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Exploring Changes in Placebo Treatment Arms in Hidradenitis Suppurativa Randomized Clinical Trials: A Systematic Review

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Abstract

Hidradenitis Suppurativa (HS) is characterized by recurrent, painful nodules in flexural areas. The objective of this study was to explore the placebo response in HS randomized clinical trials (RCTs), and to compare it briefly with the placebo response in psoriasis and atopic dermatitis. A Cochrane Review on interventions in HS was used as a starting point, and a systematic review was then undertaken using the PubMed database, yielding seven HS RCTs for inclusion in this study. This review demonstrates that there is a robust placebo response in HS most marked in physical signs but also in pain responses. This large placebo response has implications for clinical trial design. This knowledge can also help deliver improved clinical care by forming the basis of non-pharmacological treatments and help optimize current medication use to maximize the placebo effect.

Keywords

Placebo response; Clinical outcomes; Hidradenitis Suppurativa; Psoriasis; Atopic Dermatitis; Pain; Hawthorne effect; Clinical trial design

Introduction

Hidradenitis Suppurativa (HS) is a chronic dermatological disease that typically presents with recurrent, painful, suppurative nodules and draining tunnels in intertriginous areas.^{1,2,3,4} The worldwide prevalence is estimated as 1%^{5,6}. Despite the chronic nature of the disease

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and the negative impact it has on a patient's quality of life, there are only about a dozen randomized control trials (RCTs) for treatments in HS⁷.

The placebo effect is the response elicited by administration of a treatment that is inert and will never acquire therapeutic properties. Understanding the mechanisms underlying a placebo effect on HS outcomes can improve clinical trial design and optimize therapeutic options⁸.

This review describes the magnitude of changes in outcomes in placebo arms of HS RCTs, and briefly compares the size of the placebo effect in HS outcomes to that of systemic treatments for psoriasis and atopic dermatitis (AD).

Methods

The 2016 Cochrane Review on “Interventions for hidradenitis suppurativa” was used as a starting point to identify placebo-controlled trials⁷. Twelve HS RCTs were included in the Cochrane Review. Seven studies were selected based on inclusion criteria of the studies being blinded and having a placebo arm. Exclusion criteria applied to the seven studies were active properties of placebo, lack of response data collected, and unestablished primary and secondary outcomes. All studies were in the English language.

The PubMed database was then examined using the search terms “placebo” and “hidradenitis suppurativa” which resulted in twenty-nine publications. The last date this search was performed was June 28, 2018. Of those twenty-nine, only 11 were RCTs. Of these 11 RCTs, eight were already included in the Cochrane Review. The remaining three publications described four RCTs that met the aforementioned inclusion and exclusion criteria, yielding seven RCTs (all biologic therapies) for our review, verified by another study author. Our study is reported using the PRISMA approach (www.prisma-statement.org).

Primary and secondary outcomes were extracted independently by two of the study authors and then compared for uniformity. Given the numerous outcome measures reported, it was not feasible to perform a meta-analysis. A literature review of clinical trials for biologics in psoriasis and AD was conducted for comparison, focusing on physical signs as outcome measures.

Results

Hidradenitis Suppurativa

Results of the placebo and active arms of the seven selected published HS studies are shown in Table 1 in order of publication. A visual representation of the percent change for physical signs, DLQI and pain outcomes as reported for both placebo and treatment arms in the seven HS RCTs is shown in Figure 1.

For improvement of physical signs using the Hidradenitis Suppurativa Clinical Response Score (HiSCR), reductions in placebo arms ranged from 10 – 30% across the studies. HiSCR is defined as a 50% reduction in total abscess and inflammatory nodule count with

no increase in draining fistula count relative to baseline, initially developed in the context of adalimumab clinical trials. PIONEER I and II, which used adalimumab as active treatment, were the largest sized studies and hence are a focus of our interpretation. In PIONEER I and II, the HiSCR endpoint at 12 weeks was met in 26.0% and 27.6% respectively in the placebo arms⁹. HiSCR was met in the adalimumab treatment groups in 41.8% and 58.9% respectively in PIONEER I and II. There was a reduction in modified Sartorius Score (mSS) of 15.7 and 9.5 in the placebo groups compared to a reduction of 24.4 and 28.9 in the adalimumab group in PIONEER I and II, respectively. The Sartorius score, another instrument to measure physical HS signs, is a composite outcome measure comprising anatomical regions involved, lesion counts, distance between lesions, and amount of normal skin separating lesions¹⁰. The other studies used a variety of instruments to measure physical signs and showed variable responses in placebo and active treatment arms (Table 1).

Pain, a significant disability in HS, showed a mean change in Visual Analogue Score (VAS, range 0–10) of between increase of 3.17 to reduction of 8.33 in the placebo arms. The Numerical Rating Scale (NRS) for pain showed a mean reduction of 0.7 in both the placebo groups, compared to a reduction of 1.3 and 2.3 respectively in the active treatment arms for PIONEER I and II. The NRS is also scored out of ten, with ten being the worst pain imaginable. The minimum meaningful reduction in NRS pain scores appear to depend on pain intensity, needing to be larger for patients with more severe pain¹¹. Greater than 30% and 1-unit reduction in VAS for pain was met in 24.8 and 20.7% of the placebo groups, and 27.9 and 45.7% of adalimumab-treated patients in PIONEER I and II respectively. In a recent post-hoc analysis of the patient global assessment of skin pain data from the PIONEER I and II studies, there were also sizeable reductions in pain in the placebo group that persisted as the trial continued (Figure 2)¹².

The impact on quality of life in the placebo group as measured by Dermatology Quality of Life Index (DLQI) showed a mean change of –2.9 to +1.0 for DLQI in the placebo arms. In the active treatment groups across all included studies, the improvement in DLQI ranged from 3.2 to 10. There was an improvement of 2.9 and 2.3 in the placebo group for DLQI compared to an improvement of 5.4 and 5.1 in the active treatment arms of PIONEER I and II, respectively⁹. Basra et al recommends the minimal clinically important difference in DLQI score to be 4¹³. Hence, the HiSCR and the VAS elicited greater changes in the placebo arm, whereas the DLQI demonstrated smaller changes in the placebo arm.

Psoriasis

A meta-analysis of 20 psoriasis RCTs encompassing the biologics ustekinumab, adalimumab, infliximab, etanercept, and efalizumab, showed that the probability of a placebo group achieving the Psoriasis Activity and Severity Index (PASI) 75 is 4%¹⁴.

Atopic Dermatitis

The magnitude of change in the placebo arms in AD was more variable. For instance, a study on mepolizumab (anti-IL-5) showed that 4.6% of patients in the placebo arm achieved marked clinical improvement at two weeks using Physician's Global Assessment (PGA)

score of at least 50%¹⁵. Two RCTs (SOLO 1 and SOLO 2) exploring the efficacy of dupilumab, an IL-4 and IL-13 inhibitor, showed that 15% and 12% of the placebo group achieved an EASI 75 (Eczema Area and Severity Index) at week 16¹⁶. Since dupilumab is the only FDA approved biologic indicated for the treatment of AD, the authors focused their literature review on RCTs evaluating dupilumab where the placebo had no active components. The results demonstrated that the percentage of patients achieving EASI 75 in placebo arms ranged from 6% to 15%.

Discussion

This review highlights the marked clinical improvements in the placebo arm of RCTs of systemic treatments for HS. The greatest changes were seen in both physical signs of HS and pain, but were less reflected in the DLQI. The magnitude of the placebo response in psoriasis and atopic dermatitis RCTs that utilised biologics was reviewed as a point of comparison. Psoriasis was chosen as it is a prototypic and well-studied disease, and AD for its fluctuating disease course which more closely resembles that of HS.

The magnitude of the placebo arm in HS RCTs was markedly higher than those reported in psoriasis, and closer to the variable responses in the placebo arm in AD. The reasons for this remain to be studied. One consideration may be that HS is an under-diagnosed and mis-diagnosed disease, so the potential for improvement just by participating in a clinical trial is amplified. In addition, pain is an important symptom of HS, but not a common complaint in psoriasis or AD. Pain is more susceptible to the placebo effect, and influencing patients' perceptions of pain could have a greater impact on HS patients than patients with psoriasis or AD. Overall, there are different factors that could contribute to the placebo response in these different chronic dermatological diseases, such as disease course, patient experience and even pathophysiology.

There are four main elements that must be present for the placebo effect to occur: A therapeutic relationship, a rationale for clinical improvement with an anticipation of benefit, a procedure or ritual for obtaining that clinical improvement, and rapport between the patients and provider¹⁷. Verbal suggestions of the therapeutic rationales have been shown to have a powerful effect in eliciting a placebo response, likely as a result of modifying patient expectations^{18,19}. The specific agent and route of administration affects the placebo response, with more intense routes of administration such as intravenous or subcutaneous delivery are known to have a greater placebo effect²⁰. It has also been observed that in clinical practice, any intervention can produce a change in clinical outcomes, termed the Hawthorne effect. In clinical trials, this refers to the awareness of being studied and the subsequent change in behaviour to produce outcomes consistent with the expectations of the researchers²¹.

The rapport between patient and physician is very important in the placebo effect. The process of obtaining a history and physical by a health care provider before the start of a trial could aid the patient in understanding more about the disease process, and in doing so, empower the patient with knowledge that they may not have had before²². With diseases

such as HS that are associated with ostracism, the physical touch of the physician can itself be therapeutic^{22, 23, 24}.

In clinical trials, the natural course of a disease may impact the placebo effect. Regression to the mean would suggest larger changes in placebo arms of RCTs when only the most severe patients are included in the trial. All these RCTs selected patients with moderate to severe HS. It is possible that there is a direct relationship between a fluctuating disease course and the magnitude of the placebo effect. There are certain outcomes that are more susceptible to the placebo effect, such as pain and depression²⁵. The majority of patients with HS report clinically significant pain related to their disease, and it is known that the context of pain may alter the placebo experience²⁰.

RCT Design Implications

This review provides information that can be helpful in the design of future RCTs for HS. First, regarding sample size, a large placebo effect on a particular disease outcome increases the number of participants necessary to detect a clinically relevant treatment effect for that disease outcome. The estimates described in this review can be used to estimate the size of the effect expected in a placebo arm of HS RCTs for the outcomes evaluated.

Second, selecting patients with high levels of symptoms for inclusion in RCTs will lead to a natural regression back to the mean. Researchers designing RCTs for HS should anticipate higher response rates in placebo arms when patients with more severe symptoms are selected for inclusion in trials. Future studies should evaluate HS patients across the spectrum of disease severity to determine the impact of regression to the mean on outcomes in HS RCTs.

Third, there are several approaches to account for variations in the disease history²⁶. Clinical trials of longer duration could capture more of this natural variation. Also, a third “no treatment” arm without any active or inert treatment would be ideal to control for the natural history of the disease and regression to the mean.

Finally, objective and consistent outcome measures are needed to compare different therapeutics across RCTs for HS. It is possible that the placebo response is high in HS because the outcome measures that are being utilized are not sufficiently robust to optimally capture disease activity and measure improvement. There is currently an effort underway by the HISTORIC (HIdradenitis SuppuraTiva cORe outcomes set International Collaboration) group of IDEOM (International Dermatology Outcome Measures group) to develop acceptable outcome measures for HS²⁷. A Delphi process was undertaken by various stakeholder groups, including healthcare providers, patients and payers, to design a core outcome set that can be utilised uniformly. Five core domains were selected including pain, physical signs, quality of life, global assessment, and progression of course, and workgroups are now developing instruments to measure outcomes in these domains. Additional objective measures such as ultrasound imaging can also be utilized to identify subclinical tracts that can allow for earlier and more accurate diagnosis and staging²⁸. Uniform outcome measures can also aid in eventually making a meta-analysis possible for HS RCTs in the future.

Clinical Implications

A significant placebo effect is important in medicine as it can form the basis of non-pharmacological treatments and help optimize current medication use⁸. It also highlights the importance of the doctor patient relationship which can result in greater treatment adherence, patient education, empowerment, and encouragement to adopt beneficial lifestyle changes⁸. Our review suggests complimentary approaches to maximize the placebo effect in clinical practice, such as understanding the patients' belief system, verbal suggestion of improvement, understanding the impact of route of medication administration, and the value of a caring physician- patient relationship.

The limitations of this paper include the many different outcomes used in the HS studies to measure treatment success which made it challenging to quantify the placebo response. Furthermore, publication bias plays into any literature review since studies with positive findings are known to be published more frequently.

Conclusions

This systematic review demonstrates that there is a robust placebo response in HS, most marked in physical signs, but also in pain responses. This information can inform future clinical trial design and also be used to advocate for non-medicinal aspects of treating patients such as building a strong, therapeutic doctor patient relationship and providing more encouragement for behavioural change.

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Conflict of Interest:

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- All authors state no conflict related to this manuscript.

Abbreviations

AD	Atopic Dermatitis
AN	Abscess/Nodule
CRP	C-Reactive Protein
DLQI	Dermatology Quality of Life Index
EASI	Eczema Activity Severity Index

ESR	Erythrocyte Sedimentation Rate
HiSCR	Hidradenitis Suppurativa Clinical Response
HS	Hidradenitis Suppurativa
HSSI	Hidradenitis Suppurativa Severity Index
mSS	Modified Sartorius Score
NRS	Numerical Rating Score
PASI	Psoriasis Area Severity Index
PGA	Physician Global Assessment
RCT	Randomized Clinical Trial
VAS	Visual Analogue Score

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Capsule summary

- There is a robust placebo response in Hidradenitis Suppurativa (HS) randomized clinical trials, especially in physical signs and pain outcomes.
- Understanding the magnitude of the placebo response in HS can inform clinical trial design and help physicians target non-medicinal aspects of treatment.

Figure 1. Placebo response for physical signs, DLQI and pain in placebo controlled randomized clinical trials.

Percent improvement was calculated as [change from baseline/baseline] from available data in each study listed in Table 1 Results for (A) placebo arm and (B) treatment arms for various outcomes for physical signs (including 50% reduction in HSSI, Sartorius score, improvement in HS-PGA, HiSCR, disease activity score)*, DLQI and pain. Positive result indicates improvement in a given measure, negative result indicates worsening.

The numbers in parentheses in part A represent the study numbers listed in Table 1.

*HSSI: Hidradenitis Suppurativa Severity Index; DLQI: Dermatology Quality of Life Index; HS-PGA: Hidradenitis Suppurative

- Physical Global Assessment; HiSCR: Hidradenitis Suppurativa Clinical Response.

Figure 2. Changes in patient global assessment of skin pain in PIONEER I and II clinical studies. Percent of patients who reached 30%, 40%, or 50% reduction in pain assessment in placebo group (P, dotted lines) versus active treatment (A, adalimumab) group (solid lines) in a post-hoc analysis of the PIONEER I and II studies³⁵.

Table 1:

HS Studies for inclusion in Systematic Review

	STUDY*	SAMPLE SIZE PLACEBO	OUTCOME MEASURE	PLACEBO**	ACTIVE TREATMENT	ACTIVE TREATMENT
1	Grant et al, JAAD, 2010 ³²			IV	infliximab IV 5mg/kg	
		23	Percent of patients with 50% reduction in HSSI ^a from baseline at Wk 8	5%	26% (p=.092)	
			Change in mean DLQI ^b	- 1.6	- 10 (p=0.003)	
			Decrease in mean pain VAS ^c	- 0.6	- 39.8 (p < .001)	
			Change in mean CRP ^d	+ 0.4	-1.0 (p=.062)	
			Change in mean ESR ^e	+ 5.9	-11.7 (p=.012)	
			Mean PGA ^f scores at Wk 8	4.7	1.8 (p<.001)	
2	Miller et al, BJD, 2011 ³³			SC	adalimumab SC 40mg EOW ^k	
		6	Mean change in Sartorius score at Wk6 (95% CI)	+ 7.5 (-3.88 - 18.88)	- 10.67 (-18.91 to - 2.42, p=0.024)	
			Mean change in pain VAS at Wk6 (95% CI)	- 8.33 (-32.71 - 16.04)	- 21.62 (-46.14 - 2.28, p=0.31)	
			Mean change in Sartorius score at Wk12 (95% CI)	+ 5.83 (-2.70 - 14.37)	- 11.27 (-21.76 to -0.78, p=0.074)	
			Mean change in pain VAS at Wk12 (95% CI)	+ 3.17 (-33.83 - 40.17)	- 13.40 (-42.24 - 15.6, p=0.41)	
			Mean change in DLQI at Wk12 (95% CI)	+ 1.0 (-1.39 - 3.39)	- 3.67 (-8.99 - 1.66, p=0.06)	
3	Kimball et al, Annals IM, 2012 ³⁴			SC	adalimumab SC 40mg EOW ^k	adalimumab SC 40mg weekly
		51	Percent of patients with HS-PGA score with at least a 2-grade improvement at Wk16	3.9%	9.6% (p=.25)	17.6% (p=0.025)
			Mean % change from baseline ± SE: inflammatory nodules	- 13.2% ± 12.9	- 30.4% ± 11.8	- 43.40% ± 11.9 (p=0.089)
			Mean % change from baseline ± SE: abscesses	- 26.9% ± 14.3	- 54.3% ± 13.8	- 58.2% ± 16.6 (p=0.152)
			Mean % change from baseline ± SE: fistulas	+ 25.1% ± 30.4	- 13.5% ± 25.3	- 31.1% ± 26.3 (p=0.166)
			Mean change in mSS ^g from baseline ± SE:	+ 17.2 ± 9.8	- 32.0 ± 9.5	- 40.2 ± 9.8 (p=0.097)
			Mean change in DLQI ± SE	- 2.3 ± 0.9	- 3.2 ± 0.8	- 6.3 ± 0.9 (p=0.001)
			Patients 30% and 10-mm reduction in VAS (95% CI)	27.1% (15.3-41.9)	36.2% (22.7-51.5)	47.9% (33.3-62.8%, p=0.037)
	Kimball et al, NEJM, 2016 ⁹			SC		adalimumab SC 40mg weekly
4	PIONEER I	154	HiSCR ^h at Wk12	26.0%		41.8% (p=0.003)

	STUDY*	SAMPLE SIZE PLACEBO	OUTCOME MEASURE	PLACEBO**	ACTIVE TREATMENT	ACTIVE TREATMENT
			Mean change in pain NRS ⁱ (0–10) baseline to W12	– 0.7		–1.3 (p<0.05)
			Mean change in DLQI baseline to Wk12	– 2.9		–5.4 (p<0.001)
			Percent of patients with total abscess and inflammatory nodule count of 0,1, or 2	28.6%		28.9% (p=0.96)
			Percent of patients with 30% reduction and 1 unit reduction in pain score	24.8%		27.9% (p=0.63)
			Change in mean score in mSS from baseline	– 15.7		–24.4 (p=0.12)
5	PIONEER II	163	HiSCR at Wk12	27.6%		58.9% (p<0.001)
			Mean change in pain NRS (0–10) baseline to Wk12	– 0.7		–2.3 (p<0.001)
			Mean change in DLQI baseline to Wk12	– 2.3		– 5.1 (p<0.001)
			Percent of patients with total abscess and inflammatory nodule count of 0,1, or 2	32.2%		51.80% (p=0.01)
			Percent of patients with 30% reduction and 1 unit reduction in pain score	20.7%		45.7% (p<0.001)
			Change in mean score in mSS from baseline	– 9.5		– 28.9 (p<0.001)
6	Tzanetakou et al, JAMA Derm 2015 ³⁵			SC	anakinra (rIL-1RA) 100mg SC daily	
		10	Improvement in Disease Activity Score ^j from baseline at Wk12	~ + 7%	~ – 12% (p=0.07)	
			Change in Sartorius score at Wk 12	~0%	~0%	
			Change in self assessment VAS score at Wk 12	~ –15%	~ –10%	
			Change in pain VAS score at Wk 12	~ –5%	~ –10%	
			HiSCR achieved in % of patients at Wk 12	30%	78% (p=0.04)	
			DLQI ^{***}	not stated	not stated	
7	Kanni et al, JID, 2017 ³⁶			IV	MABp1 (anti-IL-1a) IV 7.5 mg/kg	
		10	Percent of patients who met HiSCR at Wk12 (95% CI)	10%	60% (p=0.035)	
			Percent change of total AN ^j count	0%	– 40% (p<0.033)	
			Decrease in VAS	30%	70%	
			Time to new exacerbation	7 weeks	11 weeks (p=0.159)	

	STUDY*	SAMPLE SIZE PLACEBO	OUTCOME MEASURE	PLACEBO**	ACTIVE TREATMENT	ACTIVE TREATMENT
			Decrease in total lesion depth >20%	22.2%	77.8% (p=0.027)	

* All studies included patients with moderate-to-severe HS

** Results extracted from their respective studies, and directionality assigned for ease of review. + indicates addition i.e. worsening in that outcome measure, – indicates reduction i.e. improvement (~ refers to data extracted from graphs with no associated precise numerical value). P values reported from original studies, active treatment versus placebo groups

*** Overall change in DLQI at week 12 was not different between the study arms except for questions relating to clothing and sexual intercourse (Q7 and Q9).

Abbreviations:

^aHSSI: Hidradenitis Suppurativa Severity Index

^bDLQI: Dermatology Quality of Life Index

^cVAS: Visual Analogue Score

^dCRP: C-Reactive Protein

^eESR: Erythrocyte Sedimentation Rate

^fPGA: Physician Global Assessment

^gmSS: Modified Sartorius Score

^hHiSCR: Hidradenitis Suppurativa Clinical Response

ⁱNRS: Numerical Rating Scale

^jAN: Abscess/ inflammatory nodule

^kEOW: Every Other Week

^lDisease activity score: sum of scores of all affected areas: 2 largest diameters in each affected area in millimeters times the degree of inflammation in each lesion.

Bolded values were converted into percentage change and utilized in the creation of Figure 1.