Published in final edited form as:

J Dermatolog Treat. 2018 September ; 29(6): 637–640. doi:10.1080/09546634.2018.1425360.

Prevalence of positive QuantiFERON Gold In-Tube testing in Hidradenitis Suppurativa

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Abstract

Hidradenitis suppurativa (HS) is a chronic, recurrent, inflammatory disease of the apocrine sweat glands. Tumor necrosis factor-alpha (TNF- α) inhibitors are commonly used to treat HS. However, prior to initiating therapy patients must be screened for mycobacterium tuberculosis (mTB) exposure. Several mTB screening tests based on interferon gamma release assays are commercially available, but the performance of these assays in the HS population is unknown. The purpose of this study was to investigate the performance of the QuantiFERON gold in-tube assay (QFT-GIT) in a cohort of patients with Hidradenitis suppurativa (HS). This prospective study was conducted through the Wound Etiology and Healing (WE-HEAL) Study. QFT-GIT testing was performed using a commercial laboratory. Patients with positive test results underwent follow-up testing to evaluate for latent tuberculosis infection (LTBI). Data was collected on demographics and disease activity scores including Hurley stage, HS Sartorius score (HSS) and active nodule (AN) count.

Of the 69 patients with a confirmed diagnosis of HS, 7 (10.1%) tested QFT-GIT positive and 5.8% were diagnosed with LTBI. QFT-GIT results did not correlate with demographic characteristics or HS disease activity.

Keywords

Hidradenitis Suppurativa; Tumor necrosis factor-alpha; QuantiFERON gold; Interferon-gamma; IFN- γ

INTRODUCTION

Hidradenitis suppurativa (HS) is a chronic, inflammatory disease of the apocrine sweat glands, characterized by recurrent abscessing inflammation(1). The severity of disease is assessed using the Hurley staging system (Table 1), and various activity scores including the Hidradenitis suppurativa Sartorius score (HSS) and active nodule (AN) count(2–5). While

the pathogenesis of inflammation in HS is not well understood, studies suggest there may be an immunologic driver of the inflammatory response in this disease (6–11).

Recent clinical trials have demonstrated efficacy of tumor necrosis factor- α (TNF- α) inhibitors in HS (12, 13). However, these agents are known to predispose to re-activation of mycobacterium tuberculosis (mTB) in patients who have previously been exposed to mTB (14–16). All patients with HS who are being considered for TNF- α inhibitor therapy therefore undergo screening for latent mTB either via tuberculin skin test, or more commonly through interferon gamma release assay (IGRA).

IGRA are commonly used to screen for mTB exposure(17). These assays assess the cell-mediated response to mTB antigens. The QuantiFERON gold in tube (QFT-GIT) assay (Qiagen, Hilden, Germany) is an ELISA-based assay which quantifies IFN- γ release in response to three mTB antigens (ESAT-6, CFP-10 and TB7.7). The result is reported as quantification of IFN- γ in international units (IU) per mL. The test is considered positive if the IFN- γ response to TB antigens is above the test cut-off after subtracting the background IFN- γ response in the negative control. An alternative IGRA, the TSPOT®.TB (Oxford Immunotec, UK), is also commercially available and uses ELISPOT assay to measure the number of antimycobacterial effector T-cells that produce IFN- γ in a sample of blood. The mTB specific antigen peptides that are assessed in the TSPOT®.TB assay are the ESAT-6 and CFP-10.

Until now, the performance of IGRA has not been specifically assessed in the HS population. The purpose of this study was to investigate performance of the commercially available QFTGIT assay in a cohort of patients with HS.

METHODS

This research was conducted through the Wound Etiology and Healing Study (WE-HEAL Study), a biospecimen and data repository approved by The George Washington University Institutional Review Board (IRB 041408, NCT 01352078). The WE-HEAL Study is conducted in accordance with applicable regulations and guidelines governing clinical study conduct and ethical principles of human subjects research that have their origin in the Declaration of Helsinki. This is a longitudinal observational study. All subjects gave written informed consent for longitudinal collection of their data while they received treatment according to standard of care.

Inclusion Criteria

This study was conducted utilizing data from the WE-HEAL subjects who had a confirmed diagnosis of HS. Diagnosis of HS was based on the Dessau Definition (Table 1). Time of data lock was July 1, 2017.

Data Management

Longitudinal clinical data were abstracted from the electronic health record (EHR) and stored using Research Electronic Data Capture (REDCap), a secure, web-based application designed to support data capture in research studies (18).

Clinical Outcome Measures

Clinical evaluation scores were completed by trained investigators during clinical visits. Prior studies have shown that interobserver variability of clinical scores including the Hidradenitis Suppurativa Sartorius score (HSS) is low (19) indicating that these are reliable measures of disease activity.

- 1. Hurley Stage**—The Hurley Staging system (Table 2) is used to assess overall HS disease severity at baseline and each subsequent visit in the GWU HS clinic. In this well validated staging system, lesions with single or multiple abscesses without sinus tracts or scarring are classified as stage I, lesions with recurrent abscesses with sinus tract formation and scarring are classified as stage II and lesions with diffuse involvement and multiple interconnected sinus tracts are classified as stage III (2).
- 2. Active Nodule (AN) Count**—Studies have shown that a 50% reduction in the AN count without increase in abscesses or draining fistulas (also known as the Hidradenitis Suppurativa Clinical Response or HiSCR) is a level that is associated with improvement in patient reported quality of life scores and pain level (20, 21). The total number of abscesses and inflammatory nodules (AN count) is assessed at baseline and each subsequent clinic visit to the HS clinic.
- 3. Modified HSS**—The modified HSS was used to assess disease activity at baseline and each clinical visit (22). This scoring system has been validated as a measure of disease activity in both longitudinal and intervention studies in HS (13, 19). The HSS score is assessed for each patient at each clinical visit to the HS clinic. A score of 3 points is assigned for each anatomic region involved; in each region, the presence of nodules scores 1 point and fistulae 6 points; the longest distance between lesions or size of the lesion is scored categorically to <5cm (1 point), 5–10cm (3 points) and >10cm (9 points); finally, an assessment of whether each lesion is Hurley Stage III (9 points) or not (0 points) is made. Regional scores are summed to achieve a total modified HSS disease activity score. The upper limit of the scale is open.
- 4. Verbal Pain Score Evaluation**—A numerical analogue pain score based on a verbal scale of pain (0–10 with 0 being no pain and 10 being worst pain ever) was collected from every patient seen in HS clinic, prior to removing dressings. This is a valid and reproducible score that is in routine clinical use (23).

QuantiFERON Gold Testing

QuantiFERON®-TB Gold In-Tube (QFT-GIT, Qiagen®) testing was performed according to manufacturer's instructions. According to protocol, specimens were transported to the laboratory within 14 hours of collection and all samples were analyzed using a single commercial laboratory (LabCorp, Burlington, NC).

Confirmatory testing

All patients who had either positive or indeterminate results on the QFT-GIT underwent follow up testing with either TSPOT®.TB or either purified protein derivative (PPD) skin

test along with infectious diseases evaluation and Chest X-Ray to determine whether the patient had latent mTB infection (LTBI).

Statistical Analysis

Data was analyzed using GraphPad Prism 5.03. Patients with positive or indeterminate QFT-GIT results were grouped into the QFT-GIT positive group for analysis. Differences in baseline demographics and in HS disease activity stratified by QFT-GIT status were examined using student's T-Test, Fisher's exact tests, and Chi-squared tests as appropriate.

RESULTS

Demographics

Of the 69 HS patients, 7 (10.1%) tested QFT-GIT positive. There were no significant differences in the age between the HS cohort that were QFT-GIT positive compared to those that were QFT-GIT negative (mean age 43.13 vs. 39.21 years, $p=0.45$). The HS cohort enrolled in the WEHEAL study is 71% female, and 65% African American with no significant difference seen in gender or race in the QFT-GIT positive and negative groups. Body mass index (BMI) was also similar in the QFT-GIT positive and negative groups (32.06 ± 5.62 vs. 33.99 ± 6.98 , $p=0.49$).

Disease activity in the QFT-GIT positive group

There were no significant differences in the numbers of patients who had Hurley stage III disease at enrollment in the QFT-GIT positive and negative groups ($p=1.00$). Disease activity as measured by HSS was similar in both groups (65.86 ± 54.61 vs. 60.11 ± 50.62 , $p=0.77$), and the mean active nodule count at enrollment was also similar in both groups (3.29 ± 2.29 vs. 3.64 ± 2.31 , $p=0.70$).

Outcome of follow up testing in QFT-GIT positive group

All of the patients who were QFT-GIT positive or indeterminate underwent additional evaluation with either TSPOT®. *TB* or either purified protein derivative (PPD) skin test along with clinical evaluation and Chest X-Ray to determine whether the patient had LTBI. Of the 7 patients with positive or indeterminate QFT-GIT results, 3 were determined to have false positive results, while 4 were diagnosed with LTBI and commenced appropriate therapy for this.

DISCUSSION

In this diverse cohort of patients with HS in Washington, DC we found a prevalence of positive QFT-GIT testing of 10.1% with 5.8% of patients confirmed to have LTBI. This prevalence is slightly higher than that seen in the general US population(24) where studies suggest a prevalence of LTBI based on QFT-GIT testing of 4.8% (95%CI 4.0–5.8).

We did not find any association between QFT-GIT test results and HS disease activity scores or demographic characteristics. The QFT-GIT test performed reliably in this population with

only 2 patients demonstrating indeterminate results. These findings indicate that the QFT-GIT remains a reliable test for screening for LTBI in the HS population.

One of the major limitations of this study was that the sample size was quite small. However, as TNF- α inhibitors become more widely used for HS, this study was important to confirm that the QFT-GIT test performs appropriately as a screening test for LTBI in the HS population. Recruitment to the WE-HEAL-HS cohort is ongoing and thus longitudinal analysis of outcomes for this population will be available.

Given the low false positive rate (only 3 of the patients with positive or indeterminate QFT-GIT tests had negative secondary testing), we postulate that the slightly higher prevalence of positive QFT-GIT testing in this study simply reflects the higher LTBI rates in an urban population rather than a higher prevalence of QFT-GIT related to HS disease. This hypothesis is further supported by the absence of any correlation between disease activity scores and QFT-GIT result. However, it will be important to replicate these findings in a larger cohort. The relatively high prevalence of LTBI in this cohort does further reiterate the importance of screening all HS patients for LTBI, independent of whether they are immediately being considered for TNF- α inhibitor therapy.

Conclusion

In this longitudinal observational cohort of HS, the prevalence of positive QFT-GIT testing was 10.1%, and 5.8% of patients were confirmed to have LTBI. The false positive rate of QFT-GIT testing in this population was low.

FUNDING SOURCE:

This work was in part supported by award R01NR013888 from the National Institute of Nursing Research and by award number UL1 TR000075 from the National Center for Advancing Translational Sciences (NCATS), National Institutes of Health, through the Clinical and Translational Science Awards Program (CTSA).

Abbreviations:

HS	(Hidradenitis Suppurativa)
TNF-α	(Tumor necrosis factor-alpha)
IFN-γ	(Interferon-gamma)
IGRA	(Interferon gamma release assay)
QFT-GIT	(QuantiFERON gold in-tube assay)
AN	(Active nodule)
HSS	(Hidradenitis suppurativa sartorius score)
mTB	(mycobacterium tuberculosis)
LTBI	(latent tuberculosis infection)

EHR (electronic health record)**REFERENCES**

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Table 1:Dessau Criteria for Diagnosis of HS: 1st International Conference on HS, 2006, Dessau, Germany (25–27)

CRITERIA	DETAILS
Presence of recurrent painful or suppurating nodules	Present on 2 or more occasions within 6 months
Involvement of typical anatomic regions:	Axilla Genitofemoral area Perineum Gluteal Area Inframammary area
Typical lesions	Nodules (inflamed or non-inflamed) Sinus tracts (inflamed or non-inflamed) Abscesses Scarring
Secondary criteria	Family history of HS

Table 2:

Hurley staging system

STAGE	
0	No active HS
I	Localized abscess, no sinus tracts
II	Recurrent abscesses with sinus tracts and scarring, single or multiple widely separated lesions
III	Diffuse involvement with multiple interconnected sinus tracts and abscesses
NA	Post-operative patient in whom Hurley score cannot be assessed either due to wound, wound VAC or integra placement.

Table 3:

Demographic and clinical characteristics of patients with positive and negative QuantiFERON-TB Gold testing.

	Negative QuantiFERON-TB Gold n= 62	Positive QuantiFERON-TB Gold n= 7	P Value
Age, Years (mean $\pm$ SD)	39.21 $\pm$ 12.47	43.13 $\pm$ 16.52	0.45
Sex (% Female)	70.97%	71.43%	1.0
Race (% African American)	64.52%	71.43%	1.0
BMI, kg/m ² (mean $\pm$ SD)	33.99 $\pm$ 6.98	32.06 $\pm$ 5.62	0.49
Pain (mean $\pm$ SD)	3.049 $\pm$ 3.319	3.00 $\pm$ 4.12	0.97
Disease Duration, years (mean $\pm$ SD)	10.82 $\pm$ 10.43	4.29 $\pm$ 3.40	0.11
Hurley Stage III	32 (51.61%)	4 (57.14%)	1.00
HSS (mean $\pm$ SD)	60.11 $\pm$ 50.62	65.86 $\pm$ 54.61	0.77
Baseline AN count (mean $\pm$ SD)	3.64 $\pm$ 2.32	3.29 $\pm$ 2.29	0.70