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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?: Colleague

Conflict of Interest

https://yoda.yale.edu/system/files/a_lescoat_yoda_project_coi_form_for_data_requestors_2019.pdf
https://yoda.yale.edu/system/files/dk_daddi_yoda_project_coi_form_for_data_requestors_2019_0.pdf
https://yoda.yale.edu/system/files/daddi_yoda_project_coi_form_for_data_requestors_2019_signed.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. NCT00077584 - AC-052-331 - A Randomized, Double-blind, Placebo-controlled, Multi-center Study to Assess the Effect of Bosentan on Healing and Prevention of Ischemic Digital Ulcers in Patients With Systemic Sclerosis
2. NCT00903331 - AC-055B201 - A Double-blind, Randomized, Placebo-controlled, Multicenter, Parallel

Group Study to Evaluate the Efficacy, Safety, and Tolerability of Macitentan in Patients With Idiopathic Pulmonary Fibrosis

3. NCT01474122 - AC-055C302 - Prospective, Randomized, Placebo-controlled, Double-blind, Multicenter, Parallel Group Study to Assess the Efficacy, Safety and Tolerability of Macitentan in Patients With Ischemic Digital Ulcers Associated With Systemic Sclerosis

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

Research Proposal

Project Title

Risk factors of DU and related outcomes from post-hoc Analyses of the DUAL-1 & DUAL 2 RCTs In the YODA project : the DADDI YODA project

Narrative Summary:

Systemic sclerosis (SSc) is an autoimmune disease characterized by vascular alterations with chronic ischemia of extremities that can be responsible for digital ulcers (DU). SSc-related DU have a detrimental impact on quality of life. In this project we propose to use data from 3 international RCTs assessing vasodilators therapy in SSc, initially aimed at reducing the number of new DU, to identify the prognostic markers associated with DU healing and prognostic factors associated with DU recurrence. These results would help to improve patient selection for the design of future DU-related RCTs and will inform management of DUs in the current era.

Scientific Abstract:

Background: Healing of DU and prevention of DU recurrence has a favorable impact on function.
Objective: to identify prognostic factors that are associated (A) with healing of all DUs and (B) DU recurrence and to develop prediction models for these outcomes.
Study Design: post-hoc analyses of DUALs and RAPIDS-2 and placebo group from RAPIDS-2 trial.
Participants: Patients with SSc and active DU at baseline from DUALs (all arms) and RAPIDS-2 (placebo group). Two third of the combined DUAL populations will be randomly selected and utilized as the prediction cohort to identify the predictors; one third of DUAL population and RAPIDS-2 placebo arm will served as internal and external validation populations respectively.
Main Outcome Measure(s): dependent variables will be (A) healing of all DU at end of FU (yes/no) ; and (B) new DU during FU (Yes/no). Explanatory variables as candidate predictors will be demographics and baseline SSc-associated parameters.
Statistical Analysis: Bivariate analysis and multivariate logistic regression models will be performed to select candidate predictors. Predictive scores will be developed and weighing of predictors will be based on the logistic regression model coefficients. The predictive value of the score will be assessed though receiver operating characteristic (ROC) curve with area under the curve (AUC). Scores will be considered as continuous variables, semiquantitative and dichotomic variable for exploratory purposes. The final prognostic scores will be then internally and externally validated using ROC and AUC.

Brief Project Background and Statement of Project Significance:

SSc is a rare chronic rheumatic disease characterized by vascular dysfunction, autoimmune features and fibrosis of skin and internal organs. Endothelin 1 is one of the key mediators of SSc-related microangiopathy. Occlusive vasculopathy can lead to digital ulcers (DUs) that have a detrimental impact on hand functioning and quality of life (1,2). Improving the healing of all DUs and preventing the recurrence of DU may thus have a positive impact on the way patients with SSc feel and function (3).
Two recent international RCTs (DUAL 1 & 2 trials, published in 2016) evaluating the efficacy of Macitentan, an endothelin 1 receptor A and B inhibitor, have failed to reach their primary endpoint, i.e. reducing the cumulative number of new DUs in SSc patients with active DU at baseline on a follow-up period of 16 weeks (4). This contrasts to RCTs done in 2000s, where bosentan, a less potent endothelin 1 receptor inhibitor, showed efficacy to reduce

the number of new DUs over a similar follow-up duration in 2 RCTs (RAPIDS 1 & 2 trials) (5,6). This discrepancy could be due to better local care of DUs and widespread use of PDE5 inhibitors (1). In addition, there may be high degree of heterogeneity that may explain these differences, suggesting that a specific subgroup of patients may experience a higher occurrence of new DUs. Beyond prevention, as DU have detrimental impact on hand function, healing of all DU (i.e. being DU free at the end of a trial), may constitute a more clinical meaningful outcome with benefit impact on hand functioning. The predictive markers of DU healing have not been extensively studied in the literature, and this project intends to fill this gap, with utilizing individual level subjects data from large RCTs. A post-hoc analysis of prospective RTCs such as the DUAL and RAPIDS studies may allow to identify predictive factors of DU healing and new DU occurrence, based on international multicentric standardized data with unprecedent sample size and assessment by well trained-clinicians. In these trials, some patients experienced persistent DUs at the end of the study whereas others had complete healing of all DUs. Patients with persistent DUs may be beyond pharmacological measures, whereas patients with complete healing of all DUs may constitute a specific population of patients that may benefit the most from pharmacological procedures with clinical meaningful impact of treatments. The development of predictive models of patients with the potential of experiencing full DU healing or who experience new DU occurrence would thus allow to identify sub-populations of patients with high probability of clinically meaningful improvement and treatment response in RCTs. Such scores will help enriching RCTs with patients that may benefit the most from pharmacological treatments.

Specific Aims of the Project:

Aim (A): to identify independent predictive factors for healing of all DUs in RCTs and to develop a predictive score allowing to identify patients that are the most susceptible to experience such a complete DU healing. To validate this score through internal and external validation.

Aim (B): to identify independent predictive factors of new DU in RCTs and to develop a predictive score allowing to identify patients that are the most susceptible to experience new DU, thus identifying a population of patients that would benefit the most from pharmacological prevention of DU recurrence. To validate this score through internal and external validation.

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 on clinical prediction or risk prediction

Research Methods

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

The DUAL studies are two international, multicentric, RCTs evaluating the efficacy of macitentan in reducing the number of new DU in SSc. Both studies were negative for their primary endpoint and secondary endpoints; including healing of all DUs. All arms from these trials are thus considered as comparable, with no or neglectable treatment effect at 16 weeks. The patients from all arms of DUAL-1 (n=289) and DUAL-2 (n=265) will thus be combined, and patients who completed measures at 16 weeks will be included. This population will be randomly divided into 2/3 that will be utilized as the prediction cohort to develop the predictive scores, and 1/3 that will be used as internal validation population for these scores (4). The RAPIDS-2 study is an international, multicentric, RCT evaluating the efficacy of bosentan in reducing the number of new DU in SSc (5). RAPIDS-2 was positive for its primary outcome, demonstrating the efficacy of bosentan in reducing the number of new DUs, thus the treatment effect is not neglectable. Therefore, only the placebo arm from RAPIDS-2 (n=90) will be used as external validation cohort of the predictive score developed within DUAL populations (7).

Main Outcome Measure and how it will be categorized/defined for your study:

Main outcome (A): healing of all DUs at the end of the study as defined in the DUAL publication: “the proportion of patients with complete healing of all digital ulcers at week 16”
Main outcome (B): new DU occurrence: randomized patients who experience a least one new DU during the study period.

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

Demographics :
-Gender
-Age
-Race (white, Black, Asian, Hispanic, Other)
-Weight
Smoking status (Never/previous/current)

Disease characteristics
-Disease subtype (diffuse versus limited according to LeRoy classification)
-Baseline mRSS (specific emphasize on 0 versus >0 at baseline)
-Interstitial lung disease
-Gastroesophageal reflux disease
-Calcinosis
-Time since first non-Raynaud phenomenon symptom onset of systemic sclerosis,
-Time since first Raynaud phenomenon diagnosis,
-Time since first DU diagnosis,
-Anti-centromere antibodies
-Anti-Scl-70 antibodies
-Total No. of DU at baseline
-Total No. of active DU

-HAQ-DI (quality of Life)
-HDISS-DU (impairment of hand functioning)
-Patient-reported global assessment score of DU severity
-Physician-reported global assessment score of DU severity
-Overall hand pain related to DU
-Overall global assessment of disease (SHAQ-VAS=sub-item of a tool assessing quality of life SSc)
-Activity limitation due to DU (SHAQ-VAS=sub item of a tool assessing quality of life SSc)
-Activity limitation due to Raynaud phenomenon (SHAQ-VAS=sub-item of a tool assessing quality of life SSc)
Concomitant medication

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

None

Statistical Analysis Plan:

The statistical analysis plan is based on the methodological standards for clinical prediction rules published by Laupacis et al (7).

For outcome (A) “healing of all DUs” we will conduct univariable analysis of baseline data associated with healing of all DUs at the end of the study in the derivation DUALs population. All candidate predictor variables with a P value of < 0.20 will be analyzed using a stepwise multivariable logistic regression model with P < 0.20 required for a variable to remain in the model. Nagelkerke’s pseudo-R2 will be used to assess the relevance of the final model. We emphasize the importance of an unbiased data driven approach instead of preconceived selection of variables. To develop the prediction score of healing of all DUs, the logistic regression model coefficients from the multivariable analysis will be rounded to the nearest whole number. A total point score for each patient will be calculated by summing the rounded coefficients. This will be the basis of the candidate score. In an exploratory perspective this score will be interpreted either as a quantitative score (raw sum of all points), as a semi-quantitative score (low probability of DU healing, medium probability, high probability), as a dichotomic score (Low probability versus high probability). We will use receiver operating characteristic (ROC) curve and area under the curve (AUC) to provide a measure of the overall ability of the model to discriminate. For the semi-quantitative and dichotomic approaches, the most relevant thresholds will be selected using ROC curves and AUC. For the dichotomic version of the score, sensitivity and specificity will be calculated as well as Likelihood positive ratio for healing of all DU.
For internal validation, the score developed in the derivation cohort will be applied to the DUAL validation population, the AUC will be calculated for the continuous score, the semi-quantitative score, and the sensitivity,

specificity and LR+ ratio for the dichotomic version will be assessed as well. AUC will be compared using Mann and Whitney. We will also compare stratum-specific proportion of patients with healing of all DU in the derivation and validation cohorts within each of the 3 probability classes using chi-square statistics for the semi-quantitative approach (low probability of DU healing, medium probability, high probability). We will also perform a similar analysis for the dichotomic interpretation of the score.
For external validation, we will perform the same analysis in the external validation population from the placebo arm of the RAPIDS-2 study.

The exact same approach will be conducted for outcome (B) “new DU occurrence”
Software Used:
RStudio
Project Timeline:

Launching the analyses: Mid/late-February 2021

Selection of predictor and creation of the candidate score: February and march 2021

Validation analyses: late March 2021

Writing of the manuscript: April 2021

Submission and reviewing: May-june 2021

Dissemination Plan:

The manuscript will be submitted to the 2021 EULAR congress, and 2021 ACR congress.
We intend to submit it to the following journals as full-length article:

Annals of Rheumatic disease
Arthritis and rheumatology
JAMA dermatology
Rheumatology (Oxford)
Other journal will be considered depending on the review and comments of the journals listed above.
Depending on the results of the analyses: outcome A and B could be separated with a dedicated manuscript for each.

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