in this review were considered based on a number of criteria. A literature search using PubMed and Cochrane Database with activated filters for Randomized Controlled Trial, humans, adults: 19-85 years was applied and yield two randomized, double blind, within-patient, placebo controlled phase II trials and one randomized phase II clinical trial. All articles chosen were obtained through PubMed and were published in the English language, between 2010 and 2011. Inclusion of articles were considered based on relevance and outcomes important to the patient and physician assistant practice. The studies excluded were articles published

before 2000 and those that included individuals younger than 18 years old. The key words used were scar improvement, avotermin, Transforming growth factor  $\beta_3$ .

Selection criteria for studies included the following: The population considered comprised healthy nonblack patients older than 18 years of age that were undergoing a surgical procedure. Two of the studies used avotermin 200ng/100 ul/linear centimeter of wound margin and one used 500ng/100ul/cm as the main intervention treatment. Comparisons included within patient controlled placebo group in order to minimized confounding factors affecting scarring. Results were based on ToScar and Visual Analog Scale score (VAS).

Two of the studies reported statistics using p values and one contained dichotomous data, which was used to calculate Absolute Risk Reduction (ARR), Relative Risk Reduction (RRR), and Numbers Needed to Treat (NNT). Table 1, depicted demographics of the chosen articles

**TABLE 1: Demographics & Characteristics of included studies**

Study	Type	#pt	Age	Inclusion criteria	Exclusion criteria	W/D	Interventions
Bush et al <sup>6</sup> (2010)	RCT	71	18-45 y.o men	Healthy individual (18-45 years) Caucasian BMI between 15 and 55kg/m <sup>2</sup>	Afro-Caribbean individuals, those with general medical conditions, skin disorders, taking medications affecting wound healing, hx of hypertrophic or keloid scarring, allergies and tattoos in biopsy area	13	Avotermin 200 mg/100ul (transforming growth factor beta-3) VS. Within patient controlled placebo
McCollum et al <sup>7</sup> (2011)	RCT	156	18 - 85 y.o men & women	bilateral removal of varicose veins by sapheno-femoral ligation and long saphenous vein stripping BMI of 15–35 kg/m <sup>2</sup>	Subjects with hx of prior surgical treatment for varicose veins, suffered from bleeding disorders, impaired wound healing, existing scars within 3 cm of potential trial wounds and oral corticosteroid therapy	4	Avotermin 500 ng per 100 ul VS. Within patient controlled placebo
So K et al <sup>8</sup> (2011)	RCT	60	18-85 y.o men and women	Subjects with a mature, stabilized, linear scar that was $\geq 1$ 5 cm in length, and it was $\geq 12$ month old scar BMI of 15 to 35kg/m <sup>2</sup>	Patients with scars distorted by joints or anatomical structures Subjects with a history of keloid scarring Subjects with medical conditions that could impair wound healing	5	Avotermin (200 ng/100ul linear cm wound margin) VS. Within patient controlled placebo

## OUTCOMES MEASURED

The outcomes measured in these studies were those relevant to Patient Oriented Evidence that Matters (POEMs) as is the case of scar appearance, improvement, and size reduction. Efficacy assessment outcomes were primarily measured by using Total Scar Score derived from the Visual Analog Scale (VAS) which is “a photograph-based scale derived from evaluating standardized digital photographs in 4 dimensions (pigmentation, vascularity, acceptability, and observer comfort) plus contour.”<sup>9</sup> All selected studies used the VAS to assess scar appearance, but differed in the time period assigned for evaluation. Bush, et al. and So, et al used monthly measurement assessments based on a 12 month period<sup>6, 8</sup> and McCollum, et al used follow up periods for assessment at 6 weeks, 3, 5, 7 and 12 month.<sup>7</sup> Scar appearance was evaluated by a lay panel and investigators. Selection of lay panel members was determined based on their ability to consistently score scars according to VAS training.<sup>6, 7, 8</sup> Standardize values for VAS included 0 mm up to 100mm with 0 mm being consistent with normal skin and 100 mm being poorest outcome according to the scale.<sup>6, 7, 8</sup> Calculation of ToScar used the mean VAS values from follow up assessment measurements.<sup>7, 8</sup> In addition to the ToScar score derived from VAS values, So, et al. also used Global Scar Comparison, silicon molds which were analyzed by the PRIMOS system and histological examination of sample tissue excised at month 7 was also done.<sup>8</sup>

Safety outcome measurements in Bush, et al and So, et al. included adverse events, local tolerability (i.e pruritis, pain and burning sensation), and observation of erythema, edema and exudate, blood analysis for immunogenicity, clinical chemistry and urinalysis.<sup>6, 8</sup> Bush, et al. also included pulse, blood pressure measurements and electrocardiogram test for assessment of safety.<sup>6</sup> Safety outcomes measurements in McCollum, et al. included urinalysis, hematologic

chemistry and blood samples to measure anti-TGF- $\beta$ 3 before and after administration of avotermin.<sup>7</sup>

## RESULTS

This systemic review evaluates two double blind within patient placebo controlled phase II clinical trial and one randomized phase II clinical trial versus placebo. All three clinical trials that are being reviewed use avotermin versus placebo as prophylactic treatment for scar reduction. McCollum, et al presented dichotomous data which was used to assess efficacy and safety. Bush, et al and So, et al presented statistical data as p values which were considered significant if  $p < 0.050$ ; however for safety, dichotomous data was provided and used to calculate, Relative Risk Increase (RRI), Absolute Risk Increase (ARI), and Number Needed to Harm (NNH). Participants in all three studies received written information and consented to participate in each trial, all of which were approved by regional independent ethics committees. All studies were conducted following the Declaration of Helsinki and either the International Conference on Harmonisation: Harmonised Tripartite Guidelines for Good Clinical Practice or International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use. All studies used intention to treat (ITT) last observation carried forward (LOCF) in efficacy analysis and safety population was determined as all patients who received administration of avotermin and were evaluated at least once.<sup>6, 7, 8</sup>

Bush, et al (2010) study investigate efficacy of different avotermin doses that was either administered as a single or double dose in individuals receiving incisional wounds.<sup>6</sup> Individuals of Afro-Caribbean descent were excluded due to high susceptibility for keloid scarring. Likewise, those with history of hypertrophic or keloid scarring, significant allergies and tattoos in biopsy areas. Additionally to those with medical conditions, skin disorders or taking medications that

might affect wound healing <sup>6</sup> A homogeneous population of Caucasian males between 18 and 45 years was included in the study.<sup>6</sup> Study was conducted between October 2003 and August 2005, 71 individuals were recruited and randomly allocated to treatment dose administration groups based on a computer generated code.<sup>6</sup>

Informations from Independent external scar assessment panel’s (IESAP) visual analog scale (VAS) score reported wounds treated with avotermin at 200ng/100ul/linear cm administered once (mean difference= 0.75 cm and p=0.0031) or twice (mean difference 0.74 cm, p=0.0140) were better in reducing scarring than those treated with placebo since month 1 to month 12.<sup>6</sup> In addition, there was a 64% and 77% scar improvement compared to placebo for use 200ng avotermin once or twice respectively.<sup>6</sup> (Table 2)

Table 2: Placebo vs Avotermin administer once (x1) or twice (x2) comparison at month 12

Treatment	Mean (SD)	Avotermin # wound pairs (%)	Control # wound pairs (%)	P value	avotermin % improvement
Placebo vs avotermin 200ng x 1	0.75 (1.266)	20 (65%)	11 (35%)	0.0031	64%
Placebo vs avotermin 200ng x 2	0.74 (1.573)	23 (74%)	8 (26%)	0.0140	77%

\* SD, standard deviation; x1once; x2 twice

Independent external scar assessment panel (IESAP) scar ranking reported approximately 65% preference of scars treated with avotermin 200mg once or twice versus placebo which reported about 31% preference; except for avotermin 200ng (twice) with p=0.0071, no other statistical significance data was reported.<sup>6</sup> (table 3)

Table 3: IESAP efficacy findings at month 12

Treatment	IESAP VAS response rate. p (%favor of avotermin; %favor of placebo)	IESAP ranking of scar. p (% favor of avotermin;% favor of placebo)
Placebo vs avotermin 200ng x 1	NS (65%:35%)	NS (62%:31%)
Placebo vs avotermin 200ng x 2	0.0071 (74%:26%)	NS (60%:33%)

\*VAS, visual analog scale; SD, standard deviation; NS, no significant p value; x1once; x2 twice

Bush, et al. report 61% systemic adverse events in experimental group, however adverse events at wound sites were similar for avotermin and controls (Table 6). Erythema, edema, exudate and thickening were equally frequent with avotermin and placebo, suggesting normal wound healing.<sup>6</sup> There were no deaths, withdrawals or discontinues from study due to adverse effects.

McCollum, et al (2011) study assessed efficacy of single intradermal injection in near wound margins following varicose vein removal.<sup>7</sup> Individuals with prior varicose veins surgery were excluded, in addition to those suffering from bleeding disorders, had impaired wound healing or an existing scar within 3 cm of potential trial wounds or were taking a corticosteroid therapy.<sup>7</sup> All considerations for exclusion were made to avoid potential confounding effects with previous scar or inability to achieve healing of scar of interest. A heterogeneous population of non-African Caribbean descent between 18 and 85 years with BMI of 15-35kg/m<sup>2</sup> who undergone bilateral saphenofemoral ligation and stripping were included in the study.<sup>7</sup> Study was conducted between November 2006 and January 2009; 156 individuals were recruited and randomly allocated to treatment dose groups.<sup>7</sup>

Lay panel ToScar analysis reported “avotermin 500ng/100ul per linear cm (500-ng dose) compared with placebo (mean ToScar difference 16.49 mm; n=40, p=0.036)” Lower doses were not statistically significant and p values were not reported.<sup>7</sup> Lay panel VAS score reported steady improvement of scar appearance based on VAS scores at all times from week 6 to month 12 for both avotermin and placebo; however avotermin 500-ng had better results compared to placebo.<sup>7</sup> Lay panel ranking reported significant improvement that warrants used of avotermin vs placebo. Based on the data reported in the study, Relative Risk (RR) determined 6.4 times higher risk of having scar improvement compared to placebo. Relative Risk Reduction (RRR) was 540%, Absolute Risk Reduction (ARR) was 27% in scar reduction rate. NNT was calculated as four,

meaning that for every four patients undergoing surgical procedures that receive 500ng/100ul/cm of avotermin, one more patient will have better scar results after procedure compared to control (Table 4).

Table 4: Efficacy of 500-ng dose avotermin in prophylactic treatment of scarring 12 month period

	CER*	EER*	RR*	RRR*	ARR*	NNT*	P value
LayPanel ranking	5%	32%	6.4	540%	27%	4	P=0.007

\*CER=Control Event Rate, EER=Experimental Event Rate, ARR=Absolute Risk Reduction, RRR= Relative Risk Reduction, NNT=Number Needed to Treat

McCullum, et al. did not report a significant site specific adverse events between avotermin (14.1%) and placebo (15.4%). Adverse events at wound sites were similar for avotermin and controls, wound infection was as frequent with avotermin as with placebo. Relative Risk Increase (RRI) was -8%, Absolute Risk Increase (ARI) -1.3%, and NNH was -77. Therefore, for every 77 patients receiving avotermin, one fewer would experience site-specific adverse events, compared to placebo (Table 6). Adverse events that were considered related to treatment include, hypotension and slow bleed from wound area, 58.3% experienced headaches. One patient died due to cerebral hemorrhage but it was discarded that it was the result of treatment; however, there were no withdrawals or discontinues.<sup>7</sup>

So, et al study evaluated efficacy of intradermal avotermin in patients undergoing scar revision surgery.<sup>8</sup> Excluded individuals included those with prior history of keloid scarring or impair wound healing, in addition to those with distorted scars in joints or anatomical structures of interest of study.<sup>8</sup> A heterogeneous population of individuals who had a qualifying scar and were older than 18 and younger than 85 years with BMI between 15 to 35 kg/m<sup>2</sup> were included.<sup>8</sup> Study was conducted between May 2006 and September 2008; 60 individuals were recruited and randomly allocated to treatment dose groups.<sup>8</sup>

Lay panel combine analysis of both experimental groups to determined ToScar score which “showed that avotermin treatment resulted in a statistically significant improvement in total scar score of 21.93 mm compared with placebo (p=0.04; 95 percent confidence interval, 1.2 to 42.6 mm).”<sup>8</sup> Lay panel VAS score reported avotermin treated scars had a greater improvement in appearance compared to placebo, the mean VAS score at month 12 for avotermin was -17.21mm and -12.90mm for placebo treated scars.<sup>8</sup> (Table 5) Profilometry results showed a change from baseline avotermin 12 month, -96.41mm<sup>2</sup> versus placebo -53.98 mm<sup>2</sup>, resulting in a difference of 27.52 and p=0.03.<sup>8</sup> (Table 5) Histological samples concluded that scar treated with avotermin resemble normal skin better than placebo.

Table 5. VAS and Profilometry Evaluation of avotermin efficacy at 12 months

<b>VAS score</b>	<b>Avotermin 200ng/100ul</b>	<b>Placebo</b>	<b>P-value</b>
Change from baseline at 12months	-17.21mm	-12.90mm	P=0.04
<b>Profilometry results</b>	<b>Avotermin</b>	<b>Placebo</b>	
Change from baseline at 12months	-94.41 mm <sup>2</sup>	-53.98 mm <sup>2</sup>	P=0.03

So, et al. did not report a significant site specific adverse events between avotermin (52%) and placebo (47%) or wound complications (pain and burning) avotermin (38%) versus placebo (37%). Adverse events at wound sites were similar for avotermin and controls. Erythema was more frequent with avotermin than with placebo, but it was transient and deemed to be consistent with normal wound healing. Relative Risk Increase (RRI) was 11%, Absolute Risk Increase (ARI) 5%, and NNH was 20 meaning that for every 20 patients receiving avotermin, one additional will experience site specific adverse events, compared to placebo. 12% of patient reported headache. There were no deaths, withdrawals, or discontinues accredited to adverse events caused by avotermin.<sup>8</sup>

Table 6. Incidence of adverse events in avotermin and placebo groups

	Avotermin	Placebo	RRI	ARI	NNH
Bush, et al.	23/38=61%				
McCollum, et al.	22/156=14.1%	24/156=15.4%	-8%	-1.3%	-77
So, et al.	31/60=52%	28/60=47%	11%	5%	20

\*RRI = Relative Risk Increase, ARI = Absolute Risk Increase, NNH = Number Needed to Harm  
**DISCUSSION**

Avotermin is one of the Transforming Growth Factor  $\beta$  that belong to the family of proteins that are known to play a vital role in wound healing and scar formation.<sup>8</sup> Studies evaluated in this review demonstrate the efficacy and safety of avotermin in the use of prophylactic prevention of scar formation. This innovative drug is not found to be approved in the United States thus far, but currently it is under investigation in the United Kingdom.

Studies evaluated in this review were compliant with validity, as all randomly allocated treatment in a concealed manner, all participants, investigators and assessor were blinded, and follow up for patients was long enough to monitor changes in scar. All three studies analyzed showed a superior improvement in scar reduction with the use of avotermin compared to the use of placebo, in addition, efficacy was subject also to dosage but not frequency. The larger the dosage of avotermin use the greater statistical significance reported.

This review supports the use of avotermin in the treatment of scarring; however there are some limitation worth to mention in the studies chosen. Small sample size depict in Bush et al with 71 participants and So et al with only 60 participants did not accurately represent the total population affected with this problem. Consequently, overestimating or underestimating true effects regarding efficacy and safety. McCollum et al had a larger population with 156 individuals which better represent and demonstrate the outcomes of general population.

## **CONCLUSIONS**

Based on this systematic review and the data presented by previous mentioned studies, avotermin (Transforming Growth Factor  $\beta_3$ ) is a safe and effective treatment for prophylactic prevention of scar formation following a surgical procedure. Studies evaluated reported significant statistical values that warrant the use of avotermin for scar prevention. Evidence also

prove that avotermin is safe to use since most of the adverse side effects were also present in placebo group and were deemed to be part of the natural healing process of a wound.

Noting that the population tested in the three trials was very similar and excluded Afro-Caribbean individuals, future studies should incorporate individuals from black descend to determine the efficacy of avotermin in a diverse population. In addition, based on the data reported, it appears avotermin use at greater doses yield more effective and valuable results in scar appearance. Forthcoming research should augment the dose of avotermin supplementation to potentially assess greater efficacy. It will also be of interest if continuing investigations assess the efficacy of avotermin in different vehicles such as topical products versus parental ones.

Further investigation would benefit from employing a larger study group that addresses a more diverse population with similar wound location and a narrower and similar age range in order to avoid masking true intervention effects.

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