Review methods were amended after registration. Please see the revision notes and previous versions for detail.

Citation

Feyzullah Aksan, Lokman Hekim Tanriverdi, Thomas A. Ullman. Efficacy and safety of anti-TNF agents on subgroups of Crohn disease based on location: A systematic review and meta-analysis of randomized controlled trials. PROSPERO 2022 CRD42022313785 Available from: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42022313785

Review question

Do anti-TNF agents have different impact on specific Crohn’s disease location subgroups for induction of remission of patients with active CD?

Searches

The following bibliographic databases will be searched without restriction on publication year. PubMed, Ovid MEDLINE R, Web of Science, and The Cochrane Central Register of Controlled Trials (Cochrane CENTRAL), all from inception to March 1, 2022. Furthermore, the reference lists of included studies, systematic reviews and meta-analysis from the last ten years on anti-TNF for management of Chron’s disease will be reviewed for additional studies.

Types of study to be included

Placebo-controlled randomized controlled trials. Only abstracts and articles published in English will be included.

Exclusion criteria:

• Studies with unclassified inflammatory bowel disease.

• Non-randomized, uncontrolled studies.

• Studies concerning combination therapy in comparison with monotherapy or surgical intervention or comparing different dosage/treatment regimens of the same drug

• Studies involving the pediatric population

• Studies including patients with mild active Crohn's disease

Condition or domain being studied

Crohn's disease (CD) is a chronic inflammatory bowel disease which can occur in any part of the digestive tract from the mouth to the anus, and peri-anal complications including fissures and fistula based on Montreal Classification of CD (1, 2). In addition, current guidelines do not differentiate the pharmacological treatment between subgroups of CD according to the location of disease or the phenotype (3, 4), though infliximab has a separate U.S. F.D.A. indication for the treatment of Crohn’s-related fistula for inducing and maintaining clinical remission in adult patients with moderately to severely active CD who have had an inadequate response to conventional therapy and reducing the number of draining enterocutaneous and rectovaginal fistulas and maintaining fistula closure in adult patients with fistulizing CD (5, 6). There are several clinical studies showed anti-TNF agents have different impact on different subgroup of CD (7).

The aim of this meta-analysis is to answer whether anti-TNF agents have different impact on specific

Crohn’s disease location subgroups for induction of remission of patients with active CD.

References

1. PMID: 28601423

2. PMID: 16151544

3. PMID: 29610508

4. PMID: 31009791

5. PMID: 34157179

6. PMID: 32578017

7. PMID: 33712743

Participants/population

Adults (? 18 years old) with moderate to severe active CD (Crohn's Disease Activity Index (CDAI) score of 220–450), CD confirmed by endoscopy or radiologic evaluation.

Intervention(s), exposure(s)

Anti-TNF agents (adalimumab, certolizumab pegol, etanercept, infliximab)

Comparator(s)/control

Placebo

Main outcome(s) [1 change]

Complete remission and partial response

Measures of effect

Number of patients achieved predefined CDAI scores at weeks 2, 4 and 26: RR

Complete remission defined as CDAI score ? 150 points at weeks 2, 4, and 26.

Partial response defined as a reduction of ?70 points (CR-70) or ?100 points (CR-100) from the baseline in the CDAI score from the baseline at weeks 2, 4 and 26: RR and MD, respectively.

Additional outcome(s) [1 change]

Mucosal healing

Fistula closure

Severe adverse events (opportunistic infections, pneumonia, septicemia, tuberculosis, drug-induced lupus-immunsupression)

Minor adverse events (infections, injection site reactions, abdominal tenderness, nausea, flatulence, nasopharyngitis, pharyngitis, and headache).

Measures of effect

RR

Data extraction (selection and coding)

Two investigators (FA and LHT) will independently search and review the studies to be considered in the systematic review with disagreements to be solved by a third reviewer (TU). Reviewers will contact the principal investigator of the selected randomized controlled trials to either complete an Excel datasheet or to provide the individual patient data collected from their trials. Data extraction will be performed by a single reviewer (FA) using a standard data extraction form before being then checked by a second reviewer (LHT). The quality of the included randomized clinical trials will be evaluated using the Jadad scale and Consolidated Standards of Reporting Trials (CONSORT) checklist.

The following data-extraction is considered mandatory: the phenotype and affected location data of each patient, baseline CDAI scores, CDAI scores at week 2, 4, and 26 or number of patients with clinical response and remission based on the previous definition on each arm.

Risk of bias (quality) assessment

The overall quality of evidence for the estimates will be evaluated by two independent reviewers (LHT and FA) using the GRADE (Grading of Recommendations Assessment, Development, and Evaluation) approach. Publication bias will be assessed using Egger's regression test.

Strategy for data synthesis

We will explore the heterogeneity and inconsistency between studies by Cochran's Q test and I^2 statistics. An I^2 value of 0% indicates that no inconsistency is seen between the results of individual trials, and an I^2 value of 100% indicates maximal inconsistency. For the groups that will be found to be homogenous, a Mantel–Haenszel fixed-effects model will be used for summary analysis, and for the groups that will be heterogeneous, a DerSimonian–Laird random-effects model will be applied. All statistical analysis and pooling were carried out via online calculators and RevMan v5.4. To investigate heterogeneity and publication bias, funnel plots will be constructed. The number of the experienced events and the total number of participants will be extracted for dichotomous outcomes. For continuous outcomes, mean values with standard deviations will be extracted.

Analysis of subgroups or subsets

Analyses of subgroups (including agent and affected location): A meta-regression analysis will be performed to explore the heterogeneity. Relevant study-level covariates, defined as those able to decrease inconsistencies measured as I^2 statistics, will be investigated to identify relevant subgroups.

Contact details for further information

Thomas A. Ullman, M.D., Professor of Medicine, Chief, Division of Gastroenterology, Montefiore Medical Center, Albert Einstein College of Medicine, Bronx, NY
lokmanhekim.tanriverdi@gmail.com

Organisational affiliation of the review

None.

Review team members and their organisational affiliations

Dr Feyzullah Aksan. Department of Internal Medicine, Montefiore Medical Center, Albert Einstein College of Medicine, Bronx, NY
Assistant/Associate Professor Lokman Hekim Tanriverdi. Department of Medical Pharmacology, Inonu University Faculty of Medicine, Malatya, Turkey.
Professor Thomas A. Ullman. Division of Gastroenterology, Montefiore Medical Center, Albert Einstein College of Medicine, Bronx, NY

Type and method of review

Individual patient data (IPD) meta-analysis, Meta-analysis, Systematic review

Anticipated or actual start date

01 March 2022

Anticipated completion date

28 February 2023

Funding sources/sponsors

None.

Conflicts of interest

Language
English

Country
Turkey, United States of America

Stage of review
Review Ongoing

Subject index terms status
Subject indexing assigned by CRD

Subject index terms
MeSH headings have not been applied to this record

Date of registration in PROSPERO
31 March 2022

Date of first submission
28 February 2022

Stage of review at time of this submission

Stage	Started	Completed
Preliminary searches	Yes	No
Piloting of the study selection process	No	No
Formal screening of search results against eligibility criteria	No	No
Data extraction	No	No
Risk of bias (quality) assessment	No	No
Data analysis	No	No

The record owner confirms that the information they have supplied for this submission is accurate and complete and they understand that deliberate provision of inaccurate information or omission of data may be construed as scientific misconduct.
The record owner confirms that they will update the status of the review when it is completed and will add publication details in due course.

Versions
31 March 2022
31 March 2022