Addressing High Placebo Response Rates in Randomized Clinical Trials for Hidradenitis Suppurativa

Amit Garg,[1] Nicole Mastacouris,[1] John R. Ingram[2] and Andrew Strunk[1]

[1]Department of Dermatology, Donald and Barbara Zucker School of Medicine at Hofstra/Northwell, New Hyde Park, New York, USA

[2]Division of Infection and Immunity, Cardiff University, University Hospital of Wales, Heath Park, Cardiff, UK

Corresponding author: Amit Garg, MD

Email: amgarg@northwell.edu

ORCiD: AG - 0000-0003-0886-6856

JRI - 0000-0002-5257-1142

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A fundamental threat to drug development programs in hidradenitis suppurativa (HS) is high placebo response rates yielding narrow separation from active arms and potentially obscuring clinically meaningful treatment differences. Among 11 Phase II/III trials, median placebo response rate using Hidradenitis Suppurativa Clinical Response (HiSCR 50) as a primary endpoint was 31% (25th percentile 26.85%; 75th percentile 36.35%) (Table 1).

Disease fluctuations with flares are common in HS. While patients may also encounter improvements in activity, in part due to regression to the mean, clinical experience indicates that moderate to severe patients are unlikely to achieve spontaneous improvement to the degree required by endpoints applied in HS trials over 12-16 weeks. Accordingly, the basis for high placebo responses in HS trials may lie in accuracy of investigator ratings or the measure used as the endpoint, and not spontaneous and significant improvement in disease.

Is it the Rater?

Unlike physical assessments in monomorphic skin diseases including plaque psoriasis, vitiligo, and alopecia areata, HS assessments are more complex due to morphologic heterogeneity. Three distinct lesions characterize HS, including abscesses, nodules and tunnels. Additionally, nodules may be inflammatory (iN) or non-inflammatory (non-iN), and tunnels may be draining (dT) or non-draining (non-dT). Moderate to severe patients also have inflammatory and non-inflammatory papules and plaques, pyogenic granuloma-like nodules (PGN), pustules, and bridged scars. Moreover, erythema, a marker used to classify lesions as inflammatory, is more difficult to discern in darker skin toned patients.

Even experienced raters have challenges with morphologic heterogeneity in HS. In an inter-rater reliability exercise among 12 experts, observed agreement on lesion identification ranged from poor to moderate.[1] Accuracy of lesion specification by non-dermatologist study personnel is unknown.

Is it the Endpoint Measure?

The benchmark for efficacy in HS trials has been HiSCR, defined as ≥50% reduction in abscess and iN (AN) count relative to baseline, and no increase in abscess or dT count.[2] The HiSCR requires

investigators to accurately identify abscesses and iNs, the latter requiring distinction from non-iNs, inflammatory papules, plaques, and PGNs. Given that abscess or dT counts cannot increase relative to baseline to achieve HiSCR, abscesses must also be distinguished from iNs, and draining tunnels must be distinguished from draining abscesses, non-dTs and bridged scars. Moreover, given that responder classification may hinge on a single erroneously counted abscess or dT, HiSCR requires precise counting of qualifying lesions with potential for miscounting as numbers increase. In a phase II trial, placebo response rates at week 12 were 4.7% using HS-PGA and 16.3% using HiSCR, suggesting that measures which are less sensitive to exact lesion count may result in lower placebo response.

Psychometric assessments of HiSCR performed by expert raters are limited. In interventional trials and observational studies, intraclass correlation coefficients (ICC) for intra-rater reliability of AN count were generally high. The ICCs for abscess and dT counts have ranged from 0.70 to 0.83 and 0.78 to 0.95, respectively.[2,3] However, given that ICC is a *relative* measure of reliability, high ICCs can correspond to large *absolute* deviations in AN count between repeated measurements by the same rater. These absolute deviations are most relevant when evaluating change over time in a patient and could contribute to false appearance of HiSCR response. To date, validation studies have focused on relative measures of reliability rather than absolute agreement of lesion count measurements.

How can we overcome these challenges?

Requirements of HiSCR to recognize, distinguish and count among and within lesion types, along with our human imperfections in doing so, both may limit rating quality in trials. The Hidradenitis Suppurativa Core Outcomes Set International Collaboration (HiSTORIC) group is addressing challenges in drug development programs through development of a core measures set that may overcome important limitations to measuring response. For example, HiSTORIC has developed and validated the HS investigator global assessment (HS-IGA) which obviates the need to distinguish lesion types and limits lesion counting.[4,5] HiSTORIC is also testing a measure which assesses color change, induration, skin openings, extent of tunnels, and surface area, without having to distinguish and count lesions.[6] HiSTORIC has supported standardization of morphologic terms for HS lesions and is also pursuing standardization of

study assessments (ie, pressure adjacent to tunnels to assess drainage; rating of PNGs). Other solutions include utilization of ultrasound as an imaging aid to identify tunnels and their branches, as well as augmenting the depth of investigator training. Addressing limitations to accurate assessment of disease activity in the physical signs domain will be critical to discriminating treatment differences, and to diminishing this fundamental gap in care for HS patients.[7]

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Table I – Randomized Placebo-Controlled Trials in Hidradenitis Suppurativa Using Hidradenitis Suppurativa Clinical Response (HiSCR 50) as a Primary Endpoint

	Study identifier[a], Completion year[b]	Active Treatment(s)	Treatment Response Rate(s) (sample size)[c]	Placebo Response Rate (sample size)[c]
Phase II	NCT03248531, 2018	Bimekizumab Adalimumab	57.3% (n=44) 59.5% (n=20)	26.1% (n=20)
	NCT03487276, 2019	Vilobelumab	40% (n=30) 51.5% (n=33) 38.7% (n=31) 45.5% (n=33)	47.1% (n=34)
	NCT03628924, 2020	Guselkumab	50.8% (n=59) 45.0% (n=60)	38.7% (n=62)
	NCT03926169, 2021	Risankizumab	46.8% (n=80) 43.4% (n=81)	41.5% (n=82)
	NCT04430855, 2021	Upadacitinib	38.3% (n=47)	23.8% (n=21)
Phase III	NCT01468207, 2014	Adalimumab	41.8% (n=153)	26.0% (n=154)
	NCT01468233, 2014	Adalimumab	58.9% (n=163)	27.6% (n=163)
	NCT03713619, 2021	Secukinumab	45.0% (n=181) 42.0% (n=180)	34.0% (n=180)
	NCT03713632, 2021	Secukinumab	42.0% (n=180) 31.0% (n=183)	31.0% (n=183)
	NCT04242498, 2021	Bimekizumab	53.8% (n=144) 52.0% (n=291)	32.3% (n=74)
	NCT04242446, 2022	Bimekizumab	45.3% (n=144) 47.8% (n=289)	28.7% (n=72)

a – Study identifier provided on ClinicalTrials.gov
b – Refers to primary completion date of study on ClinicalTrials.gov
c – Sample size defined by number of patients included in analysis

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For patients with plaque psoriasis (including psoriatic arthritis with coexistent moderate to severe psoriasis) and a body weight ≥ 120 kg who did not achieve complete skin clearance at week 16, 320 mg every 4 weeks after week 16 may further improve treatment response. Consider discontinuing if no improvement by 16 weeks of treatment. Renal or hepatic impairment: No dose adjustment needed. Elderly: No dose adjustment needed. Administer by subcutaneous injection to thigh, abdomen or upper arm. Rotate injection sites and do not inject into psoriatic plaques or skin that is tender, bruised, erythematous or indurated. Do not shake pre-filled syringe or pre-filled pen. 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