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[Intervention Protocol]

The impact of biological interventions on health-related quality of life in adults with Crohn's disease

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ABSTRACT

This is a protocol for a Cochrane Review (Intervention). The objectives are as follows:

To systematically assess the beneficial and harmful effects of the biologic treatment on HRQoL outcomes in people with Crohn's disease.

BACKGROUND

Description of the condition

Crohn's disease (CD) is a relapsing-remitting transmural inflammatory bowel disease (IBD) that may involve any part of the gastrointestinal tract from mouth to anus as well as cause extraintestinal manifestations (skin lesions, arthritis). Fatigue, abdominal pain, prolonged diarrhoea, weight loss, and fever, with or without gross bleeding, are the hallmarks of CD (Mekhjian 1979). An increase in incidence is recorded both in Western countries (North America, Europe) and in traditionally low-risk populations, such as Japan and India (Ananthakrishnan 2015). At present, the highest annual incidence in North America is 20.2 per 100,000 person-years, in Europe 12.7 per 100,000 person-years and in Asia and Middle East 5.0 per 100,000 person-years. The annual prevalence is 319 per 100,000 persons in North America and 322 per 100,000 persons in Europe (Ye 2015). The difference in incidence may be attributable to heterogeneous environmental factors. The pathogenesis of CD involves complex interactions between the exposomes, genetic predisposition, dysbiosis in gut microbiota, and dysregulated immune system (Abegunde 2016). A dysregulated immune response in CD is characterised by a leukocytic infiltration of the intestinal lamina propria (Lobaton 2014), a selectively upregulated differentiation of type 1 and 17 helper T cells (Th1/Th17) and increased levels of Th1 cytokines: tumour necrosis factor alpha (TNF-α), interferon gamma (IFN-γ), interleukin 12/23 (IL-12/23) and other interleukins in the serum or intestinal mucosa (Shanahan 2001; Behm 2008; Amiot 2015). Pharmacological therapy is considered to be the first-line treatment for Crohn disease, in addition to surgical management of complications and dietary manipulation. At the time of diagnosis, most people have predominantly inflammatory disease, but long-term inflammation can result in complications such as strictures, fistulae, and perforation (Cosnes 2002). Up to 80% of CD patients require surgery at some point during the course of their disease and more

than 10% or patients need a permanent stoma (Cosnes 2011). Nearly half of patients who have undergone a surgical resection will require at least one additional bowel resection for removal of affected bowel or to treat complications from previous surgery, such as adhesions (Krupnick 2000). Surgical admissions, living with a stoma and short bowel syndrome following extensive intestinal resections are associated with a substantially lower health-related quality of life (HRQoL) in patients with CD (Kalaitzakis 2008). Data from the United States indicates that the burden of CD attributable to surgery includes 40% of hospitalisation costs for the treatment of CD (Kappelman 2008). In the era of biologic agents, direct disease-attributable costs for CD include outpatient medications (35%), outpatient services (33%), medical (19%) and surgical hospitalisations (12%) (Kappelman 2008; Saro 2015).

Indirect costs including lost earnings, productivity and leisure time, also contribute to a lower quality of life (QoL) in CD patients. CD has an impact on productivity due to diminished ability to participate effectively while working (Gibson 2008). Due to its complexity, the monitoring of indirect costs in relation to Crohn's disease is rarely and only partially reported. Indirect costs associated with CD-related work disability accounted for 28% of the total societal cost of CD in the United States and up to 64% to 69% of the total societal cost in Europe (Yu 2008). The total societal cost is estimated to be equivalent to more than EUR 15,000 million in Europe and the United States (Floyd 2015).

HRQoL assessment tools are QoL instruments inclusive of, but not limited to the Inflammatory Bowel Disease Questionnaire (IBDQ), the Cleveland Global Quality of Life Questionnaire (CGQL), the 36-Item Short-Form Health Survey (SF-36) and the European Quality of Life-5 Dimensions (EQ-5D). The IBDQ (Guyatt 1989; Irvine 1994; Irvine 1996), SF-36 (Ware 1992), and the CGQL (Kiran 2003), are inflammatory bowel disease-specific tools for measuring HRQoL. The EQ-5D (Konig 2002), and the SF-36 are not disease specific QoL tools (Ware 1992).

The EQ-5D consists of five questions related to the five dimensions: subject's ability to move, self-care, daily activities, pain or discomfort, and psychological condition (Konig 2002). The scoring system includes a unique five-digit code where each number, from 1 to 5, represents a predefined statement under each of the five dimensions. The SF-36 is a 36 item questionnaire divided into eight domains including restrictions in physical, social, and role activities due to health problems, restrictions to role activities due to emotional problems, bodily pain, general mental health, vitality and general health perceptions (Ware 1992). An aggregate percentage score is produced for each of the domains, ranging from 0% to 100%, where 0% represents the lowest possible level of functioning (Anonymous 2018). The IBDQ comprises 32 questions covering bowel function (e.g. loose stool, abdominal pain), systemic function (e.g. fatigue), social function (e.g. work attendance) and psychic function (e.g. depression). A seven-point Likert scale is involved as a scoring system (1 indicating severe issues and 7 no issues) (Feagan 1999). Total IBDQ score can range from 32 (very poor HRQoL) to 224 (perfect HRQoL) (Irvine 1994). The CGQL rates current quality of life, current quality of physical, mental, and social well-being and current energy level, each one on a scale from 0 to 10, where 10 indicates best quality scores (Kiran 2003). Each of these instruments has been extensively validated in IBD patients.

Description of the intervention

Therapies aimed at controlling the clinical course of CD include 5-aminosalicylic acid, glucocorticosteroids, conventional immunosuppressants and biologic interventions. Contrary to most non-biological drug therapies which provide only symptomatic improvement (Burger 2011), biologics may stop the underlying inflammatory process and, therefore, influence patients' long-term outcomes. Affecting T-cell activation and inhibiting adhesion molecules and pro-inflammatory cytokines involved in cellular signal transduction pathway, biologic interventions are capable of achieving mucosal healing and deep clinical remission, resulting in a reduced need for surgery, lower hospital admission rates and increased steroid-sparing (Sandborn 2005; Neurath 2012; Rutgeerts 2012; Amiot 2015; Beppu 2015). The first licensed biologic agent for people with CD was infliximab, a chimeric mouse/human immunoglobulin (Ig)G1 anti-human TNF-α monoclonal antibody. Infliximab has been shown to neutralise TNF-α effects in vivo by blocking soluble TNF-a and binding to transmembrane TNF-α (Scallon 1995). Furthermore, randomised controlled trials (RCT) suggest clinical efficacy for other biological agents for the treatment of CD including adalimumab and certolizumab (Behm 2008), ustekinumab (MacDonald 2016), natalizumab (MacDonald 2007), vedolizumab (Sandborn 2013; Lam 2014; Sands 2014), and recombinant human interleukin-11 (Sands 2002).

How the intervention might work

An increasingly important issue in CD is QoL, which is significantly lower in people with CD compared to the general population (Cosnes 2011; Floyd 2015). Different dimensions of QoL include physical function, social and emotional well-being, ability to work and freedom from disease symptoms (Fitzpatrick 1992). HRQoL of adults with CD is impacted by disease activity which translates into work disability, disease relapses, increased hospitalisation rates and the need for treatment with biologics (van der Have 2014). Conversely, sustained remission is associated with improvement in work productivity and HRQoL (Lichtenstein 2004). Biological interventions may influence HRQoL in people with CD by increasing the frequency of sustained remission.

Why it is important to do this review

HRQoL represents a functional effect of the disease and it is one of the main issues in people with CD. Modifying the disease course, the biological treatment may have a substantial effect on HRQoL and therefore would be beneficial to be introduced earlier in the treatment with regard to HRQoL outcomes (Bodger 2002). Studies increasingly include HRQoL as a secondary outcome and no systematic review has clearly established the evidence for an improvement in HRQoL in this population. A previous literature review on the impact of biologics on HRQoL in IBD patients has been limited in the scope and time of the articles retrieved (IBD population, including both CD and ulcerative colitis) and methodological concept (articles only in English, only IBDQ and SF-36 as outcome measures) (Vogelaar 2009). This review endeavours to address an up-to-date critical view of growing evidence on the impact of biological interventions in improving HRQoL in people with CD.

OBJECTIVES

To systematically assess the beneficial and harmful effects of the biologic treatment on HRQoL outcomes in people with Crohn's disease.

METHODS

Criteria for considering studies for this review

Types of studies

RCTs assessing the impact of biological interventions on HRQoL in people with Crohn's disease irrespective of publication status, language, or blinding procedure will be included. We will consider the inclusion of non-RCTs that report on long-term harms. Data concerning adverse outcomes from non-RCTs will be reported as descriptive data in a table and will not be used for any statistical analysis. Studies that do not measure HRQoL outcomes will be excluded from this review.

Types of participants

Adults (>18 years of age) with Crohn's disease as defined by a combination of clinical, biochemical, radiological, endoscopic and histological criteria will be considered for the inclusion (Van Assche 2010).

- The clinical criteria include diarrhoea, abdominal pain, weight loss, fever, anal fissures, fistulae, abscesses and extraintestinal manifestations (e.g. skin lesions, arthritis) (Van Assche 2010).
- The biochemical criteria include leucocytosis, anaemia, elevated erythrocyte sedimentation rate and C-reactive protein, hypoalbuminemia, faecal calprotectin and stool lactoferrin (Van Assche 2010).
- The radiological criteria include bowel wall thickness of 4 mm or higher, strictures, a conglomeration of loops, fistulae, abscesses, and presence of mural oedema (Kim 2015).
- The endoscopic criteria include the discontinuous ulcerations, anal lesions and cobblestoning (Van Assche 2010).
- The histological criteria include focal chronic inflammation, focal crypt irregularity and granulomas (Magro 2013).

Although there will be no limitations based on disease activity (i.e. active or quiescent disease) for inclusion, only studies which provide definitions of active disease or remission based on validated indices will be considered for inclusion. Validated indices for the assessment of disease activity in Crohn's disease include the Crohn's Disease Activity Index (CDAI) (Best 1976), the van Hees Activity Index (AI) (van Hees 1980), or the Harvey-Bradshaw Index (Harvey 1980); Crohn's Disease Endoscopic Index of Severity (CDEIS) (Mary 1989) or Simple Endoscopic Score for Crohn's Disease (SES-CD) (Daperno 2004) will be considered for the inclusion.

Types of interventions

Studies assessing all recognised biological interventions for the treatment of Crohn's disease will be considered for evaluation. These biological interventions include, but are not limited to infliximab, adalimumab, certolizumab pegol, natalizumab, ustekinumab, briakinumab, vedolizumab, and recombinant human interleukin 10. The comparison will be placebo or an active comparator such as systemic corticosteroids, azathioprine, 6-mercaptopurine or methotrexate.

Types of outcome measures

Primary outcomes

1. Change in HRQoL scores as defined by the included studies.

Secondary outcomes

1. Adverse outcomes (type and frequency) will include the following:
1a. All adverse events;
1b. Serious adverse events; and
1c. Withdrawal due to adverse events.
Serious adverse events present any untoward medical occurrence that results in death, is life-threatening, requires hospitalisation or

causes extension of existing hospitalisation. Non-serious adverse events are defined as any medical occurrence not necessarily causal or related to the treatment, but did, however, require a dose reduction or treatment cessation (ICH 1997; National Institutes of Health 2010).

Other secondary outcomes include:

2. Improvement in workplace productivity.
3. Improvement in fatigue.

Search methods for identification of studies

Electronic searches

The following databases will be searched:

- MEDLINE (via PubMed; 1946 to present);
- Embase (via Ovid; 1974 to present);
- the Cochrane Central Register of Controlled Trials (CENTRAL) (The Cochrane Library current issue);
- the Cochrane IBD Inflammatory Bowel Disease and Functional Bowel Disorders Specialized Trial Register (IBD/FBD Group Specialized Register)
- Science Citation Index Expanded (SCIE) (Institute for Scientific Information Web of Knowledge)
- Digestive Disease Week (DDW) abstracts of RCTs (1981 to present).

The databases will be searched for RCTs using the search strategies described in Appendix 1.

Searching other resources

The review authors will search the references of all included studies and relevant review articles retrieved by the electronic searches. We will consider hand searching, particularly when abstracts and conference proceedings of associated meetings are not available online. When information in a published paper is insufficient, we will attempt to make contact with the corresponding authors to obtain additional information.

The following databases will be searched for ongoing trials:

- ClinicalTrials.gov (http://clinicaltrials.gov/); and
- World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) search portal (http://apps.who.int/trialsearch/).

If ongoing trials that have not been published are identified by these searches, the principal investigators and major co-operative groups active in this area will be approached for relevant data.

Data collection and analysis

Data from included studies will be extracted as described in the *Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0* (Higgins 2011). Data will be analysed using Review Manager 5.3 (Review Manager 2014).

Selection of studies

All studies (titles and abstracts) identified by the literature search will be independently screened for eligibility two review authors (MSB and VG) based on the inclusion criteria described above. We will obtain full-text reports when studies appear to satisfy the inclusion criteria based on the title and abstract screening, or when information is insufficient to allow for a decision. Any disagreements will be resolved by consensus, or by referring to a third review author (VVP). The number of studies identified, excluded and included, will be reported according to the PRISMA (the Preferred Reporting Items for Systematic Reviews and Meta-Analyses) checklist (Moher 2009).

Data extraction and management

Data extraction will be carried out independently by two authors (MSB, VG) using a standardised data extraction form (Higgins 2011). Where more than one publication of any study exists, reports will be grouped together and the publication with the most complete data will be reported as the primary study publication. Data from the primary publication will be used for the data analyses. Any discrepancies between published versions will be highlighted.

The following data will be extracted from the original reports:

1. General information: title, authors, journal, year, publication status;
2. Study information: design, risk of bias items (e.g. methods of randomisation, allocation concealment, blinding etc.), power calculation, a priori and post hoc analyses;
3. Intervention and control: type and dose of a medication, delivery intervals, comparator;
4. Eligibility: inclusion and exclusion criteria, total number screened and randomised;
5. Baseline characteristics (in each group): age, sex, race, disease activity (including the method of evaluation), concurrent medications used and excluded medications;
6. Follow-up: length of follow-up, assessment of compliance with treatment, withdrawals and loss to follow-up; and
7. Outcomes: primary and secondary outcomes.

It will be noted in the 'Characteristics of included studies' table if outcome data were not reported in a usable way.

Assessment of risk of bias in included studies

The Cochrane risk of bias tool will be used to assess the methodological quality of included RCTs (Schulz 1995; Moher 1998; Kjaergard 2001; Gluud 2006; Wood 2008). The risk of bias will be assessed using the following domains:

Random sequence generation

- Low risk of bias: We will rate random sequence generation as low risk of bias if a computer or random number table was used to generate the random sequence. Other examples of random sequence generation methods which will be regarded as adequate include drawing lots, tossing a coin, shuffling cards, or throwing dice.
- Unclear risk of bias: We will rate random sequence generation as unclear risk of bias if the trial was specified as randomised, but the method used for the random sequence generation was not described.
- High risk of bias: We will rate random sequence generation as high risk of bias if a method based on a non-random allocation of patients was involved (e.g. dates, names, or admittance numbers). We will exclude high risk of bias trials for the assessment of benefits, but not for harms.

Allocation concealment

- Low risk of bias: We will rate allocation concealment as low risk of bias if central randomisation was used or if an independent unit was used to store allocation information. Examples include an on-site locked computer, identically appearing numbered drug bottles or containers prepared by an independent pharmacist or investigator, or sealed opaque envelopes.
- Unclear risk of bias: We will rate allocation concealment as unclear risk of bias if the trial was specified as randomised, but the method of allocation concealment was not described.
- High risk of bias: We will rate allocation concealment as high risk of bias if the investigators who assigned participants could have been or were informed of the allocation sequence.

Blinding

- Low risk of bias: We will rate blinding of participants and personnel as low risk of bias if the trail was reported to be blind and the method of blinding was clearly described and adequate (e.g. identical placebo). We will rate the blinding of outcome assessment as low risk of bias if the study clearly reports that outcome assessors were blinded.
- Unclear risk of bias: We will rate blinding of participants and personnel as unclear risk of bias if the trial was reported to be blind, but the methods to achieve blinding were not described. We will rate the blinding of outcome assessment as unclear risk of bias if the study does not describe the blinding of outcome assessors.
- High risk of bias: We will rate the blinding of participants and personnel and outcome assessors as high risk if the trial was not blinded (e.g. open label study).

Incomplete outcome data

- Low risk of bias: We will rate incomplete outcome data as low risk of bias if the number of dropouts and reasons for withdrawal are balanced across intervention groups or if it was reported that there were no withdrawals or dropouts.
- Unclear risk of bias: We will rate incomplete outcome data as unclear risk of bias if the report does not specifically report on withdrawals or dropouts.
- High risk of bias: We will rate incomplete outcome data as high risk of bias if the number or reasons for withdrawals and dropouts were not reported.

Selective outcome reporting

- Low risk of bias: We will rate selective outcome reporting as low risk of bias if the study reports on all outcomes that were pre-defined in the study protocol, or clinically relevant and logically anticipated outcomes are reported on.
- Unclear risk of bias: We will rate selective reporting bias as unclear if insufficient information is reported to allow for an assessment of selective outcome reporting.
- High risk of bias: We will rate selective reporting bias as unclear if the study does not report on all outcomes that were pre-specified in the study protocol, or if the study only partially reports on pre-specified outcomes, or if the study reports on post hoc subgroup analyses without identifying these subgroups as post hoc. We will also rate selective outcome reporting as high risk of bias if one or more clinically relevant and logically anticipated outcomes were not reported on and data for these outcomes were likely to have been observed (i.e. when no study protocol is available).

Other bias

- Low risk of bias: We will rate other bias as low risk of bias if the trial gives the impression of being free of bias in other bias domains including no baseline imbalance across groups in sociodemographic characteristics (e.g. educational level, socio-economic status, ethnicity).
- Unclear risk of bias: We will rate other bias as unclear if the trial does not provide information, transparent or implied, on bias in other domains.
- High risk of bias: We will rate other bias as high risk of bias if other factors in the trial exist that could impose a risk of bias (e.g. baseline imbalance across groups in sociodemographic characteristics).

All included trials will be assessed for risk of bias. If the risk of bias in a trial is rated as 'low' for all of the domains, the trial will be

judged as having a 'low risk of bias'. If the risk of bias was estimated as 'unclear' or 'high', then the trial will be judged as having 'high risk of bias'.

The risk of bias for each study will be assessed independently by two review authors (MSB, VG). If evidence of for profit bias or academic bias are found in the included studies, this will be reported in the characteristics of included studies tables. The 'risk of bias' judgments will be summarized across different studies for each of the domains indicated above. Any disagreement will be resolved by discussion and consensus involving a third author (VVP). The authors of original reports will be contacted in the case that published data are unclear or missing.

The Grading of Recommendations, Assessment, Development and Evaluation (GRADE) criteria will be employed to determine the overall quality of evidence supporting the following outcomes: change in HRQoL scores, adverse events, serious adverse events, withdrawal due to adverse events, improvement in workplace productivity and improvement in fatigue (Guyatt 2011; Schünemann 2011). Evidence from RCTs begins as high-quality evidence, but can be downgraded on grounds of: (1) risk of bias, (2) indirectness of evidence, (3) inconsistency (i.e. unexplained heterogeneity), (4) imprecision of effect estimates (i.e. sparse data) and (5) publication bias. The overall quality of evidence for each outcome will be determined and classified as a high quality (i.e. further research is very unlikely to change our confidence in the estimate of effect); moderate quality (i.e. further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate); low quality (i.e. further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate); or very low quality (i.e. we are very uncertain about the estimate) (Guyatt 2008; Schünemann 2011). We will use the GRADE profiler software (http://gradepro.org/) to import and analyse data from Review Manager and produce the 'Summary of findings' tables.

Measures of treatment effect

For continuous outcomes, we will calculate the mean difference (MD) and corresponding 95% confidence interval (95% CI) if the same tool has been used to measure the same outcome across different studies. We will calculate the standardized mean difference (SMD) when different tools have been used to measure the same underlying construct. For dichotomous outcomes, we will calculate the risk ratio (RR) and corresponding 95% CI. Where studies report adverse events as dichotomous data, we will report on the proportion of participants experiencing the event in each study arm. We will report descriptive results for adverse event data that cannot be extracted as dichotomous outcomes as described above (Higgins 2011).

Unit of analysis issues

If there are multiple observations for the same outcome, we will make an effort to combine outcomes for fixed follow-up intervals. We plan to evaluate outcomes at maximum follow-up as defined by individual studies. For cross-over trials, we will use data from the first phase of the trial (i.e. before any cross-over). HRQoL outcomes and safety among different doses of biological drugs will be compared using subgroup analyses where possible. Studies with control groups using different types of interventions (e.g. placebo or active treatment), studies with cluster randomised treatment groups and studies with multiple treatment groups e.g. dose groups) will be analysed separately and will not be combined in a single meta-analysis.

Dealing with missing data

We will attempt to contact the authors of included studies to obtain missing data. In the case of missing data despite our attempts to contact authors, the following strategies will be considered. For missing dichotomous outcomes, two scenarios will be considered, the best-case scenario in which all patients with incomplete data will be assumed to be a treatment success with regard to QoL and a worst-case scenario in which all patients with incomplete data will be assumed to be treatment failures with regard to QoL. We will use sensitivity analysis to assess the impact of these assumptions on the effect estimate. We will use an available case analysis for missing continuous outcomes and assumptions about participants with missing data will not be made. We will contact the authors of studies published in abstract form for relevant missing data and these studies will only be included in the review if enough data are provided to assess outcomes and risk of bias.

Assessment of heterogeneity

We will assess heterogeneity across the included studies using the Chi^2 test. A P value of 0.10 will be considered to be statistically significant. The degree of heterogeneity, as a percentage of total variation across trials that results from heterogeneity rather than chance, will be described using the I^2 statistic. We will interpret the I^2 statistic as follows: 0% to 14% might not be important, 30% to 60% may represent moderate heterogeneity, 50% to 90% may represent substantial heterogeneity, and 75% to 100% represents considerable heterogeneity (Higgins 2011). If a considerable degree of heterogeneity is detected (i.e. $I^2 > 75\%$), data will not be pooled for meta-analysis. A fixed-effect model will be used to pool data in the absence of heterogeneity. A random-effects model will be used to pool data if significant heterogeneity is detected.

Assessment of reporting biases

We will assess reporting bias by comparing the outcomes listed in study protocols to those reported in the published studies. If protocols are not available, we will compare the outcomes specified in the methods section of the published report to those reported

in the results section of the manuscript. If more than 10 studies are included in a pooled analyses, we will explore the potential for publication bias by constructing funnel plots (Egger 1997).
Bias introduced by multiple publications will be confronted by including study results only once in a given analysis. If there is reasonable doubt that two publications report results from the same study, we will contact the trial authors to clarify the issue. Location and language bias will be addressed by searching multiple databases, including non-English language journals.

Data synthesis

The pooled RR and 95% CI will be calculated for dichotomous outcomes and the pooled MD or SMD and 95% CI for continuous outcomes. Data from individual trials will be amalgamated for meta-analysis when the interventions, patient populations, and outcomes are sufficiently similar (to be determined by consensus). A fixed-effect model will be used to pool data in the absence of heterogeneity. A random-effects model will be used if significant heterogeneity is detected (Jakobsen 2014).

Subgroup analysis and investigation of heterogeneity

Data permitting, we will perform subgroup analyses to investigate substantial heterogeneity.

Potential subgroup analyses include:

- biologic-naive patients versus patients who had already been receiving biologic treatment;
- anti-TNF versus non-anti-TNF agents; and
- different doses of the biological drugs.

Sensitivity analysis

Data permitting, we plan the following sensitivity analyses:

- the exclusion of studies published in the abstract form only; and
- the exclusion of studies of low methodological quality (i.e. high risk of bias).

We also plan to explore potential explanations for heterogeneity using a sensitivity analysis excluding any obvious outliers upon visual inspection of the forest plot.

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* *Indicates the major publication for the study*

APPENDICES

Appendix 1. Search strategies

Embase

1. random$.tw.
2. factorial$.tw.
3. (crossover$ or cross over$ or cross-over$).tw.
4. placebo$.tw.
5. single blind.mp.
6. double blind.mp.
7. triple blind.mp.
8. (singl$ adj blind$).tw.
9. (double$ adj blind$).tw.
10. (tripl$ adj blind$).tw.
11. assign$.tw.
12. allocat$.tw.
13. crossover procedure/
14. double blind procedure/
15. single blind procedure/

16. triple blind procedure/
17. randomized controlled trial/
18. or/1-17
19. TNF inhibitor*.mp.
20. (Anti-TNF OR anti TNF).mp.
21. Monoclonal antibod*.mp.
22. (Anti-tum* OR Antitum* OR Anti IL* OR Anti-IL*).mp.
23. Entanercept*.mp.
24. (Anti madcam or anti-madcam).mp.
25. (Recombinant human interleukin or interleukin* or IL*).mp.
26. Biologic*.mp.
27. (Golimumab* OR Certolizumab* OR Vedolizumab* OR Secukinumab* OR Basiliximab* OR Etrolizumab* OR Visilizumab* OR Briakinumab* OR Abrilumab* OR abrilimumab* OR Eldelumab* OR Brazikumab* OR Dectrekumab*).mp.
28. (Alicaforsen* OR Mongersen* OR Firategrast* OR Vercirnon* OR Filgotinib* OR Tofacitinib* OR Masitinib*).mp.
29. (TRK-170 OR PF 00547,659 OR anti-NKG2D OR CCX-507 OR BL-7040 OR PF-04236921).mp.
30. Exp Infliximab/
31. Exp Natalizumab/
32. Exp Adalimumab/
33. Exp Ustekinumab/
34. Or/19-33
35. Exp Crohn disease/
36. Crohn*.mp.
37. IBD.mp.
38. Inflammatory bowel disease*.mp.
39. Or/35-38
40. Exp Health related quality of life/
41. (HRQL OR HRQoL). mp.
42. (Short from-36 OR SF-36).mp.
43. Inflammatory bowel disease question*.mp.
44. EQ-5D.mp.
45. Work product*.mp.
46. Activity impair*.mp.
47. (Activities of daily living OR ADL).mp.
48. Questionnaire*.mp.
49. Or/40-48
50. 18 and 34 and 39 and 49

MEDLINE

1. random$.tw.
2. factorial$.tw.
3. (crossover$ or cross over$ or cross-over$).tw.
4. placebo$.tw.
5. single blind.mp.
6. double blind.mp.
7. triple blind.mp.
8. (singl$ adj blind$).tw.
9. (double$ adj blind$).tw.
10. (tripl$ adj blind$).tw.
11. assign$.tw.
12. allocat$.tw.
13. randomized controlled trial/
14. or/1-13
15. TNF inhibitor*.mp.
16. (Anti-TNF OR anti TNF).mp.

17. Monoclonal antibod*.mp.
18. (Anti-tum* OR Antitum* OR Anti IL* OR Anti-IL*).mp.
19. Entanercept*.mp.
20. (Anti madcam or anti-madcam).mp.
21. (Recombinant human interleukin or interleukin* or IL*).mp.
22. Biologic*.mp.
23. (Golimumab* OR Certolizumab* OR Vedolizumab* OR Secukinumab* OR Basiliximab* OR Etrolizumab* OR Visilizumab* OR Briakinumab* OR Abrilumab* OR abrilimumab* OR Eldelumab* OR Brazikumab* OR Dectrekumab*).mp.
24. (Alicaforsen* OR Mongersen* OR Firategrast* OR Vercirnon* OR Filgotinib* OR Tofacitinib* OR Masitinib*).mp.
25. (TRK-170 OR PF 00547,659 OR anti-NKG2D OR CCX-507 OR BL-7040 OR PF-04236921).mp.
26. Exp Infliximab/
27. Exp Adalimumab/
28. Exp Natalizumab/
29. Exp Ustekinumab/
30. Or/15-29
31. Exp Crohn disease/
32. Crohn*.mp.
33. IBD.mp.
34. Inflammatory bowel disease*.mp.
35. Or/31-34
36. Exp Health related quality of life/
37. (HRQL or HRQoL).mp.
38. (Short from-36 or SF-36).mp.
39. Inflammatory bowel disease question*.mp.
40. EQ-5D.mp.
41. Work product*.mp.
42. Activity impair*.mp.
43. (Activities of daily living or ADL).mp.
44. Questionnaire*.mp.
45. Or/36-44
46. 14 and 30 and 35 and 45

Cochrane CENTRAL

#1 MeSH: [Inflammatory bowel disease] explode all trees
#2 Crohn Disease
#3 Crohn
#4 IBD
#5 #1 or #2 or #3 or #4
#6 Biologic* OR Golimumab* OR Certolizumab* OR Vedolizumab* OR Secukinumab* OR Basiliximab* OR Etrolizumab* OR Visilizumab* OR Briakinumab* OR Abrilumab* OR abrilimumab* OR Eldelumab* OR Brazikumab* OR Dectrekumab* OR Infliximab* OR Adalimumab* OR Natalizumab* OR Ustekinumab*
#7 TNF inhibitor* OR Anti-TNF OR anti TNF OR Monoclonal antibod* OR Anti-tum* OR Antitum* OR Anti IL* OR Anti-IL* OR Entanercept* OR Anti madcam or anti-madcam OR Recombinant human interleukin or interleukin* or IL*
#8 Alicaforsen* OR Mongersen* OR Firategrast* OR Vercirnon* OR Filgotinib* OR Tofacitinib* OR Masitinib*
#9 TRK-170 OR PF 00547,659 OR anti-NKG2D OR CCX-507 OR BL-7040 OR PF-04236921
#10 #6 or #7 or #8 or #9
#11 Health related quality of life
#12 HRQL
#13 short form-36 or SF-36
#14 inflammatory bowel disease questionnaire or IBDQ
#15 Cleveland global quality of life questionnaire or CGQL
#16 WPAI
#17 activity impairment
#18 Activities of daily live or ADL

#19 #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18
#20 #5 and #10 and #19
Trials only
SCIE (Web of Science)
1. TS= (Inflammatory bowel disease or Crohn's Disease or Crohn or CD)
2. TS= (anti-TNF or Biological or Biologic* or etanercept or infliximab or adalimumab or Golimumab or Certolizumab or Natalizumab or Vedolizumab or Interleukin or secukinumab or onercept or basiliximab or etrolizumab or visilizumab or Ustekinumab or Briakinumab or abrilumab or abrilimumab or eldelumab or brazikumab or dectrekumab or alicaforsen or mongersen or firategrast or TRK-170 or PF 00547,659 or anti-NKG2D or vercirnon or CCX-507 or BL-7040 or filgotinib or tofacitinib or masitinib)
3. TS= (Health related quality of life or short form-36 or inflammatory bowel disease questionnaire or Cleveland global quality of life questionnaire or WPAI or activity impairment or Activities of daily live)
1 and 2 and 3
IBD Specialized register
Crohn OR IBD OR inflammatory bowel disease OR HRQL OR quality of life OR SF-36 OR short form-36 OR IBDQ OR inflammatory bowel disease questionnaire OR EQ-5D OR Cleveland Global Quality of Life Questionnaire OR CGQL OR WPAI OR fatigue OR TNF OR mab OR interleukin OR IL OR agent

WHAT'S NEW

Date	Event	Description
21 November 2018	Amended	Pre-specified outcomes for 'Summary of findings' table added to protocol

CONTRIBUTIONS OF AUTHORS

· Draft the protocol: Mirjana Stanić Benić , Vanja Giljač a

· Develop and run the search strategy: Trials Search Co-ordinator will help us to perform these tasks

· Obtain copies of trials: Mirjana Stanić Benić

· Select which trials to include: Mirjana Stanić Benić , Vanja Giljač a

· Extract data from trials: Mirjana Stanić Benić , Vanja Giljač a

· Enter data into RevMan: Mirjana Stanić Benić

· Carry out the analysis: Mirjana Stanić Benić , Vanja Giljač a

· Interpret the analysis: Mirjana Stanić Benić , Vanja Giljač a, Vera Vlahović Palč evski

· Draft the final review: Mirjana Stanić Benić , Vanja Giljač a, Vera Vlahović -Palč evski

· Update the review: Mirjana Stanić Benić

DECLARATIONS OF INTEREST

None known.