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Race and Ethnicity Gaps in Global Hidradenitis Suppurativa Clinical Trials

Kyla N. Price[a] Jennifer L. Hsiao[b] Vivian Y. Shi[c]

[a]University of Illinois College of Medicine, Chicago, IL, USA; [b]Division of Dermatology, Department of Medicine, University of California Los Angeles, Los Angeles, CA, USA; [c]Division of Dermatology, Department of Medicine, University of Arizona, Tucson, AZ, USA

Keywords
Hidradenitis suppurativa · Race and ethnicity · Clinical trials

Abstract
Background: Hidradenitis suppurativa (HS) is an often-debilitating disease characterized by chronic and recurrent painful nodules, abscesses, and sinus tracts affecting the intertriginous areas. Despite evidence in the literature of varying prevalence of HS among different racial and ethnic groups, no studies have evaluated the overall generalizability of clinical trial results considering the increased prevalence of HS among African American populations. Additionally, there is a paucity of data exploring the distribution of race and ethnicity in randomized controlled trials (RCTs) for HS. The goal of this analysis is to explore the distribution of race and ethnicity in recent HS RCTs. ***Summary:*** Using ClinicalTrials.gov and PubMed, race and ethnicity demographics were extracted from phase II and III trials published from 2000 to August 2019. Fifteen trials were included and among these trials 669 (68.0%) participants were Caucasian and 138 (14.0%) were of African descent. Asians, American Indian or Alaskan Natives, and Native Hawaiian or other Pacific Islanders comprised 29 (2.9%), 3 (0.3%), and 1 (0.1%) participant respectively. Only 15 participants were reported as Hispanic as only three trials reported ethnicity data. The remaining 144 (14.6%) participants were recorded as "other/unspecified" (36 self-identified, 108 lacked race reporting). None of the trials included sub-analysis of treatment efficacy based on race or ethnicity.

Introduction

Hidradenitis suppurativa (HS) is a debilitating systemic inflammatory disease with a wide burden of comorbidities [1, 2]. Due to recent large epidemiologic studies, the enigma of HS prevalence in different ethnicities has begun to be deciphered, and from preliminary studies, African Americans appear to be more commonly affected and with higher severity [3]. It still remains unclear whether sociodemographic and cultural characteristics play a role in developing HS [4, 5]. HS remains difficult to treat [6] and biomarkers capable of predicting drug response are crucial in order to further personalize treatment options. If personalization of the therapy is a prominent goal to achieve, generalizability of therapeutics is of paramount importance.

While the true prevalence is unknown, HS has an overall estimated prevalence ranging from 0.00033% to as high as 4.1% throughout Europe and the USA [7]. Based on US estimates, HS affects African Americans, biracial

karger@karger.com
www.karger.com/drm

Vivian Y. Shi, MD
Assistant Professor of Medicine, Division of Dermatology
University of Arizona, 7165 N Pima Canyon Dr.
Tucson, AZ 85718 (USA)
E-Mail vshi@email.arizona.edu

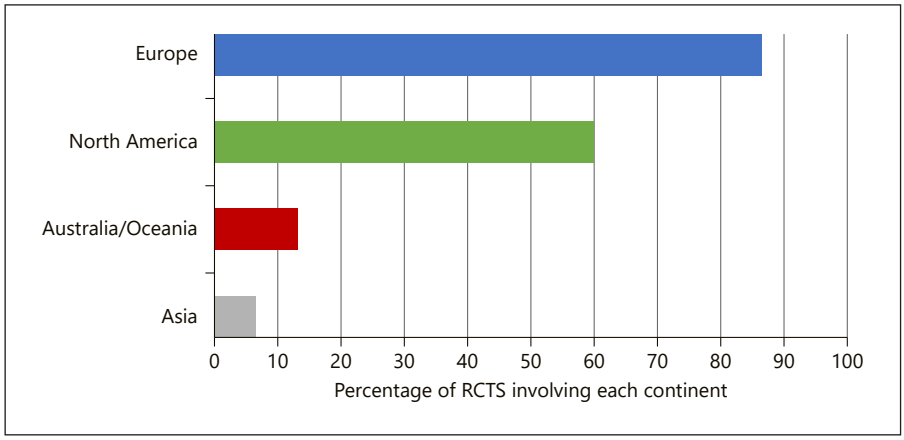

Fig. 1. Geographic distribution of phase II and III clinical trials for HS published from 2000 to August 2019.

(African American/Caucasian) individuals, and Caucasians, with a standard prevalence of 0.30, 0.22, and 0.10%, respectively [3, 7]. Conversely, HS affects Asians, Pacific Islanders, Native Americans, Latin Americans, and Native Hawaiians at much lower rates, with a standard prevalence of 0.04% [7]. The true prevalence of HS is likely higher, particularly among skin of color (SOC) populations, due to limitations in accounting for underdiagnosis, misdiagnosis, and patient reluctance to seek treatment [7]. Some of these prevalence differences in SOC groups have been related to limited access to medical care, anatomical differences, genetics, and the increased prevalence of lower socioeconomic status (SES) among these groups [1].

In the new era of emerging immunomodulators, it is essential that study populations of clinical trials attempt to represent their target populations. The goal of this review is to explore the literature of phase II and III randomized clinical trials in HS to examine the representation of racial and ethnic minorities and to assess for sub-analysis of treatment efficacy based on race and ethnicity.

Methods

We searched both ClinicalTrials.gov and PubMed for completed phase II and III clinical trials for interventional drugs for HS published between 2000 and August 2019. For ClinicalTrials.gov, the search terms used were "hidradenitis suppurativa," "acne inversa," "acne conglobata," "apocrine acne," "Verneuil's disease," and "Velpeau's disease" along with the individual systemic medication names (e.g., "adalimumab"). The drugs included in this analysis were referenced in a recent review article exploring targeted therapies for HS [8]. Trials were only included if they had associated publications with their results. Trials with vaccines, supplements, and non-English publications were excluded. For PubMed, the search terms that were used included "hidradenitis suppurativa" AND the medication name. Additionally, "hidradenitis suppurativa" was searched individually with the PubMed clinical trials filter.

Both race and ethnicity demographics were recorded for each of the studies based on the definitions as reported by the US Census Bureau [9]. For studies that did not include race or ethnicity data, the participants within these studies were labeled as "other/unspecified."

The distribution of the location of these trials was tallied based on the continent for each individual study. The represented continents were counted for each individual clinical trial.

Results

Fifteen phase II and III trials that fit the search criteria were identified and included in the analysis (Table 1). Twelve (80.0%) trials were phase II and three trials (20.0%) were phase III. Nearly half of the trials (seven trials, 46.7%) were published within the last 5 years (2015–2019). All except three trials were published in the last ten years (2010–2019). Twelve trials (80.0%) enrolled only adults, and three trials (20.0%) also enrolled adolescents 16 or 17 years of age and older. Eight trials (53.3%) were blinded and 7 trials (46.7%) were open label.

Enrollment Geography

Thirteen (86.7%) trials took place in Europe, nine (60.0%) trials in North America, two (13.3%) trials in Australia/Oceania, and one (6.7%) in Asia (Fig. 1). Almost half (seven trials, 46.7%) of the trials included sites in the USA. Four trials (26.7%) took place exclusively in the USA. The most common locations outside of the USA were Greece, The Netherlands, and Denmark. No trials were reported in Africa or South America.

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Table 1. Phase II and III clinical trials in hidradenitis suppurativa

Medication	Year	Phase	Trial locations	HS patients in cohort, *n*	Caucasian, %	African descent, %	Asian, %	American Indian or Alaskan Native, %	Native Hawaiian or other Pacific Islander, %	Other/ unspecified race, %	Hispanic, %	Sub-analysis by ethnicity?	Clinical-Trials.gov identifier	First author	Ref. No.
Adalimumab	2012	II	USA, Denmark, Germany, The Netherlands	154	71	19	–	–	–	10	–	No	NCT00918255	Kimball	12
Adalimumab	2016	III	48 study locations worldwide[1]	307	76	20	1	1	–	2	–	No	NCT01468207	Kimball	13
Adalimumab	2016	III	53 study locations worldwide[2]	326	84	9	3	0	0	4	–	No	NCT01468233	Kimball	13
Adalimumab	2011	II	Denmark	21	–	–	–	–	–	100	–	No	EudraCT: 2006-005297-48	Miller	14
Adalimumab	2010	II	USA	10	50	30	–	–	–	–	20	No	NCT00827996	Amano	15
Adalimumab	2019	III	Japan	15	–	–	100	–	–	–	–	No	NCT02904902	Morita	16
Anakinra	2013	II	USA	6	33	33	–	–	–	–	33	No	NCT01516749	Leslie	17
Anakinra	2015	II	Greece	19	–	–	–	–	–	100	–	No	NCT01558375	Tzanetakou	18
Apremilast	2019	II	The Netherlands	20	95	–	–	–	–	5	–	No	EudraCT 2016-000859-27	Vossen	19
Etanercept	2007	II	Greece	10	–	–	–	–	–	100	–	No	NCT00329823	Giamarellos-Bourboulis	20
Etanercept	2006	II	Ireland	6	–	–	–	–	–	100	–	No	NCT00329823	Cusack	21
Etanercept	2009	II	USA	15	80	20	–	–	–	–	–	No	NCT00107991	Lee	22
Infliximab	2010	II	USS	38	37	26	–	–	–	8	29	No	NCT00795574	Grant	23
MABp1	2018	II	Greece	20	–	–	–	–	–	100	–	No	NCT02643654	Kanni	24
Ustekinumab	2016	II	The Netherlands	17	–	–	–	–	–	100	–	No	NCT01704534	Blok	25

HS, hidradenitis suppurativa. [1] In countries including Australia, Canada, Czech Republic, Germany, Hungary, and the USA. [2] In countries including Australia, Canada, Denmark, France, Greece, The Netherlands, Sweden, Switzerland, Turkey, and the USA.

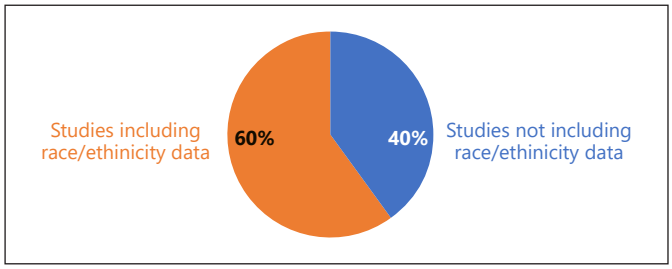

Fig. 2. Proportion of phase II and III clinical trials for HS published from 2009 to August 2019 reporting race and/or ethnicity data.

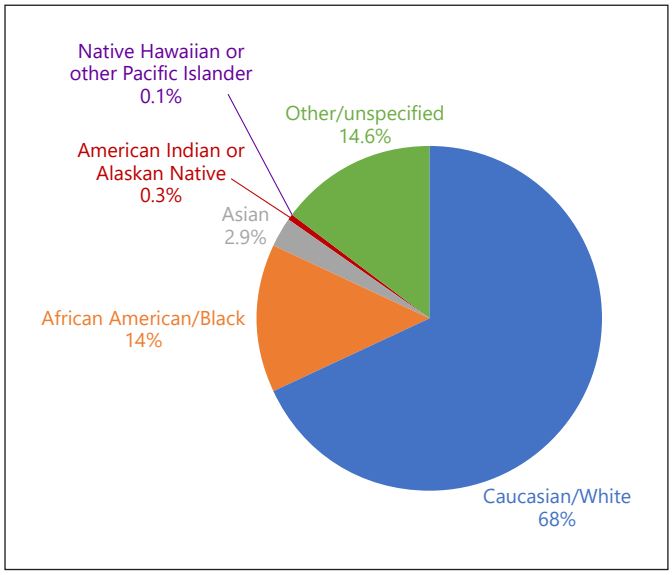

Fig. 3. Categorization of race in phase II and III clinical trials for HS published from 2009 to August 2019.

Race and Ethnicity

Of the 15 trials included in this analysis, nine trials (60.0%) included race and ethnicity data (Fig. 2). Six trials (40.0%) exclusively reported race data, and three trials (20.0%) reported race and ethnicity data. The three trials reporting ethnicity data all took place in the USA. None of the trials included sub-analysis of clinical efficacy based on race or ethnicity.

A total of 984 participants were included; 669 (68.0%) were Caucasian and 138 (14.0%) were of African descent (Fig. 3). The least represented groups were Asians, American Indian or Alaskan Natives, and Native Hawaiian or other Pacific Islanders, with 29 (2.9%), 3 (0.3%), and 1 (0.1%) participant, respectively, representing each group. The remaining 144 (14.6%) participants were considered "other/unspecified" (36 self-identified, 108 lacked race reporting). Fifteen participants (1.5%) were reported as Hispanic although only three trials reported ethnicity information.

Adalimumab

The most common investigated therapy was adalimumab in six trials (40.0%). A total of 833 participants participated in adalimumab trials; 622 (74.7%) were Caucasian, 123 (14.8%) were of African descent, 55 (6.6%) were "other" (32 self-identified, 23 due to lack of reporting), 29 (3.5%) were Asian, 3 (0.4%) were American Indian or Alaskan Native, and none were native Hawaiian or other Pacific Islander. Only one randomized controlled trial (RCT) reported ethnicity data, and subsequently only 2 participants (0.2%) were reported as Hispanic.

Discussion

Our results suggest that the population currently reflected in recent HS RCTs may not be representative of the diverse patient population affected by this disease. As numerous new pipeline biologics targeting inflammatory mediators (TNF-a, IL-1, IL-17, IL-12, IL-2) [8] are under investigation, therapies should be catered to their intended target patient populations. African Americans are significantly more affected by HS, and yet Caucasian patients comprise 68.0% of the patient population included in HS clinical trials while those of African descent comprise only 14.0%. Current evidence suggests a complex relationship between HS, low SES, metabolic syndrome, and the higher prevalence of HS in African Americans [1]. Biracial patients are also not adequately represented as typically there is no option to specify multiple racial identities. Since biracial patients are differentially affected by HS, particularly patients that are of both Caucasian and African descent, it may be important to include a separate category to allow multiracial individuals to specify their multiple racial identities.

Our results show that a majority of clinical trials took place in Europe and North America, particularly in the USA. With Europe comprising the majority of trial sites, it is likely that these locations lacked the racial diversity reflective of the US population. In order to close this gap, establishing trials in locations of relative high prevalence of diversity and including international site locations will help diversify the patient pool.

Limited research has been conducted in determining how HS treatments may differentially affect racial and ethnic groups. This gap can be lessened through outcome

sub-analysis by racial and ethnic groups. Diversity recruitment in HS trials should be prioritized. With SOC patients so disproportionately affected by HS, they should be more represented in HS trials than is currently evident. Reduced enrollment of SOC populations may be related to lack of disease awareness, healthcare access, education, and social and cultural barriers [10]. As providers, presenting more focused, one-on-one sessions to patients regarding HS and the potential benefits of clinical trials may increase diversity enrollment [11]. Additionally, social barriers related to SES can be mitigated by providing access to transportation, maximizing subject compensation, and allowing scheduling flexibility. Finally, accommodating any potential language barriers by recruiting bilingual medical staff and utilizing language interpretation services when available can also help facilitate diverse enrollment.

There is currently no standardization of HS phenotypic classification. We should acknowledge that disease presentation and morphology may differ among HS patients of various racial and ethnic backgrounds. Existing and emerging treatment options (including lifestyle modifications, complementary and alternative medicine, medical therapies, and procedures) should ideally be tailored according to each patient's immunologic and phenotypic profile.

Conclusion

With such striking differences in disease prevalence in HS, more emphasis should be placed on representing those differences in clinical trials. Of particular significance is the gap in representation of the African American population, who are disproportionately affected by HS, in recent HS RCTs. Discovering potential variances in treatment responses in different HS patient subgroups may be instrumental in providing more targeted and optimized patient care leading to improved patient outcomes.

Key Message

Despite a relatively higher prevalence of hidradenitis suppurativa (HS) in skin of color, these populations are minimally represented in HS RCTs. Future studies should encourage diverse participant enrollment, continue to report race and ethnicity data, and incorporate sub-analysis of clinical efficacy to improved generalizability of HS therapies.

Disclosure Statement

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K.N.P. and J.L.H. have no conflicts of interest to declare relevant to this paper.

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Author Contributions

All authors contributed to drafting and revision of the manuscript and approved the final version for submission.

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