INPLASY PROTOCOL

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Support: **Support is being sought.**

Review Stage at time of this submission: **Preliminary searches.**

Conflicts of interest:
None declared.

Analysis of effectiveness, costs, quality of life, adherence and safety of the use of adalimumab in adults diagnosed with moderate to severe hidradenitis suppurativa: systematic review protocol

Albuquerque, NLS[1]; Regis, FT[2]; Machado, LD[3].

Review question / Objective: **What evidence is available in longitudinal studies on the use of adalimumab for the treatment of moderate to severe hidradenitis suppurativa in adults with a diagnosis of moderate to severe hidradenitis suppurativa in which systemic antibiotic therapy has been shown to be ineffective and/or in situations where they present intolerance or contraindication to systemic antibiotics, compared to the application of usual care without the use of adalimumab, regarding the reduction in the total count of abscesses and nodules, decreased sensation of pain, therapeutic adherence, increased levels of self-esteem and quality of life, improvement in inflammatory nodules, abscesses and fistulas costs and expenses associated with the treatment of the disease?**
Condition being studied: **Moderate to severe hidradenitis suppurativa.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 03 October 2021 and was last updated on 03 October 2021 (registration number INPLASY2021100010).

INTRODUCTION

Review question / Objective: **What evidence is available in longitudinal studies on the use of adalimumab for the treatment of moderate to severe hidradenitis suppurativa in adults with a diagnosis of moderate to severe hidradenitis suppurativa in which systemic antibiotic therapy has been shown to be ineffective and/or in situations where they present**

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Condition being studied: Moderate to severe hidradenitis suppurativa.

METHODS

Search strategy: The databases to be consulted when conducting this study are listed below: MEDLINE (OVID interface, including PubMed), CINAHL Complete (EBSCO interface), ERIC (EBSCO interface), PsycINFO (EBSCO interface), Web of Science Core Collection, OVID Nursing Database, Embase, NHS Economic Evaluation Database and SCOPUS. The LILACS and SciELO databases will be included in order to identify, primarily, evidence from the Brazilian population and other Latin American nations. The following descriptors were selected for the composition of the search strategies: Hidradenite; Hidradenite Suppurative; Abscess; Dermopathies; Patient safety; Quality of life; Comparative Research on Effectiveness; and Cost-Effectiveness. In addition, keywords that are not included in the Descriptors in Health Sciences (DeCS) and Medical Subject Headings (MeSH) repositories were selected, but which are usually present in publications on the object of interest: Inflammatory skin disease; Adalimumab and Follicles. The combination of descriptors and descriptors with keywords will be performed using the Boolean operators AND, OR and NOT, thus generating the search strategies to be applied in the databases. It is noteworthy that the strategies will be adapted respecting the vocabulary of each database.

Participant or population: Adults diagnosed with moderate to severe hidradenitis suppurativa in which thetherapy with systemic antibiotics has been shown to be ineffective and/or in situations where they present intolerance or contraindication to systemic antibiotics.

Intervention: Use of adalimumab for the treatment of moderate to severe hidradenitis suppurativa.

Comparator: Cuidados/tratamentos habituais que não incluam adalimumabe.

Study designs to be included: Prospective cohort, retrospective cohort, randomized clinical trial, equivalence clinical trial and cost-effectiveness and cost-utility economic analyzes.

Eligibility criteria: The eligibility of primary studies for inclusion in the final sample of this review will be assessed by weighing the inclusion and exclusion criteria. Inclusion criteria will be: to be a study with a prospective cohort, retrospective cohort, randomized clinical trial or clinical trial of equivalence, without language and time restrictions, that address and assess quality of life, adherence, safety and monetary costs related to the use of adalimumab in adults diagnosed with moderate to severe hidradenitis suppurativa. As an exclusion criterion, there is the absence of quantitative/ numerical presentation of the comparative results between the use of adalimumab and usual treatment without this drug.

Information sources: This review will include evidence resulting from systematic search in databases in the health area and manual search performed in manuals, guidelines, Clinical Protocols and Therapeutic Guidelines and other technical materials, as well as in specific journals on the subject investigated and in the reference list of publications eligible for the final review sample. The databases to be consulted when conducting this study are listed below: MEDLINE (OVID interface, including PubMed), CINAHL Complete (EBSCO interface), ERIC (EBSCO interface), PsycINFO (EBSCO interface), Web of Science Core Collection, OVID Nursing

Database, Embase, NHS Economic Evaluation Database and SCOPUS. The LILACS and SciELO databases will be included in order to identify, primarily, evidence from the Brazilian population and other Latin American nations. In the manual search, reference lists of previously published systematic reviews on hidradenitis suppurativa will be consulted, as well as the publications that will make up the final sample of included studies. Additionally, the first author of the studies in the final sample will be contacted via email to verify if they have knowledge of other publications that potentially meet the inclusion criteria of this review, but which have not been included in the screening step. The definition of the search strategies for evidence that address the research question established in this review started with a non-systematic search performed by previously trained researchers, in order to identify the feasibility of the research question formulated for this study. Based on the observation of the feasibility of the object and the proposed research question, the following descriptors were selected for the composition of the search strategies: Hidradenite; Hidradenite Suppurative; Abscess; Dermopathies; Patient safety; Quality of life; Comparative Research on Effectiveness; and Cost-Effectiveness. In addition, keywords that are not included in the Descriptors in Health Sciences (DeCS) and Medical Subject Headings (MeSH) repositories were selected, but which are usually present in publications on the object of interest: Inflammatory skin disease; Adalimumab and Follicles. The combination of descriptors and descriptors with keywords will be performed using the Boolean operators AND, OR and NOT, thus generating the search strategies to be applied in the databases. It is noteworthy that the strategies will be adapted respecting the vocabulary of each database.

Main outcome(s): Reduction of at least 50% of the total abscess and nodule count compared to the beginning of treatment, measured using the Hidradenitis Suppurative Clinical Response (HiSCR) tool; decreased pain sensation, measured through validated numerical or analog scales, but prioritizing The Cardiff Dermatology Life Quality Index and the DLQI questionnaire, due to evidence of its satisfactory application in patients with hidradenitis suppurativa; costs and expenses associated with treating the disease; therapeutic adherence; increased levels of self-esteem and quality of life, both measured by validated instruments and widely disseminated in the literature; adverse effects and related events; and improvement in inflammatory nodules, abscesses and fistulas, as measured by Hidradenitis Suppurativa Physician Global Assessment (HS-PGA). Outcomes will be evaluated in the initial therapeutic cycle (15th day of treatment), in the second therapeutic cycle (29th day of treatment), 12 weeks after starting treatment and in the late period of up to 12 months after starting treatment.

Data management: The Rayyan Reference Manager will be used to organize the references extracted from the application of search strategies in the databases, as well as to exclude duplicates. Two independent researchers will read the titles and non-duplicated abstracts, in order to assess correspondence to the eligibility criteria established in this study. Discrepancies will be resolved by consulting a third reviewer with expertise in the object under study.

Quality assessment / Risk of bias analysis: The studies included in the final sample of this systematic review will be evaluated for the presence of bias risks. Studies with non-randomized designs will be evaluated using the ROBINS-I instrument, which includes the following domains: treatment of confounders, selection of participants, classification of non-randomized interventions, deviations from intended procedures, missing data, outcome measurement and reporting selective. Randomized clinical trials, on the other hand, will have their risk of bias assessed through the Risk of Bias 2 (Rob 2). In this, five domains are considered: biases derived from the randomization process, biases derived from deviations from the

intended interventions, biases derived from the absence of data on the outcome, biases derived from the measurement of the outcome, and biases derived from the selection of reported results. For clinical trials that adopt cluster randomization, the risks of bias on recruitment, imbalance of sociodemographic and clinical characteristics at baseline, loss of clusters and inadequately performed comparability analyzes will also be considered. From the application of the instruments, the risk of bias of the included studies will be stratified and presented in a graphical and qualitative format, according to the guidelines of the methodological framework adopted in this review. The main results related to the effectiveness of adalimumab will be presented in tables of the Summary of evidence type, which will contain: main quantitative results, quality of evidence, magnitude of effect of interventions and grading of the evidence set. These will be obtained through the application of the Grades of Recommendation, Assessment, Development and Evaluation (GRADE System), which is indicated to define how much confidence can be placed in the correspondence between the effect estimates found in primary studies and the behavior of the phenomenon of interest in the real world. This estimate will be made through the application of the GRADE System principles to assess the risk of bias among the included studies and their methodological quality. Therefore, in the scope of randomized clinical trials, the following elements will be considered: risk of bias, direction of evidence, heterogeneity, precision of effect estimates and publication bias. The set of evidence generated by the non-randomized studies will be evaluated regarding the treatment of confounders, effect magnitude and dose-response gradient.

Strategy of data synthesis: Relevant information extracted from the studies included in the final sample will be combined in a narrative synthesis for the purpose of synthesizing characteristics of the studies, investigated populations, dosing schedules, adverse reactions, follow-up time, types of expenses and an overview of the effectiveness of adalimumab on the outcomes of interest. It is planned to integrate the information by subgroups consisting of similar interventions, populations and duration. The results will be presented in tables. Based on the non-systematic search previously carried out to verify the feasibility of the proposal, it is estimated that it will be pertinent and feasible to carry out a quantitative synthesis (meta-analyses) of the results. It is considered that this synthesis is important to identify the effectiveness of adalimumab, as it will allow the generation of summary measures of effect that will represent, in the general population and in subgroups of interest, the impact of its use on the outcomes investigated in this review. The production of quantitative synthesis will be preceded by the analysis of clinical and methodological heterogeneity of the studies included in this review. In this context, the similarity of the studies regarding the elements described below will be evaluated: sociodemographic characteristics of the population, clinical condition/stage of the disease, administered dosage, design, follow-up time, sample size, losses during follow-up and adopted effect measures , among other sets of variables of interest that appear in the included references. The evaluation of heterogeneity will be carried out by two previously trained researchers. Random effects will be selected, given that in the non-systematic search, a variety of populations and household interventions were perceived. This approach will be adopted because the random effects consider in their calculation algorithm the presence of some important heterogeneity, although this is still considered acceptable. In the possibility of the presence of substantial homogeneity among a given set of studies, fixed effects can be applied to this one. For dichotomous outcomes, the results of the quantitative synthesis will provide a summary measure of the effect of home care in the form of Relative Risk or Odds Ratio, accompanied by 95% confidence intervals. When continuous outcomes are measured in the same way

between the primary studies, the results will be calculated as means and standard deviations, followed by 95% confidence intervals. Faced with continuous outcomes obtained through different scales and/or measurements, standardized mean differences will be adopted. If survival analysis results are plotted, the summary estimates generated will be in the form of Hazard Ratio with inverse variance and 95% confidence intervals. The statistical heterogeneity of the results plotted in the meta-analyses will be evaluated using the chi-square test together with the I^2 statistic. In the x^2 test, p values less than 0.10 will indicate statistically significant heterogeneity. Regardless of the degree of statistical heterogeneity identified, the reasons for the presence of heterogeneity between studies will be explored. Estimates will be obtained in Review Manager 5.2 Software (RevMan 5.2), as well as graphical representations in the form of forest graphics.

Subgroup analysis: Faced with findings of moderate or substantial statistical heterogeneity between studies, quantitative analyzes of subgroups of interest will be conducted, such as population age group, administered dosage, hidradenitis suppurativa staging, symptomatology and presence of adverse effects.

Sensitivity analysis: Sensitivity analyzes will be performed to confirm the findings on the effectiveness of home care in the outcomes of interest. For this purpose, the summary estimates of effect will be recalculated excluding studies with high risk of bias and with small sample sizes.

Language: No idiomatic restriction.

Country(ies) involved: Brazil.

Keywords: Hidradenitis; Hidradenitis Suppurativa; Comparative Effectiveness Research; Treatment Outcome; Quality of Life; Patient Safety; Health Care Economics and Organizations.

Dissemination plans: The qualitative and quantitative results of the systematic review will be synthesized and published in an open access journal. In addition, they will serve as a subsidy for conducting a budget impact analysis and updating information on the incorporation of adalimumab for the treatment of moderate to severe hidradenitis suppurativa in the scope of the Unified Health System in Brazil.

Contributions of each author:

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