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General Information

Are external grants or funds being used to support this research?: No external grants or funds are being used to support this research.
How did you learn about the YODA Project?: Data Holder (Company)

Conflict of Interest

https://yoda.yale.edu/wp-content/uploads/2024/03/SV_57KskaKADT3U9Aq-R_3Pt42m1hTLyjEnT.pdf

Certification

Certification: All information is complete; I (PI) am responsible for the research; data will not be used to support litigious/commercial aims.
Data Use Agreement Training: As the Principal Investigator of this study, I certify that I have completed the YODA Project Data Use Agreement Training

1. NCT03628924 - A Phase 2, Multicenter, Randomized, Placebo-Controlled, Double-Blind, Proof-of-Concept Study to Evaluate Guselkumab for the Treatment of Subjects With Moderate to Severe Hidradenitis Suppurativa

What type of data are you looking for?: Individual Participant-Level Data, which includes Full CSR and all supporting documentation

Research Proposal

Project Title

Exploratory Analysis of Clinical Variables Associated with Clinical Response to Guselkumab Therapy in Hidradenitis Suppurativa.

Narrative Summary:

Hidradenitis Suppurativa (HS) is a chronic painful condition with a great need for novel therapies. Guselkumab is a therapy targeting IL-23 which was unsuccessful in Phase 2 clinical trials for HS. Multiple reasons exist for the lack of success of the phase 2 study including recent molecular evidence of subgroups of patients in which IL-23 is important for the development of inflammation and another subgroup in which it is not. These subgroups are generally stratified by gender but also
contributed to by BMI and comorbidities. This study aims to examine the patient and disease characteristics of individuals who responded to Guselkumab therapy in the Phase 2 clinical trial in order to confirm or refute molecular evidence of patient subgroups which may preferentially respond to IL-23 directed therapy in HS. The identification of this patient subgroup would enable a deeper understanding of disease mechanisms as well as provide important information regarding future trial design for future therapeutic targets. It will also hopefully enable the development of evidence for patients to access an existing effective therapy for treatment of HS.

Scientific Abstract:

Background:
Hidradenitis Suppurativa is a debilitating chronic inflammatory disease in need of novel therapeutics. As a disease largely driven by IL-17 mediated inflammation, it was unexpected that Phase 2 clinical trials of IL-23 antagonism failed to meet primary endpoints in HS. The reasons for this unexpected result may be explained by recent published evidence suggesting that IL-17 production in HS may be IL-23 independent in some patient subgroups. Evidence suggests that men with lower BMIs may be associated with IL-23 dependent IL-17 production, whereas single cell data from women with HS identify IL-17 production as IL-1B and IL-6 dependent and IL-23 independent.

Objectives:
This proposed post-hoc analysis aims to characterize clinical responders and non-responders to Guselkumab in the requested phase 2 clinical trial in order to validate or refute the hypothesis that gender and BMI may be significantly associated with clinical response to IL-23 antagonism as measured by standardized clinical outcomes including HiSCR-50, HiSCR-75 and IHS4-55. If validated, this would enhance understanding of the inflammatory heterogeneity of HS, and identify potential clinical stratification markers to direct further enquiry as to effective therapeutic options for HS patients.

Study Design:
Post-Hoc analysis of data produced in the course of the Phase 2 clinical trial of Guselkumab in Hidradenitis Suppurativa.

Participants:
All participants participating in the Phase 2 study of Guselkumab in Hidradenitis Suppurativa.

Primary and Secondary Outcome Measures:
Outcome measures of treatment efficacy (HiSCR-50) will be used as well as calculation of other clinically significant outcome measures including HISCE-75 and IHS4-55.

Statistical Analysis:
Similar to our previous work references below,[6,7,8], outcome measures such as the HiSCR-50, HiSCR-75 and IHS4-55 would be calculated using the individual patient data available. Each variable of interest will be assessed for normality with the Shapiro-Wilk test and histograms. Potential associations with gender, BMI, the presence of draining tunnels, as well as other a priori potential associations (age, Hurley stage, smoking status and family history) would be assessed via univariate analysis, and then with logistic regression for HiSCR-50/HiSCR-75/IHS4-55 and with linear regression for percentage change in IHS4 and absolute change in nodule count. Outcomes of interest would be any significant differences between proportion of participants achieving clinically significant outcomes when stratified by covariates of interest.

Brief Project Background and Statement of Project Significance:

Hidradenitis Suppurativa (HS) is a chronic inflammatory skin disease [1] which significantly impacts upon quality of life [2] and physical functioning [3]. It has an estimated prevalence of 1% of the general population [1], comparable with that of chronic plaque psoriasis. It is manifests as painful, recurrent abscesses, purulent nodules and chronically draining epithelialized tunnels [1]. HS patients suffer from extreme pain, psychological distress, psychosexual impairment and significant social isolation[1-3]. Current treatment modalities are limited and only half of participants achieve a reduction of 50% in inflammatory nodules [4]. The development of new therapeutics is hampered by...
our incomplete understanding of the pathophysiology of the disease [5].

Within the field of existing HS therapeutics, we have been able to identify specific clinical features which are associated with clinical response to therapy. This was achieved via post-hoc analysis of the individual patient data of participants in the Phase 3 PIONEER 1 and PIONEER 2 clinical trials of Adalimumab in HS. Our previous work has identified epithelialised draining tunnels[6] and elevated BMI [7] as clinical variables associated with a decreased odds ratio of response to Adalimumab therapy; and a positive family history [8] as associated with a decreased time to loss of clinical effect of Adalimumab.

These publications have had significant influence in the acknowledgement of disease heterogeneity and the immunological heterogeneity directly associated with epithelialised tunnels [9,10].

The proposed project would involve a post-hoc analysis of the individual patient data from the published phase 2 study of Guselkumab in moderate to severe Hidradenitis Suppurativa which failed to meet the primary endpoint of the trial [11].

The justification for examination of this study is the recent publication of data suggesting that IL-17 production in HS is not necessarily IL-23 dependent as is the case in psoriasis[12,13]. Women in published single cell data demonstrate IL-6 and IL-1B dependent IL-17 production, whereas men demonstrate IL-23 dependent production[12,13].

We aim to test the clinical relevance of this hypothesis through post-hoc examination of the aforementioned clinical trial data, by characterizing the patient and disease characteristics of clinical responders and non-responders to Guselkumab in HS.

Similar to our previous work discussed above [6,7,8], outcome measures such as the HiSCR-50, HiSCR-75 and IHS4-55 would be calculated. Each variable of interest will be assessed for normality with the Shapiro-Wilk test and histograms. Potential associations with gender, BMI, the presence of draining tunnels, as well as other a priori potential associations (age, Hurley stage, smoking status and family history) would be assessed with logistic regression for HiSCR-50/ HiSCR-75/ IHS4-55 and with linear regression for percentage change in IHS4 and absolute change in nodule count.

**Specific Aims of the Project:**

This Project aims to characterize the patient and disease characteristics of clinical responders to Guselkumab in Hidradenitis Suppurativa compared with clinical non-responders as defined by multiple outcomes including HiSCR-50, HiSCR-75 and IHS4-55.

This aim is to test the hypothesis that clinical response to IL-23 antagonism in HS is significantly associated with gender and BMI in line with molecular data regarding drivers of IL-17 inflammation in HS.

**Study Design:**

Individual trial analysis

**What is the purpose of the analysis being proposed? Please select all that apply.**

New research question to examine treatment effectiveness on secondary endpoints and/or within subgroup populations

**Research Methods**

**Data Source and Inclusion/Exclusion Criteria to be used to define the patient sample for your study:**

The data sources used will be the individual patient data from the requested clinical trial.
All participants who participated in the trials and who maintained enrollment in the trial until the week 16 primary endpoint will be included. Any patients with incomplete demographic, disease or response data will be excluded from analysis.

**Primary and Secondary Outcome Measure(s) and how they will be categorized/defined for your study:**

The outcome measures will be used from the reported outcome measures in the study - and the standard internationally accepted definitions of these outcome measures will be used.

- **HiSCR-50:** defined as a 50% Reduction in abscess and nodule count at Week 16 (Primary endpoint) compared to baseline with no increase in abscess count or draining tunnel count.

- **HiSCR-75:** defined as a 75% Reduction in abscess and nodule count at Week 16 (Primary endpoint) compared to baseline with no increase in abscess count or draining tunnel count.

- **IHS4-55:** Defined as a 55% reduction in IHS4 score at Week 16 (Primary Endpoint) compared to baseline. IHS4 score is calculated based on the accepted formula of $IHS4 = (\text{Nodules} \times 1) + (\text{Abscesses} \times 2) + (\text{Draining Tunnels} \times 4)$

**Main Predictor/Independent Variable and how it will be categorized/defined for your study:**

Independent Variables will include HiSCR50 Responders/Non Responders; HiSCR75 Responders/Non Responders and IHS4-55 Responders Non Responders at Week 16 based on the above definitions.

The unadjusted Odds Ratios of Achieving HiSCR-50 will be calculated. Participants will be stratified into HiSCR50 Responders (Achieving HiSCR50 at Week 16) and HiSCR50 Non Responders (Not Achieving HiSCR50 at Week 16).

Adjusted odds ratios will then be calculated adjusting for the following covariates:
- Epithelialised Tunnels (Presence of draining tunnels at baseline / No draining tunnels at baseline)
- Gender (Male or Female reported gender)
- BMI Category (BMI30)

The unadjusted Odds Ratios of Achieving HiSCR-75 will be calculated. Participants will be stratified into HiSCR-75 Responders (Achieving HiSCR-75 at Week 16) and HiSCR-75 Non Responders (Not Achieving HiSCR-75 at Week 16).

Adjusted odds ratios will then be calculated adjusting for the following covariates:
- Epithelialised Tunnels (Presence of draining tunnels at baseline / No draining tunnels at baseline)
- Gender (Male or Female reported gender)
- BMI Category (BMI30)

The unadjusted Odds Ratios of Achieving IHS4-55 will be calculated. Participants will be stratified into IHS4-55 Responders (Achieving IHS4-55 at Week 16) and IHS4-55 Non Responders (Not Achieving IHS4-55 at Week 16).

Adjusted odds ratios will then be calculated adjusting for the following covariates:
- Epithelialised Tunnels (Presence of draining tunnels at baseline / No draining tunnels at baseline)
- Gender (Male or Female reported gender)
- BMI Category (BMI30)

**Other Variables of Interest that will be used in your analysis and how they will be categorized/defined for your study:**

- Smoking Status- Categorical Variable
- Family History- Categorical Variable
Age- Continuous Variable

**Statistical Analysis Plan:**

Similar to our previous work discussed above [6,7,8], outcome measures such as the HiSCR-50, HiSCR-75 and IHS4-55 would be calculated. Each variable of interest will be assessed for normality with the Shapiro-Wilk test and histograms. Potential associations with gender, BMI, the presence of draining tunnels, as well as other a priori potential associations (age, Hurley stage, smoking status and family history) would be assessed with logistic regression for HiSCR-50/ HiSCR-75/ IHS4-55 and with linear regression for percentage change in IHS4 and absolute change in nodule count.

**Software Used:**

R

**Project Timeline:**

Anticipated Start Date- As soon as data becomes available

Data cleaning and examination of the data- July 2024

Analysis - July-September 2024

Manuscript Preparation- Sept-Nov 2024

Publication Submission and Report Back to YODA- December 2024

**Dissemination Plan:**

Manuscript would be submitted for publication to an International high impact factor journal and presented at international dermatology conferences eg AAD 2025, EADV 2025

**Bibliography:**


