Cochrane Library

Cochrane Database of Systematic Reviews

Certolizumab pegol for induction of remission in Crohn's disease (Protocol)

Yamazaki H, So R, Matsuoka K, Kobayashi T, Shinzaki S, Matsuura M, Okabayashi S, Kataoka Y, Tsujimoto Y, Furukawa TA, Watanabe N

Yamazaki H, So R, Matsuoka K, Kobayashi T, Shinzaki S, Matsuura M, Okabayashi S, Kataoka Y, Tsujimoto Y, Furukawa TA, Watanabe N.
Certolizumab pegol for induction of remission in Crohn's disease.
Cochrane Database of Systematic Reviews 2017, Issue 12. Art. No.: CD012893.
DOI: 10.1002/14651858.CD012893.

www.cochranelibrary.com

WILEY

TABLE OF CONTENTS

[Intervention Protocol]

Certolizumab pegol for induction of remission in Crohn's disease

Hajime Yamazaki[1], Ryuhei So[2], Katsuyoshi Matsuoka[3], Taku Kobayashi[4], Shinichiro Shinzaki[5], Minoru Matsuura[6], Shinji Okabayashi[4], Yuki Kataoka[1], Yasushi Tsujimoto[1], Toshi A Furukawa[2], Norio Watanabe[2]

[1]Department of Healthcare Epidemiology, School of Public Health in the Graduate School of Medicine, Kyoto University, Kyoto, Japan. [2]Department of Health Promotion and Human Behavior, Kyoto University Graduate School of Medicine/School of Public Health, Kyoto, Japan. [3]Department of Gastroenterology and Hepatology, Tokyo Medical and Dental University, Tokyo, Japan. [4]Center for Advanced IBD Research and Treatment, Kitasato University Kitasato Institute Hospital, Tokyo, Japan. [5]Department of Gastroenterology and Hepatology, Osaka University Graduate School of Medicine, Suita, Japan. [6]Department of Gastroenterology and Hepatology, Kyoto University Hospital, Kyoto, Japan

Contact address: Hajime Yamazaki, Department of Healthcare Epidemiology, School of Public Health in the Graduate School of Medicine, Kyoto University, Yoshida Konoe-cho, Sakyo-ku, Kyoto, 606-8501, Japan. yamazaki-myz@umin.ac.jp.

Editorial group: Cochrane IBD Group.
Publication status and date: New, published in Issue 12, 2017.

Citation: Yamazaki H, So R, Matsuoka K, Kobayashi T, Shinzaki S, Matsuura M, Okabayashi S, Kataoka Y, Tsujimoto Y, Furukawa TA, Watanabe N. Certolizumab pegol for induction of remission in Crohn's disease. *Cochrane Database of Systematic Reviews* 2017, Issue 12. Art. No.: CD012893. DOI: 10.1002/14651858.CD012893.

ABSTRACT

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

The objectives of this systematic review are to evaluate the efficacy and safety of CZP for induction of remission in CD.

BACKGROUND

Description of the condition

Crohn's disease (CD) is a chronic inflammatory disease that mainly affects the gastrointestinal tract. CD is more common in North America and Europe than in other areas. Nonetheless, both the incidence and prevalence of CD are increasing worldwide. The highest annual incidence of CD was reported to be 5.0, 12.7, and 20.2 per 100,000 person-years in Asia and the Middle East, Europe and North America, respectively. Moreover, the highest reported prevalence of CD was 67.9, 322, and 318.5 per 100,000 people in Asia and the Middle East, Europe and North America, respectively (Molodecky 2012).

Common symptoms of CD include chronic diarrhea, abdominal pain, and weight loss (Torres 2016), and patients are typically diagnosed with CD in their 20s to 30s (Cosnes 2011). Up to one third of patients with CD have complications such as stricturing and penetrating disease at diagnosis, and half of these patients need surgery within 10 years of diagnosis (Peyrin-Biroulet 2010). After the initial surgery, one-quarter of the patients require a second surgery within five years (Frolkis 2014). Moreover, the age-adjusted risk of mortality in patients with CD is 50% higher than that of the general population (Canavan 2007).

The etiology of CD is unknown, but abnormal mucosal immune

response and impaired barrier function are considered to play an important role in the pathogenesis of CD. Altered intestinal microflora and environmental factors, such as food and smoking, have been postulated to cause immune system dysfunction in genetically susceptible individuals (Torres 2016). Regulating impaired immune response is the key to CD treatment.

Description of the intervention

The current treatment strategy for inducing remission in active CD is based on immune response modulation. Pharmacologic treatments for induction of remission in CD include corticosteroids, tumor necrosis factor-alpha (TNF-α) inhibitors, antibodies to $\alpha 4\beta 7$ integrin, and antibodies to interleukin-12/23p40. TNF-α is a proinflammatory cytokine and plays a central role in the inflammatory cascade of CD. Regulating impaired immune response with TNF-α inhibitors may be key for treatment of CD (Baumgart 2012; Nielsen 2013; Olesen 2016; Torres 2016).
Certolizumab pegol (CZP) is a TNF-α inhibitor. Unlike other TNF-α inhibitors such as infliximab (IFX) and adalimumab (ADA), CZP is a polyethylene glycolated Fab fragment of a humanized anti-TNF-α monoclonal antibody with high affinity for TNF-α. CZP has no Fc portion. CZP has different mechanistic profile than other TNF- α inhibitors because of its unique structure. CZP lacks the ability to induce regulatory macrophage formation, antibody-dependent cellular cytotoxicity, complement-dependent cytotoxicity, and apoptosis via reverse signalling. However, CZP can inhibit inflammatory mediators and increase regulatory T cell activity as effectively as IFX and ADA (Gomollon 2017; Nesbitt 2007; Olesen 2016; Shao 2009; Torres 2016).
TNF-α inhibitors including CZP are recommended for moderately-to-severely active CD (Gomollon 2017; Talley 2011; Terdiman 2013; Torres 2016). CZP is approved for the treatment of CD in the United States and Switzerland (Olesen 2016; Torres 2016). CZP is a subcutaneously delivered drug and can be self-administered. Potential serious adverse events of CZP are anaphylactic reaction, lymphoproliferative disorder, tuberculosis reactivation, and opportunistic infection (Gomollon 2017).

How the intervention might work

CZP inhibits TNF-α receptor activation by neutralizing both the transmembrane form of TNF-α (tmTNF) and soluble form of TNF-α (sTNF). Currently, tmTNF signaling is considered to have a central role in the pathogenesis of CD, and CZP can bind to both sTNF and tmTNF. CZP is regulates impaired immune response through the following possible mechanisms of action: increased regulatory T cell frequency and activity, inflammatory mediator suppression in immune cells, decreased inflammatory mediators by reverse signaling in tmTNF-expressing cells, and nonapoptotic cytotoxicity and apoptosis by blocking tmTNF-mediated TNF-α receptor activation (Olesen 2016).

Why it is important to do this review

Recent meta-analyses have inconsistent results which may be due to differences in methodology and in the selected time points for the assessment of clinical remission (Ford 2011; Kawalec 2013). In one review (Ford 2011), there was no difference between CZP and placebo in the proportion of participants who failed to achieve remission at weeks 6 to 12 (risk ratio [RR] 0.95, 95% confidence interval [CI]0.90 to 1.01). Another review (Kawalec 2013), found a benefit for induction of remission for CZP over placebo at week four (RR 1.63, 95% CI 1.32 to 2.13). We are also aware of at least one unpublished trial (NCT00291668). The current review will summarize and properly integrate all of the available evidence including unpublished randomized controlled trials (RCTs) to provide the best available evidence to assess the efficacy and safety of CZP for induction of remission in CD.

OBJECTIVES

The objectives of this systematic review are to evaluate the efficacy and safety of CZP for induction of remission in CD.

METHODS

Criteria for considering studies for this review

Types of studies

This review will include RCTs irrespective of publication status. No language status restrictions will be applied.

Types of participants

Adult patients ($\geq$ 18 years old) with active CD will be included in this review. CD will be diagnosed by standard clinical, endoscopic, radiographic, and histopathological assessment. Active CD will be defined as follows: a Crohn's Disease Activity Index (CDAI) score of greater than 150 or a Harvey-Bradshaw Index (HBI) score of greater than 4 (Best 1976; Harvey 1980).

Types of interventions

The eligible intervention will be subcutaneous administration of any dose of CZP every two to four weeks. The comparison therapy will be placebo or no treatment. Active comparators such as conventional treatment (including 5-aminosalicylic acid, immunomodulators, or corticosteroids) will not be included in this review.

Types of outcome measures

Primary outcomes

The primary outcome will be the proportion of CD patients achieving remission at week eight after CZP administration. We selected week eight because this week is the time to switch to maintenance dosing according to the approved regimen (Schreiber 2011). If the outcome was not assessed at week 8, we will select the nearest week between weeks 4 and 12 as the outcome assessment point. If only dates from two time points equally distant from week 8, such as weeks 6 and 10, are available despite inquiry with the original investigators, the earlier point (week 6) will be selected. Remission will be defined as the follows: CDAI $\leq$ 150 or HBI $\leq$ 4. If both CDAI and HBI are reported in the primary studies, the CDAI will be used for outcome assessment. The proportion of participants in remission will be calculated in accordance with the intention-to-treat (ITT) principle; the denominator will be the number of the randomized patients in each arm. Participants with missing data for the primary outcome will be assumed to be treatment failures.

Secondary outcomes

Secondary outcomes will include the proportion of participants with clinical response at week 8, endoscopic improvement at week 12, C-reactive protein (CRP) improvement at week 8, health-related quality of life at week 8, fistula closure at week 8, adverse events, serious adverse events and withdrawals due to adverse events. Clinical response will be defined as a CDAI reduction from baseline of greater than or equal to 100 or remission (CDAI $\leq$ 150) or an HBI reduction from baseline of greater than or equal to 3 or remission (HBI $\leq$ 4) (Vermeire 2010). For outcomes that are not available for week 8, we will select the nearest week between weeks 4 and 12. If only two assessment points equally distant from week 8 are available, such as weeks 6 and 10, despite inquiry with the original investigators, the earlier point (week 6) will be selected. We will follow this procedure for all outcomes that we intend to assess at eight weeks. If endoscopic outcomes are not reported for week 12, we will select the nearest week between weeks 8 and 26. We will assess endoscopic improvement by calculating the mean change from baseline in Crohn's Disease Endoscopic Index of Severity (CDEIS), Simplified Endoscopic Activity Score for Crohn's Disease (SES-CD), or Rutgeerts score (Daperno 2004; Mary 1989; Rutgeerts 1990). If only two assessment points equally distant from week 12 are available, such as weeks 10 and 14, despite inquiry with the original investigators, the earlier point (week 10) will be selected. The assessment for C-reactive protein (CRP) improvement at week eight will be based on the mean CRP change from baseline. The assessment for health-related quality of life at week eight will be based on mean change in quality of life scores from baseline as measured by a validated instrument including the Inflammatory Bowel Disease Questionnaire (IBDQ) (Guyatt 1989), or the Medical Outcomes Study Short-Form 36 (SF-36) questionnaire (Ware 1992). Potential adverse events could include but are not limited to skin reactions, headache, pyrexia, nausea, vomiting, hepatic abnormal function, infection and malignancy. Potential serious adverse events could include but are not limited to anaphylaxis, sepsis, disseminated intravascular coagulation, peritonitis, malignancy, and death.

Search methods for identification of studies

Electronic searches

We will conduct a comprehensive literature search without language restrictions. We will search the following databases to identify relevant RCTs:

- MEDLINE (inception to date);
- EMBASE (inception to date);
- CENTRAL;
- The Cochrane IBD Group Specialized Register (inception to date);
- http://ClinicalTrials.gov (trial registry);
- https://www.clinicaltrialsregister.eu/ (EU Clinical Trials Register);
- http://apps.who.int/trialsearch/ (International Clinical Trials Registry Platform); and
- http://www.ucb.com/our-science/Our-clinical-studies/cimzia-certolizumab-pegol (web site of a pharmaceutical company producing CZP).

The search strategies are reported in Appendix 1.

Searching other resources

To identify additional studies, we will search the following resources manually or through personal contacts:

- Abstracts of Digestive Disease Week, United European Gastroenterology Week, European Crohn's and Colitis

Organization Congress, and Advances in Inflammatory Bowel Diseases (2000 to date);

- References from published articles; and
- Pharmaceutical companies and experts involved in the development of CZP.

Data collection and analysis

Selection of studies

Two authors (HY and RS) will independently screen titles and abstracts, and potential eligible studies will be selected based on the above mentioned criteria. In addition, these authors will independently read the full articles of the potential eligible studies and decide which studies should be included in the present systematic review. In cases of insufficient information, we will contact the authors of the primary studies to evaluate eligibility for the inclusion. In the event of a disagreement regarding study selection, HY and RS will discuss to reach a consensus. NW will be the arbitrator when consensus is not reached.

Data extraction and management

Two authors (HY and RS) will independently extract data. We will use data extraction forms to record data from the selected studies. Any disagreement will be resolved through discussion. NW will be the arbitrator when consensus is not reached.
We will extract the following data:

- Characteristics of the primary studies: publication year, country, study recruitment period, study completion date, study type, and risk of bias items;
- Participant characteristics: country, total number of participants, number of participants randomized, number of participants analyzed in each group, age, sex, ethnicity, body mass index, disease duration, disease site, smoking status, CDAI score, HBI score, CDEIS, SES-CD, Rutgeerts score, IBDQ score, SF-36 score, CRP, fistula, concurrent CD treatment, previous CD treatment, inclusion criteria, and exclusion criteria;
- Intervention characteristics: dose, delivery route, and administration schedule of CZP;
- Comparator characteristics: placebo or no treatment control;
- Outcomes: proportion of participants who achieved clinical remission at week 8, proportion of participants with clinical response at week 8, CDAI score at week 8, HBI score at week 8, CDEIS at week 12, SES-CD at week 12, Rutgeerts score at week 12, IBDQ score at week 8, SF-36 score at week 8, CRP at week 8, fistula closure at week 8, any adverse events, adverse events leading to withdrawal, serious adverse events, time of outcome assessment in primary studies, length of follow-up, number of participants lost to follow-up, reasons for loss to follow-up, number of participants who did not complete treatment, reasons for incomplete treatment, and criteria for evaluating outcomes in primary studies.

We will contact the authors of the primary studies if information in published reports is insufficient.

Assessment of risk of bias in included studies

Two authors (HY and RS) will independently assess the quality of included studies using the Cochrane risk of bias tool (Higgins 2011). Primary studies will be rated as high, low, or unclear risk of bias. In cases of disagreement that cannot be resolved between HY and RS, NW will be consulted. We will assess the following risk of bias items: random sequence generation (selection bias), allocation concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias), selective reporting (reporting bias), and other potential sources of bias.
We will rate random sequence generation as low risk of bias if the method for random sequence generation was described as a random number table, computer-generated, coin tossing, shuffling cards or envelopes, throwing dice, drawing of lots or minimization. We will rate random sequence generation as high risk of bias if the method of generation was not random. Examples include a systematic approach such as date or record number or a non-systematic approach such as preference and availability. We will rate random sequence generation as unclear risk of bias if insufficient information was reported to allow for a judgement. We will rate allocation concealment as low risk of bias if allocation could not be foreseen by participants and investigators. Adequate methods of allocation concealment include centralized allocation such as telephone, web-based, or pharmacy-controlled randomization, sequentially numbered drug containers of the same appearance, or sequentially numbered, opaque, sealed envelopes. We will rate allocation concealment as high risk of bias if the allocation sequence was likely to be foreseen. Examples include an open random allocation schedule or envelopes without safeguards. We will rate allocation concealment as unclear risk of bias if insufficient information was reported to allow for a judgement. We will rate blinding of participants and personnel and blinding of outcome assessors as low risk of bias if proper methods were employed to prevent knowledge of treatment assignment (e.g. double-blinding with an identical placebo) or if no blinding or incomplete blinding of participants or personnel was unlikely to affect assessment of the outcome (e.g. a serious adverse event resulting in death). We will rate blinding of participants and personnel and blinding of outcomes assessors as high risk of bias if blinding was likely to be broken and this could affect outcome assessment or if there was no blinding or incomplete blinding of participants or personnel

or outcome assessors which could affect outcome assessment. We will rate blinding of participants and personnel and blinding of outcome assessors as unclear risk of bias if insufficient information was reported to allow for a judgement. We will rate incomplete outcome data as low risk of bias when there are no missing outcome data; when missing outcome data are unlikely to be related to the true outcome; when the numbers of dropouts and reasons for withdrawal are balanced between treatment groups; when compared to the observed event, the proportion of missing outcomes does not have a clinically relevant impact on the effect estimate for dichotomous outcomes; when the expected effect size among missing outcomes does not have clinically relevant impact on the observed effect size for continuous outcome data; or when missing data were imputed using proper methods. We will rate incomplete outcome data as high risk of bias when missing outcome data are likely to be related to true outcome; when numbers or reasons for missing data are imbalanced across treatment groups; when compared with the observed event, the proportion of missing outcomes has a clinically relevant impact on the effect estimate for dichotomous outcomes; when the expected effect size among missing outcomes has a clinically relevant impact on the observed effect size for continuous outcomes; when an 'as-treated analysis' was substantially performed; and when missing data were imputed using improper methods (e.g. simple imputation). We will rate incomplete outcome data as unclear risk of bias when insufficient information was reported to allow for a judgement. We will rate selective reporting as low risk of bias when the protocols of primary studies are available, and all of the primary and secondary study outcomes related to this systematic review, were reported in a pre-defined way; and when the study protocols were unavailable, but all of the expected outcomes, related to this systematic review, are reported. We will rate selective outcome reporting as high risk of bias when pre-defined primary outcomes related to this systematic review are not thoroughly reported; when primary outcomes related to this systematic review, are measured or analyzed in a way that is different from the protocol; when reported primary outcomes related to this systematic review are different from those in the protocol; when outcomes related to this systematic review are not completely reported; and when key outcomes related to this systematic review are not included in primary studies. We will rate selective outcome reporting as unclear risk of bias when insufficient information was reported to allow for a judgement. We will rate studies as low risk of bias for other sources of bias when the study appears to be free of other potential sources of bias. We will rate studies as high risk of bias for other sources of bias when other sources of bias could have an impact on the study outcomes. For example, fraudulent studies or baseline imbalances in demographic factors. We will rate studies as unclear risk of bias for other sources of bias when the study reported insufficient details to allow for a judgement. We will contact study authors for additional information to clarify the risk of bias when the study reports do not provide enough detail to allow for a clear judgement.

Measures of treatment effect

For dichotomous outcomes, we will calculate the risk ratio (RR) and corresponding 95% CI. ITT analyses will be conducted for dichotomous outcomes, whereby all drop outs will be assumed to be treatment failures. We will calculate the mean difference (MD) and 95% CI for continuous outcomes. When different scales are used to measure the same construct, we will calculate the standardized mean difference (SMD) and 95% CI.

Unit of analysis issues

We will collect outcomes per randomized participant. For crossover trials, we will use data from the first phase before the crossover. Cluster RCTs will not be included in this review. If events will occur more than once (e.g. adverse events), we will report on the proportion of participants who experience at least one event. To avoid double counting of the comparator for multi-arm studies (multiple dose groups), the number of patients in the comparator group (i.e. placebo or no treatment control) will be divided across the number of eligible CZP arms. To deal with multiple observations for the same outcome in primary studies, we will precisely define the outcome assessment points for both primary and secondary outcomes.

Dealing with missing data

When there are missing data, we will contact the authors of the primary studies to obtain the missing data and the reason for the missing data. If it not possible to obtain the missing data, we will report so in the manuscript. For dichotomous outcomes, all missing data will be treated as treatment failures in the ITT analyses. We will conduct sensitivity analyses using available case data to assess the impact on the effect estimate. For continuous outcomes, we will not use any imputation methods, we will use only the available data.

Assessment of heterogeneity

Clinical heterogeneity will first be assessed with regard to patient characteristics, such as previous treatment and concurrent medication. If the studies are clinically homogenous, statistical heterogeneity will be evaluated using Chi^2 test and I^2 statistic. A P value of less than or equal to 0.10 for the Chi^2 test will be considered statistically significant heterogeneity. The I^2 statistic estimates the degree of statistical heterogeneity. We will consider an I^2 value of 25% to indicate low heterogeneity, a value of 50% to indicate moderate heterogeneity and a value of 75% to indicate high heterogeneity. If statistical heterogeneity exists, we will perform a visual inspection of the forest plots to identify potential outliers causing the heterogeneity. Moreover, sensitivity and subgroup analyses will be conducted to explore potential sources of heterogeneity when significant or moderate-high heterogeneity exists (Higgins 2003; Higgins 2011).

Assessment of reporting biases

We will search for both registered and published trials, and we will report on the proportion of registered trials that are unpublished. We will contact the investigators of the unpublished trials to provide data related to outcomes in this systematic review. If we cannot obtain these data, we will report as such in this review. When there are 10 or more eligible trials in a pooled analysis, we will generate funnel plots to evaluate potential publication bias. The presence of publication bias will be suspected if the plots are asymmetric, and we will report as such in this review. Moreover, when we find unclear or high risk of bias for selective reporting, we will also contact the study authors to provide unpublished outcome data. If we cannot obtain these data, we will report so in the manuscript.

Data synthesis

When included studies are sufficiently similar from the clinical and statistical viewpoints, meta-analyses will be conducted. Data will be synthesized using Review Manager 5.3, and a random-effects model will be used for meta-analyses. A P value of less than 0.05 will be considered statistically significant.
On the basis of the characteristics of participants, interventions, and outcomes in primary studies, clinical similarity will be determined by consensus between HY and KM. In cases of disagreement between HY and KM, TK will be consulted to resolve the disagreement. In cases of high heterogeneity (I^2 statistics $\geq$ 75%), meta-analyses will not be conducted, and each study will be described in detail.

Subgroup analysis and investigation of heterogeneity

If sufficient data are available, the following subgroup analyses will be conducted for primary outcomes:

- Disease severity at baseline (150 < CDAI < 220, 220 $\leq$ CDAI $\leq$ 450, CDAI > 450);
- CRP levels at baseline (CRP levels < 10 mg/L, CRP levels $\geq$ 10 mg/L);
- Doses of CZP (CZP < 200 mg, 200 mg $\leq$ CZP < 400 mg, 400 mg $\leq$ CZP < 600 mg, CZP $\geq$ 600 mg); and
- Previous treatment with other TNF-α inhibitors (yes, no).

Sensitivity analysis

When a meta-analysis is conducted, we will perform the following sensitivity analyses for primary outcomes.

- Excluding studies judged to be at high risk of bias for any domain of the risk of bias tool;
- Excluding studies judged to be at high or unclear risk of bias for any domain of the risk of bias tool;
- Using available case data instead of ITT analysis for missing dichotomous outcome data
- Selecting later outcome assessment points if only dates from two time points equally distant from the defined outcome assessment points are available despite inquiry with the original investigators. For example, if only dates from two time points equally distant from week 8, such as weeks 6 and 10, are available, week 10 will be selected in the sensitivity analysis.
- Limiting the included studies that administered CZP strictly in accordance with the approved regimen which is subcutaneous administration of 400 mg CZP at weeks 0, 2, and 4, and then every 4 weeks.

Summary of findings

We will produce 'Summary of findings' tables using the GRADEpro Guideline Development Tool for the following outcomes: clinical remission, clinical response, and serious adverse events.
The Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach will be used to evaluate the certainty of the evidence supporting each outcome. Evidence from RCTs starts as high quality, but can be downgraded due to risk of bias, inconsistency across studies, indirectness of evidence, imprecision of effect estimate, and publication bias (Schünemann 2011). If serious limitations are present, we will downgrade the evidence level by one. Moreover, very serious limitations will lead to downgrading of the evidence by two levels (Schünemann 2011). HY and RS will independently assess the certainty of evidence for each outcome and the overall quality of the evidence will be rated as:

- High: We are very confident that the true effect lies close to that of the effect estimate;
- Moderate: We are moderately confident in the effect estimate: the true effect is likely to be close to the effect estimate, but it could be substantially different;
- Low: Our confidence in the effect estimate is limited: the true effect may be substantially different from the effect estimate; or
- Very low: We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the effect estimate.

In cases of disagreement between HY and RS, NW will be consulted to resolve disagreement.

ACKNOWLEDGEMENTS

The authors thank John K MacDonald and Tran M Nguyen for their assistance with the development of this protocol.

This project was supported by Japanese Society for Inflammatory Bowel Disease.

Partial funding for the Cochrane IBD Group (April 1, 2016 - March 31, 2018) has been provided by Crohn's and Colitis Canada (CCC).

REFERENCES

Additional references

Baumgart 2012
Baumgart DC, Sandborn WJ. Crohn's disease. *Lancet* 2012; **380**:1590–605.

Best 1976
Best WR, Becktel JM, Singleton JW, Kern F Jr. Development of a Crohn's disease activity index. National Cooperative Crohn's Disease Study. *Gastroenterology* 1976; **70**:439–44.

Canavan 2007
Canavan C, Abrams KR, Mayberry JF. Meta-analysis: mortality in Crohn's disease. *Alimentary Pharmacology and Therapeutics* 2007;**25**:861–70.

Cosnes 2011
Cosnes J, Gower-Rousseau C, Seksik P, Cortot A. Epidemiology and natural history of inflammatory bowel diseases. *Gastroenterology* 2011;**140**:1785–94.

Daperno 2004
Daperno M, D'Haens G, Van Assche G, Baert F, Bulois P, Maunoury V, et al. Development and validation of a new, simplified endoscopic activity score for Crohn's disease: the SES-CD. *Gastrointestinal Endoscopy* 2004;**60**:505–12.

Ford 2011
Ford AC, Sandborn WJ, Khan KJ, Hanauer SB, Talley NJ, Moayyedi P. Efficacy of biological therapies in inflammatory bowel disease: systematic review and meta-analysis. *American Journal of Gastroenterology* 2011;**106**:644–59.

Frolkis 2014
Frolkis AD, Lipton DS, Fiest KM, Negron ME, Dykeman J, deBruyn J, et al. Cumulative incidence of second intestinal resection in Crohn's disease: a systematic review and meta-analysis of population-based studies. *American Journal of Gastroenterology* 2014;**109**:1739–48.

Gomollon 2017
Gomollon F, Dignass A, Annese V, Tilg H, Van Assche G, Lindsay JO, et al. 3rd European Evidence-based Consensus on the Diagnosis and Management of Crohn's Disease 2016: Part 1: Diagnosis and Medical Management. *Journal of Crohn's and Colitis* 2017;**11**:3–25.

Guyatt 1989
Guyatt G, Mitchell A, Irvine E J, Singer J, Williams N, Goodacre R, et al. A new measure of health status for clinical trials in inflammatory bowel disease. *Gastroenterology* 1989; **96**:804–10.

Harvey 1980
Harvey RF, Bradshaw JM. A simple index of Crohn's-disease activity. *Lancet* 1980;**1**:514.

Higgins 2003
Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ* 2003;**327**: 557–60.

Higgins 2011
Higgins JPT, Altman DG, Sterne JAC (editors). Chapter 8: Assesing risk of bias in included studies. In: Higgins JPT, Green S editor(s). *Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (updated March 2011)*. The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org.

Kawalec 2013
Kawalec P, Mikrut A, Wisniewska N, Pilc A. Tumor necrosis factor-alpha antibodies (infliximab, adalimumab and certolizumab) in Crohn's disease: systematic review and meta-analysis. *Archives of Medical Science* 2013;**9**:765–79.

Mary 1989
Mary JY, Modigliani R. Development and validation of an endoscopic index of the severity for Crohn's disease: a prospective multicentre study. Groupe d'Etudes Therapeutiques des Affections Inflammatoires du Tube Digestif (GETAID). *Gut* 1989;**30**:983–9.

Molodecky 2012
Molodecky NA, Soon IS, Rabi DM, Ghali WA, Ferris M, Chernoff G, et al. Increasing incidence and prevalence of the inflammatory bowel diseases with time, based on systematic review. *Gastroenterology* 2012;**142**:46–54.

Nesbitt 2007
Nesbitt A, Fossati G, Bergin M, Stephens P, Stephens S, Foulkes R, et al. Mechanism of action of certolizumab pegol (CDP870): in vitro comparison with other anti-tumor necrosis factor alpha agents. *Inflammatory Bowel Diseases* 2007;**13**:1323–32.

Nielsen 2013
Nielsen OH, Ainsworth MA. Tumor necrosis factor inhibitors for inflammatory bowel disease. *New England Journal of Medicine* 2013;**369**:754–62.

Olesen 2016
Olesen CM, Coskun M, Peyrin-Biroulet L, Nielsen OH. Mechanisms behind efficacy of tumor necrosis factor inhibitors in inflammatory bowel diseases. *Pharmacology and Therapeutics* 2016;**159**:110–9.

Peyrin-Biroulet 2010
Peyrin-Biroulet L, Loftus E V Jr, Colombel JF, Sandborn WJ. The natural history of adult Crohn's disease in population-based cohorts. *American Journal of Gastroenterology* 2010; **105**:289–97.

Rutgeerts 1990
Rutgeerts P, Geboes K, Vantrappen G, Beyls J, Kerremans R, Hiele M. Predictability of the postoperative course of Crohn's disease. *Gastroenterology* 1990;**99**:956–63.

Schreiber 2011
Schreiber S. Certolizumab pegol for the treatment of Crohn's disease. *Therapeutic Advances in Gastroenterology* 2011;**4**(6):375–89.

Schünemann 2011
Schünemann HJ, Oxman AD, Vist GE, Higgins JPT, Deeks JJ, Glasziou P. Chapter 12: Interpreting results and drawing conclusions. In: Higgins JPT, Green S editor(s). *Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (updated March 2011)*. The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org, 2011. Available from www.cochrane-handbook.org.

Shao 2009
Shao L M, Chen M Y, Cai J T. Meta-analysis: the efficacy and safety of certolizumab pegol in Crohn's disease. *Alimentary Pharmacology and Therapeutics* 2009;**29**:605–14.

Talley 2011
Talley N J, Abreu M T, Achkar J P, Bernstein C N, Dubinsky M C, Hanauer S B, et al. An evidence-based systematic review on medical therapies for inflammatory bowel disease. *American Journal of Gastroenterology* 2011;**106**(Suppl 1):S2-25; quiz S26.

Terdiman 2013
Terdiman JP, Gruss CB, Heidelbaugh JJ, Sultan S, Falck-Ytter YT, Practice AGA Institute Clinical, et al. American Gastroenterological Association Institute guideline on the use of thiopurines, methotrexate, and anti-TNF-alpha biologic drugs for the induction and maintenance of remission in inflammatory Crohn's disease. *Gastroenterology* 2013;**145**:1459–63.

Torres 2016
Torres J, Mehandru S, Colombel JF, Peyrin-Biroulet L. Crohn's disease. *Lancet* 2016;**389**:1741–55.

Vermeire 2010
Vermeire S, Schreiber S, Sandborn W J, Dubois C, Rutgeerts P. Correlation between the Crohn's disease activity and Harvey-Bradshaw indices in assessing Crohn's disease severity. *Clinical Gastroenterology and Hepatology* 2010;**8**: 357–63.

Ware 1992
Ware JE Jr, Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. *Medical Care* 1992;**30**(6):473–83.

* *Indicates the major publication for the study*

APPENDICES

Appendix 1. Search strategies

MEDLINE (inception to date)

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. (exp animal/ or animal.hw. or nonhuman/) not (exp human/ or human cell/ or (human or humans).ti.)
16. 14 not 15

17. exp Crohn disease/ or Crohn*.mp.
18. (inflammatory bowel disease* or IBD).mp.
19. 17 or 18
20. 16 and 19
21. (CDP870 OR 'CDP 870' OR CDP-870 OR 'certolizumab pegol' OR certolizumab OR cimzia).mp.
22. 20 and 21

EMBASE (inception to date)

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. (exp animal/ or animal.hw. or nonhuman/) not (exp human/ or human cell/ or (human or humans).ti.)
20. 18 not 19
21. exp Crohn disease/ or Crohn*.mp.
22. (inflammatory bowel disease* or IBD).mp.
23. 21 or 22
24. 20 and 23
25. exp certolizumab pegol/
26. (CDP870 OR 'CDP 870' OR CDP-870 OR 'certolizumab pegol' OR certolizumab OR cimzia).mp.
27. 25 or 26
28. 24 and 27

CENTRAL (inception to date)

#1. crohn* OR IBD OR "inflammatory bowel disease*"
#2. CDP870 OR 'CDP 870' OR CDP-870 OR 'certolizumab pegol' OR certolizumab OR cimzia
#3. #1 and #2

Cochrane IBD Group Specialized Register (inception to date)

#1 (CDP870 OR 'CDP 870' OR CDP-870 OR 'certolizumab pegol' OR certolizumab OR cimzia).ti.
#2 Crohn.ti.
#3 1 and 2

CONTRIBUTIONS OF AUTHORS

Draft the protocol: Hajime Yamazaki, Ryuhei So, Katsuyoshi Matsuoka, Taku Kobayashi, Shinichiro Shinzaki, Minoru Matsuura, Shinji Okabayashi, Yuki Kataoka, Yasushi Tsujimoto, Toshi A Furukawa, Norio Watanabe

Develop and run the search strategy: Hajime Yamazaki, Yuki Kataoka, Cochrane IBD Group Information Specialist

Obtain copies of studies: Hajime Yamazaki, Katsuyoshi Matsuoka, Taku Kobayashi, Shinji Okabayashi

Select which studies to include: Hajime Yamazaki, Ryuhei So

Extract data from studies: Hajime Yamazaki, Ryuhei So

Enter data into RevMan: Hajime Yamazaki

Carry out the analysis: Hajime Yamazaki, Yuki Kataoka, Yasushi Tsujimoto, Toshi A Furukawa, Norio Watanabe

Interpret the analysis: Hajime Yamazaki, Katsuyoshi Matsuoka, Taku Kobayashi, Shinichiro Shinzaki, Minoru Matsuura, Shinji Okabayashi

Draft the final review: Hajime Yamazaki, Ryuhei So, Katsuyoshi Matsuoka, Taku Kobayashi, Shinichiro Shinzaki, Minoru Matsuura, Shinji Okabayashi, Yuki Kataoka, Yasushi Tsujimoto, Toshi A Furukawa, Norio Watanabe

Update the review: Hajime Yamazaki, Ryuhei So, Katsuyoshi Matsuoka, Taku Kobayashi, Shinichiro Shinzaki, Minoru Matsuura, Shinji Okabayashi, Yuki Kataoka, Yasushi Tsujimoto, Toshi A Furukawa, Norio Watanabe

DECLARATIONS OF INTEREST

Hajime Yamazaki: None known

Ryuhei So: None known

Katsuyoshi Matsuoka received research grants from Eisai, and Abbvie outside of this work; lecture fees from Mitsubishi Tanabe Pharma, Eisai, Abbvie, Kyorin Pharmaceutical, JIMRO, Ajinomoto Pharmaceutical, Janssen, Astellas, Asahi Kasei Medical, Mochida Pharmaceutical, Kissei, Kyowa Hakko Kirin, and Takeda Pharmaceutical.

Taku Kobayashi received recearch grant from Asahi Kasei, Otsuka, Abbvie, Mitsubishi-Tanabe, JIMRO ,Zaria, EA Pharma and consulting or lecture fees from Asahi Kasei, Abbvie, Kyorin, Mitsubishi-Tanabe, JIMRO, Zeria, EA Pharma, Mochida and serves as an advisory board member for Janssen, Takeda, Pfizer, and Mochida.

Shinichiro Shinzaki received fees for expert testimony from Kyorin pharmaceutical; grants/grants pending from the Japan Society for the Promotion of Science; payment for lectures from Mitsubishi Tanabe Pharma, Eisai, AbbVie, EA Pharma, Mochida pharmaceutical and Zeria pharmaceutical.

Minoru Matsuura received lecture fees from Mitsubishi-Tanabe Pharma, Abbvie, EA Pharma Co., Ltd., KYORIN Pharmaceutical, ZERIA Pharmaceutical, AstraZeneka, Daiichi-Sankyo, Mochida Pharmaceutical, JIMRO, Astellas Pharma Inc. and Nippon Kayaku Co., Ltd.

Shinji Okabayashi: None known

Yuki Kataoka: None known

Yasushi Tsujimoto: None known

Toshi A Furukawa has received lecture fees from Eli Lilly, Janssen, Meiji, MSD, Otsuka, Pfizer and Tanabe-Mitsubishi, and consultancy fees from Sekisui Chemicals. He has received royalties from Igaku-Shoin and Nihon Bunka Kagaku-sha publishers. He has received research support from Mochida and Tanabe-Mitsubishi.

Norio Watanabe: None known

SOURCES OF SUPPORT

Internal sources

- No sources of support supplied

External sources

- Japanese Society for Inflammatory Bowel Disease, Japan.
Research grant