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2014-0291

General Information

Key Personnel (in addition to PI): **First Name:** Abhijit
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Are external grants or funds being used to support this research?: External grants or funds are being used to support this research.

Conflict of Interest

coi_disclosure.pdf

Certification

Certification: Yes
Data Use Agreement Training: As the Principal Investigator of this study, I certify that I have completed the YODA Project Data Use Agreement Training

Associated Trial(s): NCT00265083 - A Multicenter, Randomized, Double-blind, Placebo-controlled Trial of Golimumab, a Fully Human Anti-TNFa Monoclonal Antibody, Administered Subcutaneously, in Subjects with Active Ankylosing Spondylitis
NCT01248793 - A Phase 3, Multicenter, Randomized, Double-blind, Placebo-controlled Study Evaluating the

Efficacy and Safety of Golimumab in the Treatment of Chinese Subjects with Ankylosing Spondylitis
NCT00202865 - Evaluation of Low Dose Infliximab in Ankylosing Spondylitis (CANDLE)
What type of data are you looking for?: Full CSR

Research Proposal

Project Title

Comparative effectiveness of tumor necrosis factor alpha inhibitors in ankylosing spondylitis

Narrative Summary:
Tumor necrosis factor alpha inhibitors (TNFi) are mainstay treatment for ankylosing spondylitis. Five TNFi have been approved in the United States. However, a comparison of the efficacy and safety of these agents in ankylosing spondylitis is lacking. This study is to estimate the relative efficacy and safety of the five TNFi and help clinicians and patients in decision making.

Scientific Abstract:
Background: Five tumor necrosis factor-alpha inhibitors (TNFi) have shown considerable efficacy in placebo-controlled trials for the treatment of ankylosing spondylitis (AS) refractory to non-steroid anti-inflammatory drugs. However, to date, only one head-to-head trial was conducted to compare the efficacy and safety of infliximab and etanercept.
Objective: The aim of this study is to integrate available evidence and estimate the relative short-term efficacy of different TNFi in AS.
Study Design: Systematic review and meta-analysis
Participants: Adult patients with ankylosing spondylitis, treated with TNFi, in a randomized controlled trials.
Main outcome measures: change of BASDAI and BASFI at week 12 and at week 24.
Statistical analysis: Bayesian multiple treatment comparison

Brief Project Background and Statement of Project Significance:
Five tumor necrosis factor-alpha inhibitors (TNFi) have shown considerable efficacy in placebo-controlled trials for the treatment of ankylosing spondylitis (AS) refractory to non-steroid anti-inflammatory drugs. To date, only one head-to-head trial was conducted to compare the efficacy and safety of infliximab and etanercept. A comparison of effectiveness and safety of different TNFi is lacking. The aim of this study is to integrate available evidence and estimate the relative short-term efficacy of different TNFi in AS. The information on comparative effectiveness of TNFi in AS will help decision making in clinical practice.

Specific Aims of the Project:
Aim1. To compare the efficacy of TNFi in AS, using BASDAI change and BASFI change at week 12 and week 24 as primary end points.
Aim2. To compare the safety of TNFi in AS, using numbers of total adverse events, severe adverse events, severe infections, tuberculosis infection as secondary end points.

What is the purpose of the analysis being proposed? Please select all that apply. Summary-level data meta-analysis
Summary-level data meta-analysis will pool data from YODA Project with other additional data sources
Data Source and Inclusion/Exclusion Criteria to be used to define the patient sample for your study:
Searches: We conducted a systematic search of PubMed, EMBASE and Cochrane Database for published randomized control trials of TNFi in ankylosing spondylitis up to May 20th, 2014 in all languages, and supplemented it with manual searches of reference lists from previous systematic review articles.
Types of study to be included:
Inclusion criteria:
- Adult Patient fulfills the modified New York criteria for diagnosis of ankylosing spondylitis;
- intervention: TNFi; comparator: placebo or a different TNFi;
- Randomized controlled trials.
Exclusion criteria:

- Case series, case report;
- Abstract, unpublished data;
- studies on Axial SpA, if a subgroup analysis of AS was not reported.
Literature review and data extraction were done by two independent reviewers. Any disagreement was resolved by discussion. Extracted data included study design, participant characteristics, and relevant outcomes.

Main Outcome Measure and how it will be categorized/defined for your study:
Main outcome measures that we are interested include Bath ankylosing spondylitis disease activity index (BASDAI) changes and Bath ankyloing spondylitis function index (BASFI) changes at week 12 and week 24. BASDAI is a validated self-administered 6-question tool to assess disease activity in patients with ankylosing spondylitis. BASFI is a validated 10-question tool to assess functional limitationi in patients with ankylosing spondylitis. Both are the most commonly reported continuous outcome measures in ankylosing spondylitis trials.

Main Predictor/Independent Variable and how it will be categorized/defined for your study:
The main predictor is individual TNFi, including adalimumab, certolizumab, etanercept, golimumab and infliximab, and placebo. Study arms from the selected trials will be grouped based on the TNFi used in the trial arm, and different dosing regimens of the same TNFi are grouped together.

Other Variables of Interest that will be used in your analysis and how they will be categorized/defined for your study:
We will examine the treatment effects by duration of AS at enrollment, baseline BASDAI and CRP, and year of study publication to investigate if temporal trends in severity varied over time and affected relative effect sizes.

Statistical Analysis Plan:
Statistical analysis: The requested summary data, together with those collected from literature and/or provided by other trial sponsors will be used for data analysis, using Bayesian network meta-analysis. This will be implemented using Markov Chain Monte Carlo (MCMC), via the R package gemtc (http://cran.rproject.org/web/packages/gemtc/index.html). We assume consistency (i.e., indirect effects can be derived from differences in the corresponding direct effects) during modeling. The relative effect sizes are reported as posterior mean differences along with 95% credible intervals. Drug rankings are derived from the MCMC results by evaluating the rank of each drug at each MCMC iteration based on size of the effect of the drug compared to placebo, and evaluating the relative frequency of each ranking over the MCMC iterations. The outcome data on BASDAI and BASFI that would be provided by YODA would be pooled with published results on golimumab from other studies in the literature that provided the needed data in the publication to increase the sample of studies included in the network meta-analysis and increase the representation of golimumab in the comparisons.

Project Timeline:
Systematic review – the systematic review of randomized controlled trials of TNFi in AS has been completed.
Meta-analysis – preliminary analysis has been completed, awaiting for authors and/or sponsors providing missing data for final analysis.
Manuscript draft and submission for publication – anticipated in December 2014.

Dissemination Plan:
One journal article will be produced using the requested data (and with data obtained from literature and other sponsors). The target audiences are clinicians and clinical researchers.

Bibliography:
Giardina AR, Ferrante A, Ciccia F, et al. A 2-year comparative open label randomized study of efficacy and safety of etanercept and infliximab in patients with ankylosing spondylitis. Rheum Int 2010; 30:1437-40.

Migliore A, Broccoli S, Bizzi E, Laganà B. Indirect comparison of the effects of anti-TNF biological agents in patients with ankylosing spondylitis by means of a mixed treatment comparison performed on efficacy data from published randomised, controlled trials. J Med Econ 2012; 15:473-80.

Shu T, Chen GH, Rong L, et al. Indirect comparison of anti-TNF-? agents for active ankylosing spondylitis: mixed treatment comparison of randomized controlled trials. Clin Exp Rheumatol 2013; 31:717-22.

Supplementary Material: tnfi_protocol.pdf