Comparing persistence of new biologics to conventional anti-TNF alphas in adult patients with inflammatory bowel disease: a systematic review and meta-analysis protocol

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ABSTRACT

Background Biological therapy is a cornerstone of managing moderate-to-severe inflammatory bowel disease (IBD), ulcerative colitis (UC) and Crohn’s disease (CD). New biologics have been evolving over the past 20 years and selection of an agent remains challenging. Drug persistence measures the duration of time from initiation to discontinuation of a therapy, which can be a surrogate marker of drug tolerance and efficacy.

Objectives The study aimed to compare drug persistence of new generation biologics for the treatment of UC and CD (vedolizumab, ustekinumab, certolizumab, tofacitinib, natalizumab and golimumab) with conventional anti-tumor necrosis factor alphas (anti-TNF alphas) (adalimumab and infliximab) in adult patients with IBD. Results of the study may provide guidance on the preferred first and subsequent lines of biological treatments in patients with IBD.

Methods and analysis Search via electronic databases including EMBASE, MEDLINE, PubMed and clinical trial databases will be conducted on 10 March 2023 with eligible studies included from inception of 2017 to 2023. The primary outcomes are 1-year persistence of individual biologics with comparison of new biologics versus conventional anti-TNF alphas. A meta-analysis will be conducted using Review Manager V.5 and outcome will be presented as relative risk. Heterogeneity will be assessed with forest plot, $\chi^2$ and $I^2$, followed with sensitivity analysis and subgroup analysis. Finally, the Grading of Recommendations Assessment, Development and Evaluation system will be used to assess the quality of evidence.

Ethics and dissemination Ethical approval is not required as no private information of participants will be used. Results of the present study will be disseminated in a peer-reviewed journal or conference presentation.

PROSPERO registration number CRD42023392236.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- Study selection, data extraction and quality assessment will be performed independently by two researchers to reduce risk of bias.
- Search of unpublished clinical trials to reduce risk of publication bias.
- Observational studies may pose significant risk of selection bias.
- Measured outcome of persistence does not differentiate reason of discontinuation.

INTRODUCTION

Australia has one of the highest prevalence in the world for inflammatory bowel diseases (IBD), consisting of Crohn’s disease (CD) and ulcerative colitis (UC). Pricewaterhouse-Coopers Australia calculated it to be between 75,302 and 92,571 in 2018 and is estimated to increase to almost 100,000 in 2022. IBD poses a high economic burden to the healthcare system with significant length of hospital stay. Australian Institute of Health and Welfare data for 2013–2014 indicates that there were more than 21,386 admissions to public hospitals for CD and UC, with an average length of stay of 5.2 days for CD and 6.5 for UC.

Medications are used to induce and maintain remission in patients with IBD, which reduces the number of hospital admissions and surgical interventions. Common treatments include 5-aminosalicylates, glucocorticoids, immunomodulators and biological therapies.

Biological therapies are the last line of medical treatment in line with the Pharmaceutical Benefits Scheme (PBS) criteria in Australia for accessing treatment and are frequently used in moderate-to-severe IBDs not controlled by other agents such as immunomodulators.

These therapies have been extensively studied with evidence on their efficacy.
towards IBD over the past 20 years. Infliximab was the first biologic used in IBD since 2001 in Australia and became available on the Australian PBS for CD in 2007 and UC in 2012 evidenced by A Crohn's Disease Clinical Trial Evaluating Infliximab in a New Long-term Treatment Regimen in Patients With Fistulizing Crohn's Disease II study (ACCENT II)\(^3\) for CD and the Active Ulcerative Colitis Trials (ACT 1 and 2)\(^4\) for UC.

Adalimumab was listed in 2008 for CD with supporting evidence from The Crohn’s Trial of the Fully Human Antibody Adalimumab for Remission Maintenance (CHARM)\(^5\) and listed for UC in 2013 with evidence from Antibody Adalimumab for Remission Maintenance evidence from The Crohn's Trial of the Fully Human Antibody Adalimumab for Remission Maintenance (CHARM)\(^5\) and listed for UC in 2013 with evidence from the Ulcerative colitis long-term remission and maintenance with adalimumab (ULTRA) studies.\(^6\)

These two anti-TNF alphas have been the cornerstone of moderate-to-severe IBD for years until evidence of newer agents come in place. These include vedolizumab (listed in 2015 for both CD and UC with evidence from the Efficacy and Safety of Vedolizumab Subcutaneously as Maintenance Therapy in Ulcerative Colitis (VISIBLE I) study\(^7\) and the Study of Vedolizumab (MLN0002) in Patients With Moderate to Severe Ulcerative Colitis (GEMINI I) study\(^8\)) and ustekinumab (listed in 2017 for CD with evidence from the IM-UNITI studies\(^9\)), golimumab (listed in 2017 for UC with evidence from the Program of Ulcerative Colitis Research Studies Utilizing an Investigational Treatment–Subcutaneous (PURSUIT-SC) study\(^10\)) and tofacitinib (listed in 2021 for UC with evidence from A Study Evaluating The Efficacy And Safety Of CP-690,550 In Patients With Moderate To Severe Ulcerative Colitis (OCTAVE) trials\(^11\)).

Persistence, also known as drug survival, is ‘the duration of time from initiation to discontinuation of therapy’. Poor persistence can result in suboptimal treatment results and has been used as a surrogate marker of poor tolerance and low efficacy of medication.\(^12\)\(^13\) It is also a reflection of patient and physician drug preferences.

Demuth et al published a systematic review and meta-analysis on persistence of vedolizumab in IBD in 2018\(^14\) to address real-world effectiveness of the agent. However, evidence on comparisons between biological agents are lacking and the choice of optimal first and subsequent line biologics remain unclear.

The aim of this study is to compare persistence of different newer biologics with conventional anti-TNF alphas (adalimumab and infliximab) in patients with IBD over 18 years of age. Results of the study may provide guidance on the preferred first and subsequent lines of biological treatments in patients with IBD.

**MATERIALS AND METHODS**

The methods of this systematic review will be developed according to the recommendations of the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols 2015 Checklist.\(^15\) This review protocol has been published in the International Prospective Register of systematic reviews (PROSPERO).

**Patient and public involvement**

Patients and/or the public were not involved in the design, conduct, reporting or dissemination plans of this research.

**Eligible criteria for study selection**

**Types of studies**

Eligible studies included prospective, retrospective and cross-sectional observational studies evaluating persistence of biologics for IBD, including new agents (vedolizumab, ustekinumab, certolizumab, tofacitinib, natalizumab and golimumab) and conventional anti-TNF alphas (infliximab and adalimumab) among participants aged >18 years with IBD. There will be no limitations on language and publication time.

**Types of participants**

Patients over 18 years of age who have been diagnosed with IBD including UC and CD with a confirmed clinical or endoscopic diagnosis. Patients are required to have commenced on/previously commenced on biologics in the intention of providing or maintaining remission of his or her IBD.

**Types of interventions**

New biologics indicated for IBDs including vedolizumab, ustekinumab, tofacitinib, certolizumab, golimumab, natalizumab and conventional anti-TNF alphas including adalimumab and infliximab with no restriction on treatment regime.

**Types of outcomes**

The outcome measured is persistence to biologics as reported in included studies. Persistence is defined as the percentage of patients who remained on and have not switched the index medication over the entire follow-up period. Discontinuation is defined as no administration/dispensing record of the index medication at due time of the next dose, which varies based on treatment frequency.\(^16\)

**Primary outcomes**

One-year pooled persistence of individual biologics with comparison of newer biologics versus conventional anti-TNF alphas in patients with bio-naive UC and CD.

One-year pooled persistence of individual biologics with comparison of newer biologics versus conventional anti-TNF alphas in patients with UC and CD when used as subsequent lines of therapy (second line, third line and third line or above).

**Secondary outcomes**

Two years pooled persistence of individual biologics with comparison of newer biologics versus conventional anti-TNF alphas in patients with bio-naive UC and CD.

Two years pooled persistence of individual biologics with comparison of newer biologics versus conventional anti-TNF alphas in patients with UC and CD when used as
subsequent lines of therapy (second line, third line and third line or above).

**Information source and search strategy**

Literature research from inception in MEDLINE, EMBASE, PubMed and grey literature search including but not limited to Australian New Zealand Clinical Trials Registry, ClinicalTrials.gov and EU Clinical Trials Register will be carried out by authors (THY and YK), using terms include (IBD, CD, UC, persistence, adalimumab, infliximab, ustekinumab, golimumab, tofacitinib, natalizumab, certolizumab and biologic). Detailed search strategies are shown in online supplemental appendix 1. There will be no limitations on language, and the search will be undertaken on 10 March 2023 with regular search for new studies.

**Selection of studies**

Selected articles will be independently reviewed by two authors (THY and YK).

After screening all titles and abstracts of papers identified via search strategy, papers will be categorised into potentially relevant or not relevant according to eligibility criteria. Full texts of all potentially relevant papers will then be attempted to retrieve, and all retrieved full texts will then be screened according to eligibility criteria. During full-text screening, disagreements will be resolved by discussion. If consensus is unable to be reached, the dispute will be settled by a third author (RWL). The process of study selection is shown in figure 1.

**Data extraction process**

The following information will be extracted from each full-text articles that met eligibility criteria: Study design; country of study; outcome (persistence)—12 months (primary)/24 months; definition of persistence; number and general characteristics of participants, for example, age, gender, disease severity, comorbidities and concomitant drugs; previous treatments as well as dosage and regime of biological treatment. Data extraction will be carried out by author THY and YK and spreadsheet software Microsoft Excel will be used for data collection. In the event of missing data, we will contact original author for further information.

**Study risk of bias assessment**

The methodological quality of included studies will be assessed via Risk Of Bias In Non-randomised Studies – of Interventions assessment tool. The tool is developed to assess non-randomised studies with seven domains of consideration. Risk of bias of each domain will be judged as either low, moderate, serious, criterial risk of bias or no information. Risk of bias of all included studies will be evaluated by author THY and YK individually with differences to be resolved with discussion and consensus.

**DATA ANALYSIS**

**Effect measures**

Study-specific prevalence of persistence to biologics will be evaluated by calculating the proportion of persistent

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**Figure 1** Flow diagram of the study selection process.
subjects on the total number of participants for each study in the form of %. When specific numbers are not provided in certain studies, Kaplan-Meier curves will be used as an alternative to estimate persistence in time point of interest (12 and 24 months).

Assessment of heterogeneity
Statistical heterogeneity will be assessed visually by inspection of forest plots and $\chi^2$ test. P value of <0.05 will be considered as statistically significant.

$I^2$ test will also be used to assess heterogeneity. This test describes the percentage of variability in effect estimated that is due to heterogeneity rather than sampling error. As per Cochrane handbook, we will define $I^2$ test over 75% as considerable heterogeneity, 50–90% as possible substantial heterogeneity, 30–60% as potential moderate heterogeneity and less than 40% as might not be important. We will consider sensitivity analysis and subgroup analysis to further examine heterogeneity.

Sensitivity analysis
We will perform sensitivity analyses to explore potential influence by the following factors on effect size.
► Repeat analysis after excluding studies with serious risk of bias.
► Repeat analysis after excluding the largest studies to minimise the dominance effect of a single study.

Subgroup analysis
Subgroup analysis will be considered for heterogeneity assessment if sufficient data are available.

Assessment of reporting biases
Potential impact will be addressed with comprehensive search for eligible studies in multiple sources and removal of duplication data. We will also analyse publication bias via funnel plot visually if more than 10 articles are included.

Synthesis methods
Study specific persistence to newer biological agents and conventional anti-TNF alphas will be compared using random effect models with Mantel-Haenszel method.
Results will be presented as relative risks as our primary interest are measuring persistence of agents by certain time point (12 and 24 months) instead of measuring the rate of decline over the years. 95% CI/p<0.05 will be considered as statistically significant.

Grading the quality of evidence
Quality of evidence will be assessed via GRADE (Grades of Recommendation, Assessment, Development and Evaluation) approach (GRADE 2008), which defines the quality of a body of evidence in the extent that how confident we are for the estimation of effect is close to the true quantity of specific interest. GRADE assessed quality of evidence with five domains:
1. Risk of bias.
2. Imprecision.
3. Inconsistency.
4. Indirectness.
5. Publication bias.

ETHICS AND DISSEMINATION
Ethical approval is not required for this study as no private information of participants will be involved. Results of the present study will be disseminated in a peer-reviewed journal or conference presentation. Important protocol amendments will be documented and updated on PROSPERO.

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Contributors
THY and RWL conceived the study. THY drafted the protocol. YK, PN, AP and RWL revised it. THY developed the search strategies and will run it. THY and YK will select studies and extract data. THY will analyse the data. All authors have read and approved the final edition of the manuscript.

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Competing interests
RWL is an advisory board member of AbbVie, Aspen, BMS, Celgene, Celtrion, Chiesi, Ferring, Glutagen, Hospira, Jansen, Lilly, MSD, Novartis, Pfizer, Prometheus Biosciences, Takeda; research grant recipient of Celtriton, Shire, Jansen, Takeda, Gastroenterological Society of Australia, NHMRC, Guty Group, Pfizer and Joanna Tiddy grants University of Sydney. AP is an advisory board member of AbbVie and received speaker fees from AbbVie and Takeda.

Patient and public involvement
Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

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Supplemental material
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REFERENCES
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