Division of Pharmacology and Pharmacotherapy
Faculty of Pharmacy
Doctoral Programme in Drug Research
University of Helsinki
Finland

Costs, effectiveness and cost-effectiveness of biological drugs in the treatment of rheumatoid arthritis and inflammatory bowel diseases

Saara Huoponen

DOCTORAL DISSERTATION

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Supervisors Professor Marja Blom (Pharmacoeconomics)
Faculty of Pharmacy
University of Helsinki
Helsinki, Finland

Docent Pirjo Räsänen (Health Technology Assessment)
Faculty of Pharmacy
University of Helsinki
Helsinki, Finland

Director of External Evaluation
Helsinki University Hospital
Helsinki, Finland

Reviewers Professor Kaija-Leena Kolho (Pediatrics)
Faculty of Medicine
University of Helsinki
Helsinki, Finland

Chief Physician
Helsinki University Hospital
Helsinki, Finland

Docent Leena Forma (Health Economics)
Faculty of Social Sciences (Health Sciences)
Tampere University
Tampere, Finland

Opponent Research Professor Hennamari Mikkola
Head of Research Unit
The Social Insurance Institution of Finland
Helsinki, Finland

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ABSTRACT

Background: Rheumatoid arthritis (RA) and inflammatory bowel diseases (IBD), including Crohn´s disease (CD), ulcerative colitis (UC) and IBD unclassified, are chronic inflammatory disorders. In Finland, the prevalence of RA is estimated to be around 0.8% based on the data collected in the late 1980s, whereas the prevalence of IBD is around 0.9% in 2019. In the case of an insufficient response or intolerance to conventional drugs in the treatment of RA and IBD, biological drugs are a treatment option. Until May 2019, the European Medicines Agency (EMA) has approved ten biological drugs for the treatment of RA, four for CD, and four for UC. Biological drugs have proven to be an effective treatment for RA and IBD, and they have comparable efficacy and not significantly differing safety profiles. However, they are significantly more expensive than conventional drugs. Because of the high costs of original biological drugs, interest has grown in biosimilars and EMA has approved four biosimilars for the treatment of RA and two for IBD. RA and IBD, as chronic diseases, have a negative impact on patients' lives, and, therefore, they decrease health-related quality of life (HRQoL). Furthermore, poorly treated RA and IBD may cause disability and uncontrollable costs for social and health care.

Objectives: The aim of this study was to evaluate the costs, effectiveness, and cost-effectiveness of biological drugs in the treatment of RA and IBD.

Methods: Systematic literature reviews (SLRs) were performed to identify published data on the cost-effectiveness of biological drugs for RA and IBD (study I and II). The SLRs were performed following current recommendations for SLR of economic evaluations to improve the quality and reliability of the study. A patient-level simulation model (study III) was developed to predict costs and outcomes associated with four biological drugs (abatacept, tocilizumab, rituximab and Tumour Necrosis Factor Alpha (TNF) inhibitors) in the treatment of RA patients who have previously been treated with TNF inhibitors. Following lack of efficacy or adverse events, the patients were switched to another biological drug until all four options were exhausted. The patients' baseline characteristics and regression models used in the simulation were based on observational data from the National Register for Biological Treatments for RA patients in Finland. Several subgroup and deterministic sensitivity analyses were conducted. In the single-centre prospective observational study (IV), all IBD patients receiving maintenance infliximab therapy at Helsinki University Hospital (HUS) were switched to biosimilar infliximab (CT-P13). HRQoL was measured using the generic 15D utility measurement and the disease-specific Inflammatory Bowel Disease Questionnaire (IBDQ). Crohn´s Disease Activity Index (CDAI) or Partial Mayo Score (pMayo), and faecal calprotectin (FC) served for evaluation of disease activity. Data were collected at time of switching and at 3 and 12 months after switching. Patients´ characteristics and clinical background information were collected from patient records and costs were obtained from the clinical patient administration database of the hospital.

Results: The SRL (I) of the cost-effectiveness of biological drugs for the treatment of RA showed that biological drugs did not seem to be cost-effective among conventional synthetic disease-modifying anti-rheumatic drug (csDMARD) naïve or csDMARD resistant RA patients with the cost-effectiveness threshold of 35000 €/QALY (Quality-Adjusted Life Year), but they might be cost-effective among csDMARD resistant patients with the threshold of 50,000-100,000 €/QALY. Rituximab was the only

biological drug that seemed to be cost-effective among RA patients with a previous exposure to TNF inhibitors. According to the patient-level simulation model (III), drug costs were the lowest for rituximab in RA patients who had been previously been treated with TNF inhibitors, but when administration costs and costs of switching were included, drug costs were the lowest for TNF inhibitors. Abatacept was associated with the highest drug costs, whereas rituximab was associated with the highest outpatient and inpatient care costs. In total, TNF inhibitors had the lowest and rituximab the highest direct costs (including drug costs, administration costs, costs of switching, outpatient and inpatient care costs). The amount of QALY gained ranged from 9.41 for rituximab to 9.66 for TNF inhibitors. TNF inhibitors, abatacept, and tocilizumab had lower costs and higher QALYs than rituximab, and were therefore dominant in comparison to rituximab. According to the SLR (II), biological drugs seemed to be cost-effective for the treatment of active severe IBD with the cost-effectiveness threshold of 35,000 €/QALY, but the cost-effectiveness remained unclear in the maintenance treatment. Based on the prospective observational study (IV), no statistically significant difference was observed over one year following switching to the IFX biosimilar when the generic 15D instrument for the measurement of HRQoL in IBD patients was used. HRQoL measured with the IBDQ was, in CD patients, statistically significantly better (p=0.018) 3 months after switching to the infliximab biosimilar than at time of switching. Statistically significant finding was not observed in UC patients. Disease activity, in light of CDAI, pMayo and FC, was similar over one year following switching in IBD patients. The costs of biosimilar infliximab were around one third of the costs of originator one, whereas costs related to secondary healthcare (excluding the costs of infliximab) were similar before and after switching to biosimilar.

Conclusions: The patient-level simulation model based on Finnish real-world data showed that TNF inhibitors, abatacept, and tocilizumab were dominant in comparison to rituximab in RA patients, who had been previously been treated with TNF inhibitors. Significant differences were not observed in effectiveness between biological drugs. As TNF inhibitors had the lowest costs and highest QALYs, so they were the most cost-effective treatment option. In contrast to the results of patient-level simulation model, rituximab was the most cost-effective biological drug among RA patients with an adequate response to TNF inhibitors based on SLR. The systematic search of the literature revealed that biological drugs seemed to be cost-effective for the treatment of active and severe IBD. Based on the Finnish observational data, it suggested that HRQoL and disease activity of the infliximab-biosimilar were comparable to the originator one in the maintenance treatment of IBD. The costs of the infliximab-biosimilar were significantly lower than the costs of the originator one, and switching from originator infliximab to a biosimilar one had no effect on costs related to secondary healthcare (excluding the costs of infliximab).

TIIVISTELMÄ

Tausta: Nivelreuma (RA) ja tulehdukselliset suolistosairaudet (IBD), joihin kuuluvat Crohnin tauti (CD), haavainen paksusuolitulehdus (UC) sekä määrittämätön IBD, ovat kroonisia tulehdussairauksia. Suomessa RA:n esiintyvyyden on arvioitu olevan 1980-luvun lopulla kerättyihin aineistoihin perustuen noin 0,8 % aikuisväestöstä, kun taas IBD:n esiintyvyys on noin 0,9 % vuonna 2019. Biologiset lääkkeet ovat hoitovaihtoehto RA:n ja IBD:n hoidossa, mikäli tavanomaisista lääkkeistä ei ole saatu vastetta tai tavanomainen lääke on sopimaton. Toukokuuhun 2019 mennessä Euroopan lääkevirasto (EMA) on hyväksynyt kymmenen biologista lääkettä nivelreuman hoitoon, neljä CD:n hoitoon sekä neljä UC:n hoitoon. Biologisten lääkkeiden on osoitettu olevan vaikuttavia hoitoja RA:n ja IBD:n hoidossa, ja niillä on verrattavissa oleva tehokkuus, eivätkä niiden turvallisuusprofiilit eroa merkitsevästi toisistaan. Biologiset lääkkeet ovat kuitenkin merkitsevästi kalliimpia kuin tavanomaiset lääkkeet. Biologisten lääkkeiden korkeiden kustannusten vuoksi kiinnostus on kasvanut biosimilaarivalmisteita kohtaan. EMA on hyväksynyt neljä biosimilaaria nivelreuman hoitoon ja kaksi IBD:n hoitoon. RA ja IBD ovat kroonisia sairauksia, jotka heikentävät potilaan terveyteen liittyvää elämänlaatua (HRQoL). Huonosti hoidettu RA ja IBD saattavat aiheuttaa myös työkyvyttömyyttä ja hallitsemattomia kustannuksia sosiaali- ja terveydenhuollolle.

Tavoitteet: Tämän tutkimuksen tavoite oli arvioida biologisten lääkkeiden kustannuksia, vaikuttavuutta ja kustannusvaikuttavuutta RA:n ja IBD:n hoidossa.

Menetelmät: RA:n ja IBD:n kustannusvaikuttavuudesta julkaistu tutkimustieto kartoitettiin tekemällä kaksi järjestelmällistä kirjallisuuskatsausta (tutkimukset I ja II). Järjestelmälliset kirjallisuuskatsaukset tehtiin noudattaen voimassa olevia suosituksia taloudellisia arviointeja käsitteleville katsauksille. Potilastason simulaatiomalli (tutkimus III) kehitettiin ennustamaan neljään biologiseen lääkkeeseen (abatasepti, tosilitsumabi, rituksimabi ja tuumorinekroositekijä alfan (TNF) estäjät) liittyviä kustannuksia ja lopputulosmuuttujia RA-potilailla, joita oli aiemmin hoidettu TNF-estäjillä. Biologinen lääke vaihdettiin toiseen biologiseen lääkkeeseen tehon puutteen tai haittavaikutusten vuoksi kunnes kaikki neljä vaihtoehtoa oli käytetty. RA-potilaiden lähtötiedot ja simulaatiossa käytetyt regressiomallit perustuivat ROB-FIN –rekisteriaineistoon. Tutkimuksessa tehtiin useita alaryhmäanalyyseja sekä deterministisiä herkkyysanalyyseja. Prospektiivisessa, havainnoivassa yksikeskustutkimuksessa (tutkimus IV), kaikilla IBD-potilailla, jotka saivat infliksimabi-hoitoa ylläpitohoitona Helsingin yliopistollisessa sairaalassa (HUS), vaihdettiin infliksimabi alkuperäisestä valmisteesta biosimilaariin (CT-P13). HRQoL mitattiin geneerisellä 15D utiliteettimittarilla ja sairausspesifisellä Inflammatory Bowel Disease Questionnaire (IBDQ) -mittarilla. Tautiaktiivisuuden mittaamiseen käytettiin Crohn´s Disease Activity Index (CDAI) ja Partial Mayo Score (pMayo) –mittareita sekä ulosteen kalprotektiinimääritystä (FC). Tiedot kerättiin 3 ja 12 kuukautta sen jälkeen, kun alkuperäinen valmiste oli vaihdettu biosimilaariin. Potilaiden tausta-ja kliiniset tiedot kerättiin potilasrekistereistä ja kustannukset sairaalan potilastietojärjestelmästä.

Tulokset: Järjestelmällinen kirjallisuuskatsaus biologisten lääkkeiden kustannusvaikuttavuudesta RA:n hoidossa (I) osoitti, että biologiset lääkkeet eivät näyttäisi olevan kustannusvaikuttavia RA-potilailla, jotka eivät ole aiemmin saaneet tavanomaista lääkehoitoa tai ovat resistenttejä tavanomaisille lääkkeille kustannusvaikuttavuuden kynnysarvolla 35000 €/QALY (laatupainotettu elinvuosi). RA-potilailla, jotka ovat resistenttejä tavanomaisille lääkkeille, biologiset lääkkeet

saattavat kuitenkin olla kustannusvaikuttavia kynnysarvolla 50000–100000 €/QALY. RA-potilailla, jotka olivat saaneet aiemmin TNF-estäjähoitoa, rituksimabi oli ainut biologinen lääke, joka näytti olevan kustannusvaikuttava kustannusvaikuttavuuden kynnysarvolla 35000 €/QALY. Potilastason simulaatiomallin (III) perusteella rituksimabilla oli matalimmat lääkekustannukset RA:n hoidossa potilailla, joita oli aiemmin hoidettu TNF-estäjillä. Kun annostelu- ja lääkevaihdon kustannukset otettiin huomioon, TNF-estäjillä oli matalimmat lääkekustannukset. Abataseptilla oli korkeimmat lääkekustannukset, kun taas rituksimabilla oli korkeimmat avo- ja sairaalahoidon kustannukset. Kaiken kaikkiaan TNF-estäjillä oli matalimmat ja rituksimabilla korkeimmat suorat kustannukset (sisältäen lääkekustannukset, annostelukustannukset, lääkevaihdon kustannukset sekä avo- ja sairaalahoidon kustannukset). QALY-arvo vaihteli 9,41:stä (rituksimabi) 9,66:een (TNF-estäjät). TNF-estäjillä, abataseptilla ja tosilitsumabilla oli matalemmat kustannukset ja korkeammat QALYt kuin rituksimabilla. Näin ollen ne dominoivat rituksimabia. Kustannusvaikuttavuuden kynnysarvolla 35000 €/QALY biologiset lääkkeet näyttivät olevan kustannusvaikuttavia aktiivisen ja vaikean IBD:n hoidossa, mutta ylläpitohoidossa biologisten lääkkeiden kustannusvaikuttavuus oli epäselvä (II). Prospektiivisen havainnoivan tutkimuksen (IV) perusteella ylläpitohoidossa olevien IBD-potilaiden HRQoL ei eronnut tilastollisesti merkitsevästi yhden vuoden seurannassa, kun verrattiin alkuperäistä infliksimabi-hoitoa infliksimabi-biosimilaariin. Sairausspesifisellä IBDQ-mittarilla mitattuna HRQoL oli CD-potilailla tilastollisesti merkitsevästi parempi (p=0,018) kolme kuukautta biolosimilaarivaihdon jälkeen kuin vaihdettaessa infliksimabi-biosimilaariin. Tilastollisesti merkitsevää eroa ei havaittu UC-potilailla. IBD-potilaiden tautiaktiivisuus CDAI:n, pMayo:n ja FC:n perusteella oli samankaltainen IBD-potilailla ensimmäisen vuoden aikana, kun verrattiin alkuperäistä infliksimabi-hoitoa infliksimabi-biosimilaariin. Infliksimabi-biosimilaarin kustannukset olivat noin yksi kolmasosa alkuperäisen lääkkeen hinnasta, kun taas erikoissairaanhoidon kustannukset (poissulkien infliksimabin lääkekustannukset) olivat samansuuruiset ennen ja jälkeen biosimilaarivaihdon.

Johtopäätökset: Suomalaiseen rekisteritietoon perustuva potilastason simulaatiomalli osoitti, että TNF-estäjät, abatasepti ja tosilitsumabi dominoivat rituksimabia RA-potilailla, jotka olivat aiemmin käyttäneet TNF-estäjiä. Biologisten lääkkeiden välillä ei havaittu merkitseviä eroja vaikuttavuudessa. TNF-estäjät olivat kustannusvaikuttavin hoitovaihtoehto, koska niillä oli matalimmat kustannukset ja korkeimmat QALYt. Toisin kuin potilastason simulaatiomallissa, järjestelmällisen kirjallisuuskatsauksen perusteella rituksimabi oli kustannusvaikuttavin biologinen lääke RA-potilailla, jotka olivat saaneet riittämättömän vasteen aiemmasta TNF-estäjähoidosta. Järjestelmällisen kirjallisuuskatsauksen perusteella biologiset lääkkeet näyttivät olevan kustannusvaikuttavia aktiivisen ja vaikean IBD:n hoidossa. Suomalaiseen tietoon perustuvan prospektiivisen havainnoivan tutkimuksen perusteella infliksimabi-biosimilaari oli HRQoL:n ja tautiaktiivisuuden perusteella verrattavissa alkuperäiseen infliksimabi-hoitoon ensimmäisen vuoden aikana IBD:n ylläpitohoidossa. Infliksimabi-biosimilaarin kustannukset olivat merkitsevästi alhaisemmat kuin alkuperäisen infliksimabi-valmisteen, eikä infliksimabi-biosimilaarivaihdolla ollut vaikutusta erikoissairaanhoidon kustannuksiin (poissulkien infliksimabin lääkekustannukset). Tämän väitöskirjan tuloksia arvioitaessa nykypäivään on otettava huomioon, että lääkehoito, erityisesti biologisten lääkkeiden osalta, on muuttunut huomattavasti järjestelmällisten kirjallisuuskatsausten kirjallisuushakujen suorittamisen jälkeen.

CONTENTS

LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following publications:

I Joensuu JT, Huoponen S, Aaltonen KJ, Konttinen YT, Nordström D, Blom M (2015): The Cost-Effectiveness of Biologics for the Treatment of Rheumatoid Arthritis: A Systematic Review. PLoS One 10(3): e0119683. doi:10.1371/journal.pone.0119683

II Huoponen S, Blom M (2015): A Systematic Review of the Cost-Effectiveness of Biologics for the Treatment of Inflammatory Bowel Diseases. PLoS ONE 10(12): e0145087. https://doi.org/10.1371/journal.pone.0145087

III Huoponen S*, Aaltonen KJ*, Viikinkoski J, Rutanen J, Relas H, Taimen K, Puolakka K, Nordström D, Blom M (2019): Cost-effectiveness of abatacept, tocilizumab and TNF-inhibitors compared with rituximab as second-line biologic drug in rheumatoid arthritis. PLoS ONE 14(7): e0220142. https://doi.org/10.1371/journal.pone.0220142
*Authors share equal contribution

IV S. Huoponen, A. Eberl, P. Räsänen, R.P. Roine, T. Sipponen, P. Arkkila*, M. Blom*: Health-related quality of life and costs of switching originator infliximab to biosimilar one in treatment of inflammatory bowel disease. *Submitted.*
*Authors share equal contribution

The studies are referred to in the text by their roman numerals (I-IV). The original publications are reprinted with the permission of the copyright holders.

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ABBREVIATIONS

15D	15D Health-Related Quality of Life (HRQoL) Instrument
ABA	Abatacept
ACR	American College of Rheumatology
ADA	Adalimumab
ANA	Anakinra
AZA	Azathioprine
bDMARD	Biological Disease-Modifying Anti-Rheumatic Drug
BMI	Body Mass Index
boDMARD	Biological Originator Disease-Modifying Anti-Rheumatic Drug
bsDMARD	Biosimilar Disease-Modifying Anti-Rheumatic Drug
CEA	Cost-Effectiveness Analysis
CEAC	Cost-Effectiveness Acceptability Curve
CD	Crohn´s Disease
CHEERS	The Consolidated Health Economic Evaluation Reporting Standards
CRP	C-reactive protein
CUA	Cost-Utility Analysis
CTZ	Certolizumab pegol
CDAI	Crohn´s Disease Activity Index
DAS28	Disease Activity Score 28
DDD	Defined Daily Dose
csDMARD	Conventional Synthetic Disease-Modifying Anti-Rheumatic Drug
ECCO	The European Crohn´s and Colitis Organisation
EQ-5D	EuroQol Health-Related Quality of Life (HRQoL) Instrument
EULAR	European League Against Rheumatism
EMA	European Medicines Agency
ESR	Erythrocyte sedimentation rate
ETA	Etanercept
FDA	The Food and Drug Administration
Fimea	The Finnish Medicines Agency
FC	Faecal calprotectin
GOL	Golimumab
HAQ	Health Assessment Questionnaire
HAQ-DI	Health Assessment Questionnaire Disability Index
HCQ	Hydroxycloroquine
HRQoL	Health-Related Quality of Life
HTA	Health Technology Assessment
HUS	Helsinki University Hospital
IBD	Inflammatory Bowel Disease
IBDQ	Inflammatory Bowel Disease Questionnaire
IBDU	Inflammatory Bowel Disease Unclassified
ICER	Incremental Cost Effectiveness Ratio

IFX	Infliximab
IL	Interleukin
IV	Intravenous
LEF	Leflunomide
6-MP	Mercaptopurine
MTX	Methotrexate
NICE	The National Institute for Health and Care Excellence
pMayo	Partial Mayo score
PSC	Primary sclerosing cholangitis
QALY	Quality-Adjusted Life Year
RA	Rheumatoid Arthritis
RCT	Randomised Controlled Trial
RF	Rheumatoid Factor
ROB-FIN	National Register for Biologic Treatment in Finland
RTX	Rituximab
SAR	Sarilumab
SC	Subcutaneous
SF-36	The Short Form 36 Health Survey
SLR	Systematic Literature Review
SSZ	Sulfasalazine
TNF	Tumour Necrosis Factor Alpha inhibitor
TOC	Tocilizumab
tsDMARD	Targeted Synthetic Disease-Modifying Anti-Rheumatic Drug
TTO	The Time trade-off
UC	Ulcerative Colitis
UST	Ustekinumab
VAS	The Visual Analog Scale
VAT	Value Added Tax
VED	Vedolizumab

GLOSSARY

Cost-effectiveness analysis	Cost-effectiveness analysis (CEA) is a methodology of economic analysis that compares two or more alternative choices in terms of both their costs and their outcomes. Outcomes are measured in the same natural units such as symptom-free days gained, cases prevented or life years gained.
Cost-effectiveness threshold	A cost-effectiveness threshold describes the willingness to pay for an additional Quality-Adjusted Life Year (QALY), and it determines whether the intervention should be regarded cost-effective or not.
Cost-utility analysis	Cost-utility analysis (CUA) is a methodology of economic analysis, and a specific type of cost-effectiveness analysis (CEA). CUA compares two or more alternative choices in terms of both their costs and their outcomes, and, in contrast to CEA, the outcomes are measured in units of utility or preference, often as Quality-Adjusted Life Years (QALY).
Biological drug	A biological drug is made from proteins and other substances produced by the body. The term biological drug comprises a variety of products with natural origin, e.g. vaccines, blood and blood components, gene therapy, and recombinant protein sources. Biological drugs also refer to the subgroup of large and complex molecules that represent targeted therapy including monoclonal antibodies and receptor fusion proteins.
Biosimilar	A biosimilar is a medicine which is similar and comparable to the original biological drug. The biosimilar contains the same active substance as the original biological drug, but a different version of it.
Dominance	An intervention dominates another if its additional health benefits are higher and its costs are lower. Similarly, an intervention can be said to be dominated if it is less effective with additional healthcare costs.
Discounting	Discounting is a method used to adjust future costs and benefits to their present market. This method is based on the assumption that costs and consequences incurred in the near future are more important than those incurred in the more distant future. Therefore, future values should be adjusted using the discount rate to reflect their present-day value. In Finland, the recommended discount rate is 3% for both costs and benefits, and, furthermore, the costs and benefits should be presented undiscounted.
Effectiveness	Effectiveness is assessed in real-world circumstances, and effectiveness studies are usually conducted during Phase IV, post-marketing studies or surveillance.

Efficacy	Efficacy is assessed in clinical trials in ideal conditions, typically in randomised control Phase I-III trials, which represent the key source for the efficacy evidence in medicines.
Inflammatory bowel disease	Inflammatory bowel diseases (IBD), including Crohn´s disease (CD), ulcerative colitis (UC) and IBD unclassified (IBDU), are chronic inflammatory disorders of the gastrointestinal tract. Symptoms of IBD are heterogeneous, but commonly include abdominal pain, weight loss and diarrhoea.
ICER	Incremental Cost-Effectiveness Ratio (ICER) is the outcome measure of the cost-effectiveness analysis (CEA). ICER represents the difference in costs between two alternatives divided by the difference in effectiveness between the same two alternatives.
QALY	Quality-Adjusted Life Year (QALY) is an outcome measure of health which takes into account and combines within a single measure both changes in the quantity and the quality of life. QALY is applicable for all individuals and diseases, and it enables comparison across different diseases.
Rheumatoid arthritis	Rheumatoid arthritis (RA) is a chronic inflammatory autoimmune disease and progressive disease primarily impacting the peripheral joints, leading to tenderness, swelling, pain, and loss of physical function.
Sensitivity analysis	Sensitivity analysis is used to evaluate the impact of uncertainty in an economic evaluation. The most common approach for dealing with uncertainty, especially parameter uncertainty, is called deterministic sensitivity analysis, where the key variables for both costs and effectiveness are varied in order to assess the impact on study results. There are also several other ways to deal with uncertainty, such as threshold analysis, scenario analysis and probabilistic sensitivity analysis.
Systematic literature review	A summary of existing published literature using pre-set criteria and a protocol. Systematic literature review (SLR) contains a focused research question, a formal and comprehensive search for relevant literature, explicit criteria for selecting studies to be included, and rigorous appraisal for the studies to be included. SLR may also evaluate the quality of reviewed literature. In narrative reviews, the research question is broad, the literature search is not usually specified, and the results are not reported systematically.

1. INTRODUCTION

Rheumatoid arthritis (RA) and inflammatory bowel diseases (IBD), including Crohn´s disease (CD), ulcerative colitis (UC) and IBD unclassified (IBDU), are chronic inflammatory disorders. RA primarily affects the peripheral joints, leading to tenderness, swelling, pain, and loss of physical function [1,2], whereas IBD are characterised by chronic inflammation of the gastrointestinal tract associated with symptoms including abdominal pain, weight loss and diarrhoea [3,4]. The precise etiology of RA and IBD is unknown, but RA and IBD may arise from an interaction between genetic and environmental factors [3,5–7]. IBD are usually diagnosed in early adulthood [8], while two thirds of patients with new RA are under 65 years old in Finland [9]. RA, especially the more severe cases, is associated with a shortened life expectancy compared with the general population [10,11]. Overall mortality is also increased in IBD patients [12].

In Finland, the prevalence of RA is estimated to be around 0.8% of the adult population based on the data collected in the late 1980s [13], and the incidence about 44.5 per 100,000 of the adult population based on the Finnish registry data collected between 2000 and 2007 [14]. During the last two decades IBD has become a global disease, and the incidence of IBD has increased especially in the newly industrialised countries [15]. Although the incidence of IBD is stabilising in western countries, its burden remains high, as the prevalence surpasses 0.3% in North America, Oceania, and most European countries. In Finland, however, the incidence of IBD has been rising since the latter part of the 20th century, and the mean annual incidence of IBD is 34.0 (9.2 in CD and 24.8 in UC) per 100,000 inhabitants in Finland based on the registry data between 2000 and 2007 [16], and the prevalence of IBD is 0.9% in 2019 [17].

There is no curative treatment for RA [1] and IBD [3,18], and patients usually require lifelong medical treatment. The target of the RA and IBD treatment is remission, as well as preventing recurrence, recovering and maintaining the working ability and improving the patients´ quality of life. In case of an insufficient response or intolerance to conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs) in the treatment of RA, biological disease-modifying anti-rheumatic drugs (bDMARDs) should be considered [1,19]. Until May 2019, the European Medicines Agency (EMA) has approved ten biological drugs for the treatment of RA: adalimumab (ADA), certolizumab (CTZ), etanercept (ETA), golimumab (GOL), infliximab (IFX), abatacept (ABA), tocilizumab (TOC), sarilumab (SAR), rituximab (RTX), and anakinra (ANA) (www.ema.europa.eu). A treatment with biological drugs should be also considered for moderate to severe IBD refractory or intolerant or dependent to corticosteroids, and for IBD patients who are not candidates for surgery [3,18]. Until May 2019, four biological drugs (IFX, ADA, ustekinumab (UST) and vedolizumab (VED)) have been approved for the treatment of CD in Europe, whereas four biological drugs (ADA, IFX, GOL and VED) have been authorised for UC (www.ema.europa.eu). Biosimilars contain the same active substance as the original biological drug, but a different version of it, and they are comparable to the originator drug in terms of efficacy and safety. Until May 2019, EMA has approved four biosimilars, including IFX, ADA, ETA and RTX, for the treatment of RA, whereas biosimilars of IFX and ADA have been approved for the treatment of IBD. Until May 2019, two Janus Kinase Inhibitors, tofacetinib and baricitinib, have been approved for the treatment of adult RA patients who have responded inadequately to, or who are intolerant to one or more DMARDs, and one Janus Kinase Inhibitor, tofacetinib, is indicated for

the treatment of adult patients with moderately to severely active UC who have had an insufficient response or intolerance to conventional treatment or a biological drug. In this thesis, we focus on biological drugs used in the treatment of RA and IBD.

During the last two decades, the use of the biological drugs has increased significantly. Although biological drugs have been proven to be an effective treatment for RA and IBD, and they have comparable efficacy and not significantly differing safety profiles, they are significantly more expensive than conventional drugs [1,20–24] [25–33]. Biological drugs for RA and IBD are an important target for economic evaluations because of the associated high costs.

RA and IBD as chronic diseases have often a negative impact on patients´ lives, and therefore, they decrease health-related quality of life (HRQoL). Poorly treated RA and IBD may cause disability and uncontrollable costs for social- and healthcare. IBD primarily affect young adults, causing an increasing economic burden [8,34]. When the costs of long-term diseases and the costs related to disability, domestic work and career choice are considered, the cost of unpaid work for RA and IBD patients has been evaluated to be around 608 € per month in Finland based on the data collected in 2017, whereas the respective amount is approximately 754 € for the employer and 1,570 € for society [35]. Appropriate medical treatments, especially biological drugs, are assumed to improve health status and to reduce the need for surgery and inpatient care, and, furthermore, to reduce the burden on resources outside the healthcare system such as absenteeism from work.

The motivation for this study was the high costs of biological drugs, and their rising use in the treatment of RA and IBD. Biological drugs are part of the treatment guidelines of RA and IBD and cause significant costs for the limited healthcare resources available. Because of the high costs of original biological drugs, interest has grown in biosimilars that are comparable to the originator drugs in terms of efficacy and safety. Health economic evaluations enable the efficient use of limited healthcare resources, and their use is becoming increasingly important as health care expenditures rise due to an increase in chronic diseases, the aging of the population and the availability of more costly treatment options [36]. Health economic evaluations are interested in effectiveness assessed in real-world circumstances, and, therefore, real-world data based on Finnish healthcare were used in this study.

In this doctoral thesis, studies I and II focus on the critical appraisal of evidence, whereas studies III and IV adopt methods of health economic evaluations. The motivation to undertake the systematic literature review (SLR) (studies I and II) was to identify methods and results of cost-effectiveness analyses on biological drugs in the treatment of RA and IBD internationally. Moreover, SLR is a good starting point for developing a health economic model which combines clinical data and cost data from many sources. The patient-level simulation model (study III) and prospective observational study (IV) evaluated costs and effectiveness of biological drugs in the treatment of RA and IBD in the Finnish healthcare setting. The aim of this study was to evaluate the costs, effectiveness and cost-effectiveness of biological drugs in the treatment of RA and IBD.

2. REVIEW OF THE LITERATURE

This review of the available literature concentrates on the interventions and methods used in this study. First, the background of the RA and IBD is described, and some examples on instruments how to measure disease activity of these diseases are given. Furthermore, the treatment guidelines of RA and IBD are described, and a short overview of the costs of biological drugs used in the treatment of RA and IBD in Finland is given. This review of the literature also provides a brief introduction to the principles of economic evaluation and methods of critical appraisal of evidence, focusing on SLR.

2.1.Rheumatoid arthritis

2.1.1.Background of rheumatoid arthritis

RA is a chronic inflammatory autoimmune disease and progressive disease primarily affecting the peripheral joints, leading to tenderness, swelling, pain, and loss of physical function [1,2]. RA is also associated with reactive depression that worsens the overall health and quality of life [37,38]. RA, especially the more severe cases, is associated with a shortened life expectancy compared with the general population [10,11].The incidence of RA is higher in women than in men, and it has been estimated to be the highest in Northern Europe and North America, where the estimated prevalence is 0.5-1.0% of the population [39]. The prevalence of RA is estimated to be around 0.8% of the adult Finnish population based on the data collected in the late 1980s [13], and the incidence about 44.5 (58.6 in women and 29.5 in men) per 100,000 of the adult population based on the Finnish registry data collected between 2000 and 2007 [9]. Two thirds of patients in Finland with new RA are under 65 years old.

2.1.2.Measures of disease activity in rheumatoid arthritis

Disease activity measures are used in clinical trials and for monitoring the course of the disease in daily clinical practice. There are several disease activity measures, such as laboratory tests and imaging, which provide a view of disease activity in RA. Disease Activity Score 28 (DAS28) is a combined index to measure disease activity in RA, and it is extensively validated in RA [2,40]. The number 28 refers to the 28 joints that are examined in this assessment. DAS28 consists of four different items: the number of swollen and tender joints, the erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP), and the patient's global assessment of general health using the visual analogue scale (VAS). VAS is one of the most commonly used rating scale approaches, which consists of a line on a page, with clearly defined end points and with or without other marks along the line. The DAS28 can be calculated using the following formula:

*DAS28-ESR = 0.56 * √(tender28) + 0.28 * √(swollen28) + 0.70 * ln(ESR) + 0.014 * GH*
*DAS28-CRP = 0.56 * √(tender28) + 0.28 * √(swollen28) + 0.36 * ln(CRP + 1) + 0.014 * GH + 0.96*

tender28 = the number of tender joints of the 28 that are measured
swollen28 = the number of swollen joints of the 28 that are measured
ESR = the erythrocyte sedimentation rate, mm/hour
CRP = C-reactive protein
GH = the patient's global assessment of general health measured on Visual Analog Scale (VAS) of 100 mm

These results provide the overall disease activity score ranging from 0 to 9.4, indicating how active RA is at this moment [2,40]. A DAS28 score of <2.6 is considered to be remission, ≥2.6 to <3.2 low disease activity, ≥3.2 to ≤5.1 moderate disease activity and >5.1 high/severe disease activity [2,40]. A change of 1.2 in DAS28 is considered an important change [41].

2.1.3.Medical treatment of rheumatoid arthritis

According to the Finnish Current Care Guideline, the target of the RA treatment is remission, which is defined as the absence of symptoms, and to recover and maintain the working ability and functional capacity of patient [1]. There is no curative treatment for RA, and the treatment is usually continued for years or decades. Anti-rheumatic treatment should be started without delay [1,19,42]. The medication of RA treatment can be divided into two categories: synthetic disease-modifying anti-rheumatic drugs and biological disease modifying anti-rheumatic drugs (bDMARDs) [19,43]. Active RA should be monitored every 1-3 months. The treatment should be adjusted if any improvement has not been achieved 3 months after the start of the treatment or the target of the treatment has not been reached 6 months after the start of the treatment.

Synthetic disease-modifying anti-rheumatic drugs

Synthetic disease-modifying anti-rheumatic drugs can be further classified into conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs) and targeted synthetic disease-modifying anti-rheumatic drugs (tsDMARDS) [19]. csDMARDs include chemical agents such as methotrexate (MTX), sulfasalazine (SSZ), and leflunomide (LEF). According to the Finnish Current Care Guideline, treatment of RA should initially be treated with a combination of MTX, SSZ and hydroxychloroquine (HCQ) (RACo-combination treatment), together with a low-dose glucocorticoid and intra-articular injections of a glucocosteroid into affected joints [1]. In contrast, the European League Against Rheumatism´s (EULAR) recommendations for the management of early arthritis advocate the use of MTX monotherapy with or without short-term high-dose glucocorticoid instead of csDMARD combination therapy [19,44]. According to both Finnish Current Care Guideline and EULAR recommendations, MTX is the anchor drug for patients with RA, and, if MTX is contraindicated, treatment may be started with other csDMARD such as LEF or SSZ [1,19]. Both guidelines also suggest that in case of insufficient treatment response or intolerance to csDMARDs, bDMARD should be added to the csDMARD. Based on EULAR recommendations, tsDMARD may be an alternative instead of bDMARD [19]. tsDMARDs refers to Janus kinase inhibitors, which are targeted molecules interfering with specific signal-transduction pathways [44]. Until May 2019, the EMA has approved two Janus kinase inhibitors for the treatment of RA in Finland: tofacitinib and baricitinib (www.ema.europa.eu). These tsDMARDs have been approved for the treatment of adult RA patients who have responded inadequately to, or who are intolerant to one or more disease-modifying anti-rheumatic drugs.

Biological disease-modifying anti-rheumatic drugs (bDMARDs)

In case of an insufficient response or intolerance to csDMARDs, bDMARDs may be considered [1,19]. In May 2019, ten bDMARDs have been approved for the treatment of RA: ADA, CTZ, ETA, GOL, IFX, ABA, TOC, SAR, RTX, and ANA (Table 1) (www.ema.europa.eu). Biological drugs have proven to be an effective treatment for RA, and they have comparable efficacy and not significantly differing safety

profiles [1,20–24]. However, ANA has been shown to be less efficacious than other bDMARDs [45]. bDMARDs are recommended to be used in combination with MTX rather than as monotherapy due to better efficacy and reduced immunogenicity [1,19]. The early effective treatment, and the use of MTX and biological drugs, are associated with lower mortality [46]. Based on the EULAR recommendations, bDMARD can be tapered if a patient is in sustained remission [19]. However, the Finnish Current Care guideline states that drug holidays and prolonged intervals between the administration of IFX, GOL and CTZ should be avoided to reduce the risk of anti-drug antibodies. In case one tumour necrosis factor alpha (TNF) inhibitor fails, another TNF inhibitor, another bDMARD with another mode of action or tsDMARD may be considered. If a second TNF inhibitor fails, bDMARD with another mode of action or tsDMARD should be used.

Table 1. Biological disease-modifying anti-rheumatic drugs (bDMARDs) used in the treatment of rheumatoid arthritis (www.ema.europa.eu).

Biological drug	**Strength**	**Group**	**Dose**	**Route of adminis-tration**	**Biosimilar available in Finland (5/2019)**
Abatacept	250 mg	T-cell co-stimulation inhibitor	500-1000 mg at weeks 0, 2, 4, then every 4 weeks (doses according to body weight: <60 kg = 500 mg; 60-100 kg = 750 mg; >100 kg = 1000 mg)	iv	No
	125 mg	T-cell co-stimulation inhibitor	125 mg once a week	sc	No
Adalimumab	125 mg	TNFα inhibitor	40 mg every two weeks	sc	Yes
Anakinra		IL-1 receptor inhibitor	100 mg once a day	sc	No
Certolizumab pegol	200 mg	TNFα inhibitor	400 mg at weeks 0, 2, 4, then 200mg every two weeks or 400mg once a month	sc	No
Etanercept	25 mg	TNFα inhibitor	25 mg twice a week	sc	Yes
	50 mg	TNFα inhibitor	50 mg once a week	sc	Yes
Golimumab	50 mg	TNFα inhibitor	50 mg once a month (100mg once a month for body weight > 100 kg)	sc	No
Infliximab	100 mg	TNFα inhibitor	3 mg/kg at weeks 0, 2, 6, then every 8 weeks	iv	Yes
Rituximab	500 mg	B-cell inhibitor	1000 mg at week 0 and 2, the need for further courses should be evaluated 24 weeks following previous course	iv	Yes
Sarilumab	200 mg	IL-6 receptor inhibitor	200 mg every 2 weeks	sc	No
Tocilizumab	200 mg	IL-6 receptor inhibitor	8 mg/kg every 4 weeks	iv	No
	162 mg	IL-6 receptor inhibitor	162 mg once a week	sc	No

IL=interleukin, iv=intravenous, TNF=tumour necrosis factor, sc=subcutaneous

bDMARDs can be further divided into biological originators (boDMARDs) and biosimilars (bsDMARDs) [47]. Biosimilars are medicines which are similar and comparable to the biological originator. Biosimilars contain the same active substance as the reference medicine, but a different version of it. Until May 2019, EMA has approved four biosimilars, including IFX, ADA, ETA and RTX, for the treatment of RA (Table 1) (www.ema.europa.eu). According to the EULAR recommendations, all EMA-approved bDMARDs have similar efficacy and safety as the respective originator bDMARDs, and, therefore, bsDMARDs should be preferred if they are considerably cheaper than boDMARD, other bDMARDs, or tsDMARDs [19,21,48].

2.2. Inflammatory bowel diseases

2.2.1. Background of inflammatory bowel diseases

IBD, including CD, UC and IBDU, are chronic inflammatory disorders of the gastrointestinal tract [3,4]. CD affects the small and the large bowel, and less often other parts of the gastrointestinal tract, whereas UC is usually located in both the large intestine and the rectum. CD may also affect various organs and tissues outside the gut, most commonly the skin, the joints, and the eyes. Extraintestinal manifestations, such as arthritis and uveitis, may be associated with IBD [3,4]. Primary sclerosing cholangitis (PSC) affects 3-10% of IBD patients [49]. IBD are chronic diseases associated with episodes of remission and various degrees of activity. Symptoms of IBD are heterogeneous, but commonly include abdominal pain, weight loss and diarrhoea. Blood and mucus in stools are seen less frequently in CD than in UC patients. IBD are associated with the increased mortality [50].

The precise etiology of IBD is unknown [3,4]. IBD arise from an interaction between genetic and environmental factors [5,51]. Current smoking is associated with an increased risk of CD, but not UC, whereas former smoking is associated with an increased risk of UC. IBD can occur at any age, but most patients are diagnosed before they are 30 years old [8]. There is no single test for the diagnosis of IBD [3,4]. The diagnosis of IBD is based on the combination of assessment of clinical symptoms, blood tests, findings in imaging, endoscopy, and histological assessment of bowel biopsies. During the last two decades the worldwide incidence of IBD has increased, especially in newly industrialised countries of Asia, South America and Africa [15]. Although incidence of IBD is stabilising in western countries, its burden remains high as prevalence surpasses 0.3% in North America, Oceania, and most European countries. In Finland, however, the incidence of IBD has been rising since the latter part of the 20th century, and the mean annual incidence of IBD is 34.0 (9.2 in CD and 24.8 in UC) per 100,000 inhabitants in Finland based on the registry data between 2000 and 2007 [16], and the prevalence of IBD is around 0.9% in 2019 [17].

2.2.2. Measures of disease activity in inflammatory bowel diseases

Numerous tools are available to assess clinical disease activity, which aid objective assessment of disease and guide therapeutic and monitoring strategies in IBD [52,53]. One of the most commonly used clinical activity indexes for CD is the Crohn´s Disease Activity Index (CDAI). The CDAI assesses the parameters of soft/liquid stool frequency, abdominal pain, well-being, presence of extra-intestinal manifestations, fistulas, abdominal mass, use of anti-diarrheal agent, anaemia and weight loss [54]. The CDAI score ranges between 0 and 600, and a CDAI score of less than 150 is considered to be remission, while a CDAI score greater than 450 is considered to be severe disease. Response is increasingly defined as a decrease in CDAI ≥ 100 points [55].

The Mayo Clinic Score has been used for assessing therapeutic endpoints in adult clinical trials in UC [53,56]. Clinical improvement is defined as the reduction of baseline scores by ≥3 points and a clinical remission by ≤2. A partial Mayo Score (pMayo) has been shown to correlate well with the full scoring system [57] . pMayo consists of two questions (diarrhea and rectal bleeding) for the patient to answer and one question for the physician to answer (physician´s global assessment). The numerical results provide a score ranging from 0 to 9 that represents an estimate of clinical activity of UC, and clinical remission is defined as pMayo <1 [56].

2.2.3. Treatment of inflammatory bowel diseases

Treatment of IBD is aimed at relieving the symptoms and complications of IBD as well as preventing recurrence and improving the patient's quality of life [3,18]. There is currently no cure for CD and UC, and, therefore, IBD patients usually require lifelong medical treatment. The choice of medical treatment depends on the disease activity, extent, location, behaviour of disease, and previous treatment. In Finland, the treatment of IBD is based on the treatment guidelines from the European Crohn´s and Colitis Organisation (ECCO) (www.crohnjacolitis.fi).

Medical treatment of Crohn´s disease

Corticosteroids are the first-line treatment option in mildly active CD, and aminosalicylates, such as mesalazine and SSZ, may be added if necessary [3]. Budesonide may be used in localised ileocaecal CD. Corticosteroids are also suitable initial therapies for moderately active CD, whereas systemic corticosteroids should be used for severely active CD. Patients with active CD refractory or who are intolerant to corticosteroids, and who are not candidates for surgery, should be treated with immunosuppressants, such as azathioprine (AZA), mercaptopurine (6-MP), MTX or biological drugs, as monotherapy or in their combination.

Thiopurines, including AZA and 6-MP, or MTX should be considered in the maintenance treatment of CD patients who are dependent on corticosteroid treatment [3]. AZA and 6-MP may be used as an adjunctive treatment or corticosteroid-sparing agent, and they are the most widely used immunomodulators for IBD. MTX is used for CD patients with an intolerance to thiopurines. TNF inhibitors are indicated for moderate to severe disease. In case remission has achieved by biological drugs, it is appropriate to also use the same biological drug in the maintenance treatment. In case of loss of response to TNF inhibitor, dose increase or interval shortening should be considered, and, if this fails, TNF inhibitor should be switched to another TNF inhibitor with another mode of action or VED. Corticosteroids have not been shown to be efficacious in maintaining remission, and the corticosteroid exposure should be minimised due to adverse effects associated with long-term corticosteroid therapy. It is also notable that all patients do not need medical maintenance treatment at all. In localized disease, surgery should be always considered as a treatment option.

Medical treatment of ulcerative colitis

For the induction of remission of mild to moderate distal UC, the first-line treatment option is topical mesalazine [18]. A combination of topical and oral mesalazine is more efficacious, and this combination may be necessary especially in more extensive diseases [58]. Topical mesalazine has shown to be more efficacious than topical corticosteroids [59]. Intravenous corticosteroids are

recommended for the treatment of severe active UC [18]. If this fails, cyclosporine, tacrolimus or biological drugs may be considered. If the TNF inhibitor fails, an alternative TNF inhibitor, VED, or surgery should be considered. Biological drugs are also used for the treatment of moderate UC refractory to thiopurines. Tofacitinib, Janus Kinase Inhibitor, is indicated for the treatment of adult patients with moderately to severely active UC who have had an insufficient response or intolerance to conventional treatment or a biological drug (www.ema.europa.eu).

Topical mesalazine is the first-line treatment option in UC maintenance treatment, and a combination of oral and topical mesalazine may be used as a second-line maintenance treatment [18]. Mesalazine maintenance treatment should be continued long-term. In the maintenance treatment of steroid-refractory UC, thiopurines or biological drugs should be considered. In case remission has been achieved by biological drugs, it is appropriate to also use the same biological drug in the maintenance treatment.

Biological drugs in the treatment of inflammatory bowel diseases

Biological drugs are used for the remission induction and maintenance in the treatment of moderate to severe IBD [3,18]. In recent years the threshold for starting TNF inhibitor therapy has been lowered in patients with a poor prognosis. Continuous treatment with TNF inhibitors reduces the risk of surgery and hospitalisation in CD. A first-line biological drug should be chosen based on efficacy and safety profile, route of administration, patient preferences and cost-effectiveness. Until May 2019, IFX, ADA, UST and VED have been approved for the treatment of CD refractory to standard medications in Europe, whereas ADA, IFX, GOL and VED have been authorised for UC refractory to standard medications (Table 2) (ww.ema.europa.eu). TNF inhibitors are the first biological option for IBD [60]. In case a TNF inhibitor fails, VED and UST should be considered. Primary lack of response should be determined to TNF inhibitor in 12 weeks, to VED in 12-14 weeks and to UST in 16 weeks [3,18,60,61]. If a patient has responded to TNF inhibitor, it is appropriate to also use the TNF inhibitor in the maintenance treatment [3,18]. Trough levels and formation of anti-drug antibodies are measured from patient´s serum samples as a part of clinic work during the biological drug therapy in Finland, and these measurements are valuable tools in optimizing biological drug therapy [62,63]. However, there is no clear guideline on when it is safe to stop TNF inhibitor treatment [64]. According to the study by Molander et al, up to 67 % of patients with IBD in deep remission (i.e. no clinical symptoms, concomitant endoscopic remission and normal faecal calprotectin (FC) concentration (<100µg/g)) at the time of cessation of TNF inhibitor treatment remained in clinical remission during the one-year follow-up [65]. The prospective multicenter study suggested that withdrawal of TNF inhibitor treatment could be possible after 1 year of treatment while patients were in deep remission, especially in UC. In the case of relapse after withdrawal of TNF inhibitor maintenance treatment, retreatment with TNF inhibitor was effective in 94% of IBD patients.

Table 2. Biological drugs used in the treatment of inflammatory bowel diseases (www.ema.europa.eu).

Biological drug	Strength	Group	Indication (CD / UC)	Dose	Route of adminis-tration	Biosimilar available in Finland (5/2019)
Adalimumab	125 mg	TNFα inhibitor	CD and UC	80-160 mg at week 0, 40-80 mg at week 2, then 40 mg every two weeks	sc	Yes
Golimumab	50 mg	TNFα inhibitor	UC	200 mg at week 0, 100 mg at week 2, then 50-100 mg every four weeks	sc	No
Infliximab	100 mg	TNFα inhibitor	CD and UC	5 mg/kg at weeks 0, 2, 4, then every 8 weeks	iv	Yes
Ustekinumab	45 mg and 90 mg	IL-12 and IL-23 receptor inhibitor	CD	6 mg/kg (iv) at week 0, 90 mg (sc) at week 8, then 90 mg (sc) every 12 weeks	induction: iv mainte-nance: sc	No
Vedolizumab	300 mg	integrin a4β7	CD and UC	300 mg at weeks 0, 2, 6 then 300 mg every eight weeks	iv	No

CD = Crohn´s disease, IL = interleukin, iv = intravenous, TNF = tumour necrosis factor, sc = subcutaneous, UC = ulcerative colitis

Until May 2019, biosimilars approved for the treatment of CD and UC are IFX and ADA (Table 2) (www.ema.europa.eu). In June 2013, the biosimilar IFX, CT-P13, was accepted by EMA for all indications of the originator product [66]. For IBD, the indication was extrapolated from studies showing the efficacy of biosimilar IFX in ankylosing spondylitis and RA [67,68]. This extrapolation of indication raised concerns among national and international IBD societies regarding the safety and interchangeability of biosimilars [69]. The effectiveness, efficacy and safety of biosimilar IFX in IBD patients has been shown in previous studies [62,70–74].

2.3. Costs and market share of biological drugs used in the treatment of rheumatoid arthritis and inflammatory bowel diseases in Finland

Biological drugs, and their high costs, create a burden for the limited healthcare resources available. In 2017, four biological drugs (ADA, IFX, RTX and ETA) out of the ten bestselling drugs were used in the treatment of RA or IBD in Finland in 2017 [75]. Consumption and total costs of biological drugs used in the treatment of RA and IBD in 2013-2018 in Finland are described in Figures 1 and 2 [75–81]. Although these biological drugs are used in the treatment of RA or IBD, they are also indicated for many other diseases, and the costs of biological drugs in other indications are also included in Figures 1 and 2. Drug consumption is expressed as defined daily doses (DDD) per 1,000 inhabitants and per day, whereas total costs are based on the biological drugs sold by wholesalers to pharmacies and hospitals, and they are presented as wholesale prices excluding value-added tax (VAT) [75–81]. In 2018, all IFX, RTX and VED products were sold to hospitals, whereas the proportion of drugs sold to hospitals and other healthcare units was 54%, 36%, 17% and 11% for TOC, ABA, UST and ANA, respectively [81]. The proportion of hospital drugs was 1-2% for ADA, CTZ and GOL, while all ETA products were sold to pharmacies. The restricted basic reimbursement was confirmed for SAR in Finland in 2019, and therefore, SAR was not used in previous years [82].

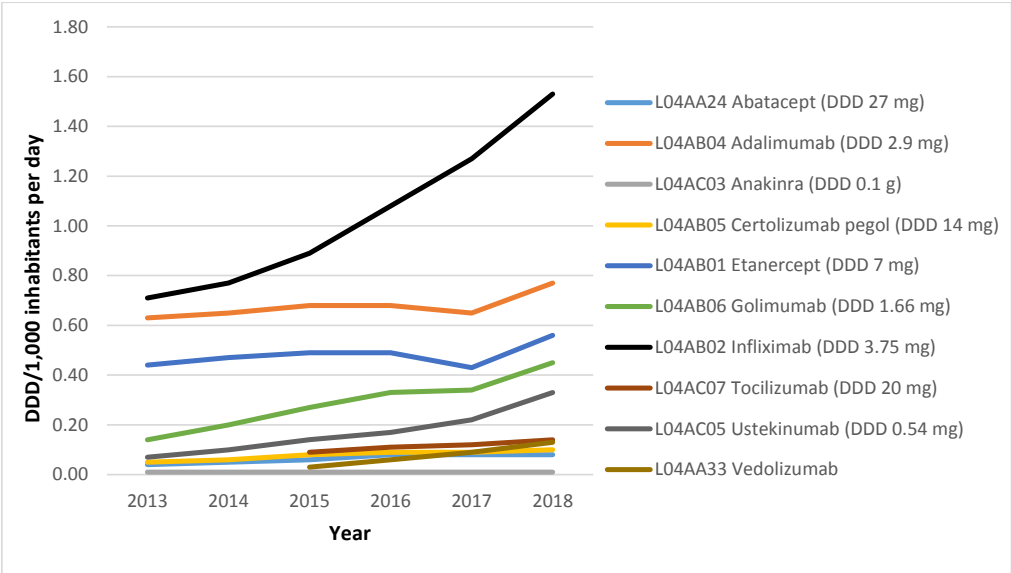

Figure 1. Drug consumption of biological drugs in Finland in 2013-2018 [75–81].
Data for rituximab were not available.
DDD=defined daily dose

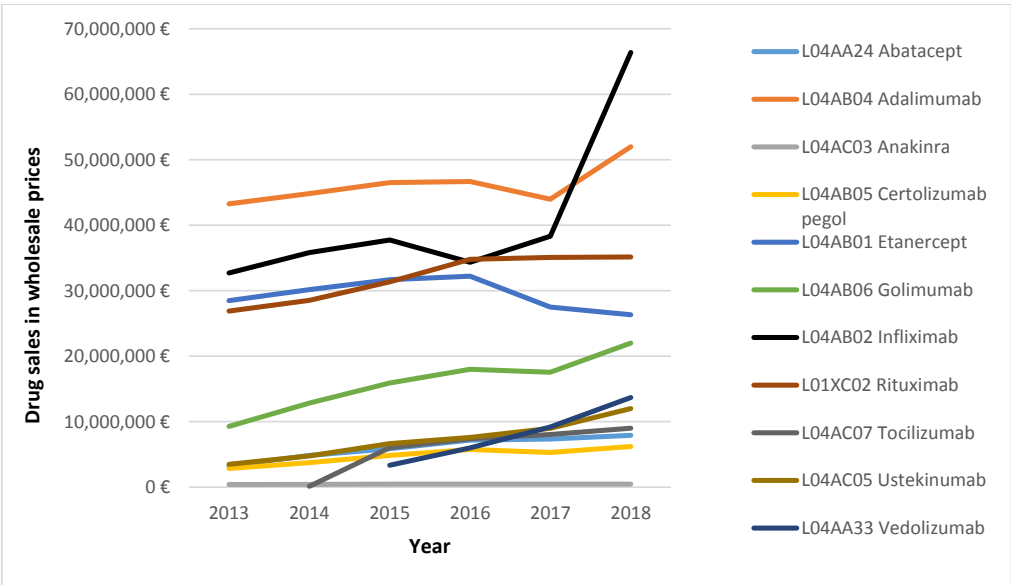

Figure 2. Total costs of biological drugs expressed as wholesale prices excluding VAT and using fair prices in Finland in 2013-2018 [75–81].
Vedolizumab received marketing authorisation in 2014, and the costs of vedolizumab in 2014 were not available.

Because of the high costs of original biological drugs, interest has grown in biosimilars that are comparable to the original drugs in terms of efficacy and safety. Many original biological drugs have reached, or are approaching, patent expiry near in the future. At the moment, biosimilars of ADA, ETA, IFX and RTX used in the treatment of RA or IBD are on the market in Finland [83]. Biosimilar IFX came on the market in Finland in November 2013, and was the first biosimilar for the treatment of RA and IBD. Biosimilars of ETA (indicated for RA) and ADA (indicated for RA and IBD) have been on the market since February 2018 and November 2018, respectively [83]. RTX biosimilar indicated for the treatment of RA has been on the market in Finland since January 2019 [83]. In Finland, the wholesale price confirmed for a first biosimilar alternative can be a maximum of 70% of the confirmed wholesale price of the originator product [84].

The opinion of the Finnish Medicines Agency (Fimea) is that biosimilars are interchangeable with the originator drugs under the supervision of a healthcare worker [85,86]. In case there is a comparable and alternative biosimilar available for the originator, physicians have an obligation to prescribe the least expensive biosimilar available to advance the prescription of biosimilars [75]. In Finland, the proportion of patients who have switched from an IFX originator to a biosimilar one has been high, and, for example, all IBD patients receiving IFX maintenance treatment at Helsinki University Hospital (HUS) were switched to biosimilar IFX in the beginning of 2016 [62]. According to the study by Fimea, most Finnish physicians have a positive view on the uptake of biosimilars and they consider the value of originator biological drugs and biosimilars to be equal [87]. However, only half of the physicians has prescribed biosimilar as the first biological drug and switched patient´s previous originator drug to biosimilar. Reasons why physicians have not prescribed biosimilars are in most cases related to physicians´ personal opinions and desire for prescription autonomy, patients´ desire to use originator or the high price of biosimilar even it is cheaper than originator.

2.4. Economic evaluation of medical treatments

The purpose of any type of economic evaluation is to inform decisions about which of the available actions ought to be recommended, approved for widespread use, or reimbursed for specific groups of patients [36]. Economic evaluations provide information on the benefits and costs of the expensive treatments to aid optimal utilisation of limited healthcare resources. In health economic evaluation, the aim is to determine the most cost-effective option for allocation.

2.4.1. Efficacy and effectiveness

Health economic evaluations are interested in *effectiveness* instead of *efficacy* [36,88]. In the literature, the terms *efficacy* and *effectiveness* are sometimes used interchangeably. Efficacy is assessed in clinical trials in ideal conditions, whereas effectiveness is assessed in real-world circumstances. Efficacy is usually measured in controlled settings, typically randomised control Phase I-III trials, which represent the key source for the efficacy evidence in medicines. In contrast, effectiveness studies are conducted in the real-world environment during Phase IV, post-marketing studies or surveillance [88].

2.4.2. Health-related quality of life

HRQoL is a broad theoretical construct developed to explain and organise measures that evaluate the individual´s self-reports of health status, attitudes, values and perceived levels of satisfaction and

general well-being [36,88]. HRQoL instruments can be divided into two categories: disease-specific and generic measures. Generic HRQoL measures are comprehensive instruments that allow comparison between different diseases, whereas disease-specific HRQoL measures are designed to be relevant to a particular disease.

2.4.2.1. Disease-specific health-related quality of life measures

Disease-specific measures concentrate on the main quality of life impacts of clinical field concerns [36,88]. Therefore, their use in economic evaluation is limited to comparisons of treatments in question, but they are usually more responsive to changes of HRQoL in a specific condition than generic instruments. Several disease-specific tools exist for evaluating HRQoL in different treatments. Examples of widely used disease-specific HRQoL instruments are Health Assessment Questionnaire (HAQ) for RA [89–92] Inflammatory Bowel Disease Questionnaire (IBDQ) for IBD [93].

HAQ contains the HAQ Disability Index (HAQ-DI) and global and pain VAS. HAQ-DI is a well-validated, reliable and robust measure of functional disability in RA, and is extensively used both in clinical trials and clinical practice in RA [89–92]. HAQ-DI contains 20 items distributed across eight dimensions on the ability to perform activities of daily living during the past week. The response options range from 0 (with no difficulty) to 3 (unable to do so). The highest scores of each dimension are summed and divided by 8, resulting in a possible range of total scores from 0 (no difficulty) to 3 (unable to do so). The HAQ-DI score of less than 1 is considered to represent mild to moderate disability, 1-2 moderate to severe disability and 2-3 severe to very severe disability. HAQ-DI has been shown to be highly correlated with many generic and disease-specific measures of HRQoL [94]. According to the study by Laas et al., the HAQ score of Finnish RA patients is 0.623 (SD 0.675) – 0.843 (SD 0.639) [89].

IBDQ as a standardised questionnaire for the assessment of HRQoL in IBD is considered the gold standard for use in clinical trials [93]. The IBDQ includes 32 items, which are divided into four domains: gastrointestinal symptoms (10 items), systemic symptoms (5 items), emotional function (12 items) and social function (5 items). Each item is scored on a 7-point scale, ranging from 1 to 7 (worst to best of health). The total IBDQ scores may range from 32 to 224, with higher scores reflecting better health. The IBDQ has been shown to be responsive to clinically important changes in disease activity [93]. The scores of patients in remission are usually 170 points or more [93]. An absolute change in IBDQ score of 16 points defines a minimum clinically important change, and a mean decrease in relapse is around 32 points [93,95]. According to the study by Haapamäki et al., the mean IBDQ score of Finnish IBD patients is 164 [96].

2.4.2.2. Generic health-related quality of life instruments

Generic HRQoL measures do not focus on the impacts of a particular disease, but they encompass the major elements of changes in quality of life [36,88]. The generic instruments can be classified into two groups: profile and single index score instruments.

The Short Form 36 Health Survey (SF-36) is a profile instrument, comprising 36 items divided into eight dimensions including physical functioning, role limitations because of physical problems, bodily pain, social functioning, general mental health, role limitations due to emotional problems, vitality, and general health perceptions [88]. The SF-36 survey can be summarised into eight domain scores and into two summary scores, the physical and mental component summary scores.

The three most widely used techniques to directly measure patient health-state preferences are the rating scale and its variants, the standard gamble, and the time trade-off (TTO) [36,88]. One of the most commonly used rating scale approaches is VAS (or rating scale), which consists of a line on a page, with clearly defined end points and with or without other marks along the line. When scores are assigned by standard gamble, which include uncertainty, they are true utilities, whereas if scores are assigned using methods that do not involve uncertainty such as TTO and VAS, they are values.

One of the most widely used multi-attribute utility instruments is EQ-5D from the EuroQol Group [36,88]. The EQ-5D evaluates five dimensions of health status: mobility, self-care, usual activity, pain/discomfort, and anxiety/depression. Depending on the system used, each attribute has three (EQ-5D-3L) or five levels (EQ-5D-5L) from no problems to major problems [36,88,97]. The EQ-5D-3L consists of 243 possible health states, whereas the EQ-5D-5L has 3,125 health states [97]. Value sets for the EQ-5D-3L have been generated using either the TTO or VAS valuation technique, and, in Finland, VAS has been used as a valuation technique [36,88,98]. A standard EQ-5D-5L value set is not available in Finland. The National Institute for Health and Care Excellence (NICE) in the United Kingdom recommends using the 3L valuation set instead of 5L valuation set [99]. Based on the Finnish Health 2000 survey, the mean EQ-5D score is 0.835 (SE 0.003) for general population, 0.636 (SE 0.017) for RA patients and 0.742 (SE 0.023) for IBD patients [100].

Another multi-attribute utility instrument 15D, which is a 15-dimensional, standardised, and self-administered instrument that can be used both as a profile and as a single index score measure covering the most important dimensions of health including mobility, vision, hearing, breathing, sleeping, eating, speech (communication), excretion, usual activities, mental function, discomfort and symptoms, depression, distress, vitality, and sexual activity [101,102]. Each dimension is divided into five levels, from no problems to extreme problems. The single-index 15D score, representing the overall HRQoL on a scale of 0-1 (0 = being dead, 1 = no problems in any dimensions), and the dimension level values (0 = being dead, 1 = no problems in the dimension) are calculated from the health state descriptive system by using a set of population-based preference or utility weights. A change of approximately +/-0.015 in the total 15D score is considered clinically or practically important because people can usually sense such a magnitude of change [103]. The 15D has been used in studies for various chronic conditions and medical procedures. The mean 15D score from the Finnish Health 2000 Survey (data collected between August 2000 and July 2001) is 0.910 (SE 0.001) for general population, 0.831 (SE 0.008) for RA patients and 0.868 for IBD patients [100]. According to the Finnish study, which is based on the data collected prospectively from May 2002 until April 2003, the mean 15D score of RA patients is 0.815 (SD 0.115) – 0.840 (SD 0.122) [89], and it is 0.874 (SD 0.097) for IBD patients based on the Finnish data collected between September 2006 and February 2008 [96].

2.4.3. Quality-Adjusted Life Years

Generic single index score instruments are based on the measurement of utility scores [36,88]. Utility refers to the value of a health state and is measured by evaluating the preferences of an individual or society for the given state. Utilities can be obtained using direct or indirect methods. A number of methods of utility estimation have been developed that generate a score from 0 (death) to 1 (perfect health). Utility scores are used as the quality weights when computing Quality-Adjusted Life Years (QALYs). Quality-adjusted life year (QALY) is an outcome measure used to quantify the effectiveness of a particular intervention, and it is designated to combine impact of qains in quality of life and in

quantity of life associated with an intervention [104]. Generic index instruments can be used directly to calculate QALYs for cost-utility analysis (CUA), which is discussed in more detail in the chapter 2.4.5. [36,88].

Instead of generic HRQoL measures, it is much more common to include a disease-specific instrument in clinical trials [36,88]. However, decision-makers often desire that health effects are expressed as QALYs, since this allows them to make comparisons over a wide range of therapeutic areas. Furthermore, the QALYs are appropriate for use in CUA. The mapping techniques provide a solution to this problem. They are based either on the estimation of the relationship between a disease-specific measure and a generic measure using statistical association or on the estimation of exchange rates between instruments [105].

2.4.4. Costs

Costs in health economics refer to the resources consumed during the provision of healthcare [88]. Costs are classified as direct, indirect (productivity), and intangible costs [36,88,106]. Direct costs denote the resources consumed, and they include, for example, hospitalisation, surgery, physician visits, medications, laboratory tests, and transportation and any additional costs related to medical care [88]. In contrast, indirect costs are costs due to the loss of productivity related to illness or death. Health economic evaluations generally use only the direct medical and healthcare costs. However, this may lead to an underestimation of the true cost of the disease as indirect costs are excluded. Both direct and indirect costs are usually presented in monetary terms, whereas intangible costs, which refer to pain and suffering due to disease or its treatment, are more difficult to quantify in monetary terms.

An economic evaluation can be presented from different economic viewpoints [36,88]. Resources used and their costs for the same intervention will vary depending on the perspective used in the economic evaluation. Typical viewpoints include the perspectives of patient, hospital, healthcare system and society [107]. The widest perspective is societal, which considers both direct and indirect costs regardless of to whom they occur. The QALY includes the impact of morbidity, and therefore double-counting may be seen as a problem if indirect costs are included in cost-effectiveness analysis (CEA) [106]. Another challenge related to the use of indirect costs is the valuation of patients´ time due to variability in their earnings and leisure activities [36]. Furthermore, different labour costs and healthcare systems in different countries make it challenging to compare results reliably.

2.4.5. Methods for the health economic evaluation

A cost-minimisation analysis compares the costs of alternative interventions, which have equal consequences [36,88]. Cost-benefit analyses express the consequences of an intervention in monetary terms. The field of cost-effectiveness analysis (CEA) is the most typical form of economic evaluation for healthcare interventions. CEA involves the comparison of health interventions based on both costs and effectiveness, and it measures the consequences e.g. in natural units, such as life years gained, disability-days saved or pain-free days, or in quality of life as measured using health-related quality of life instrument. The CEAs provide valuable information for healthcare decision-makers and enable efficient spending. CUA is a specific type of CEA, and the only difference is that consequences are measured in units of utility or preference, often as a QALY [36,108]. CUA can be considered the gold standard as a methodology to evaluate the cost-effectiveness of healthcare

choices. The advantage of CUA is that it allows comparability across all CUA studies. CUA is a specific type of CEA, but for simplicity only CEA was referred later in this thesis and covered both approaches.

2.4.6. Incremental cost-effectiveness

The outcome measure of the CEA is the Incremental Cost-Effectiveness Ratio (ICER) (or Incremental Cost-Utility Ratio, ICUR), representing the difference in costs between two alternatives divided by the difference in effectiveness between the same two alternatives [36,88]. The formula for ICER is as follows:

$$ICER = (Cost_{new} - Cost_{old}) / (Effectiveness_{new} - Effectiveness_{old})$$

An intervention dominates another if its additional health benefits are higher and its costs are lower [36,109]. Similarly, an intervention can be said to be dominated if it is less effective with additional healthcare costs. If an alternative offers incremental health benefits but some additional healthcare costs, the key question is whether the intervention can be regarded as cost-effective or not. A cost-effectiveness threshold determines whether the intervention should be regarded as cost-effective or not, and it is discussed in more detail in the chapter 2.4.8.

2.4.7. Modelling in the economic evaluation

CEA can be conducted using an empirical, observational, or modelling approach [36]. The modelling study appears to be the most common type of CEA, combining clinical data and cost data from many sources. CEA models can use either cohort-level or patient-level simulation modelling to estimate outcomes for the population considered in the model [110].

A decision tree analysis is a common form of health economic model depicting the logical structure of a choice under certain conditions [88]. Decision tree models are usually used in evaluations with a short time horizon [110]. In decision tree models, each individual may follow a unique path through the decision three based on the samples drawn from statistical distributions, or a certain proportion may follow each path in the traditional manner.

A Markov model as a cohort-level model estimates the outcomes for the cohort of patients [110]. In the Markov model, mutually exclusive health states are evaluated at regular intervals to determine the population of each health state. The movement between each state within one cycle is based on the transition matrix which determines the flow of patients through the model. One limitation of Markov model is its `memoryless´ nature, because transitions are only dependent on the state in which the individual resides, and they are independent of past events. Another potential limitation is that in case heterogeneous patient characteristics have a nonlinear relationship with the outcomes, the use of average patient characteristics in the Markov model may provide a biased estimate. This bias may be eliminated by conducting subgroups for homogenous patient groups. However, this may be problematic if a large number of different subgroups are needed.

In a patient simulation model, a sufficiently large number of patients are simulated to estimate mean outcomes for the population considered in the model, and the starting characteristics are sampled from relevant population distributions [110]. Therefore, the model should provide an unbiased estimate, even the relationship between patient characteristics and model outcomes would be non-linear. Furthermore, instead of the Markov model, the patient-level simulation model allows patient histories to be recorded and it can capture heterogeneity in the patient population.

2.4.8. Handling uncertainty in the economic evaluation

Every economic evaluation will contain some degree of uncertainty, imprecision, or methodological controversy [111]. According to Briggs et al., uncertainty can be categorised in four concepts: stochastic uncertainty (random variability in outcomes between identical patients), parameter uncertainty (the uncertainty in the estimation of the parameter of interest), heterogeneity (the variability between patients), and structural uncertainty (the assumptions inherent in the decision model). The impact of uncertainty in health economic evaluations can be tested by sensitivity analysis [36]. The most common approach for dealing with uncertainty, especially parameter uncertainty, is called deterministic sensitivity analysis, where the key variables for both costs and effectiveness are varied in order to assess the impact on study results. There are also several other ways to deal with uncertainty, such as threshold analysis, scenario analysis and probabilistic sensitivity analysis.

A cost-effectiveness threshold, describing the willingness to pay for an additional QALY, determines whether the intervention should be regarded as cost-effective or not. The accepted cost-effectiveness threshold varies across different countries depending on the availability of healthcare resources and technology, as well as on general valuations, and some healthcare systems have published the threshold values used in their decision making. NICE has a threshold of £20,000-£30,000 per QALY gained, but also up to £50,000 in the case of end-of-life treatments is used in the deliberative decision-making process [112]. In Finland, there is currently no published cost-effectiveness threshold in decision-making. The probability that an intervention is more cost-effective than another as a function of the cost-effectiveness threshold can be presented using a cost-effectiveness acceptability curve (CEAC), which is a graphical representation of the cost-effectiveness as compared between two interventions.

2.5. Critical appraisal of evidence

A systematic literature review (SLR) is a method of research that identifies, selects and critically appraises existing published literature using a pre-set criteria and protocol [36,88]. SLRs discuss all relevant literature within a given area, and they provide a more objective summary of literature of interest than do traditional literature reviews. Although SLRs are less likely to be influenced by article selection bias, conclusions from the discussed literature are still subjective and are subject to reviewer bias [88]. SLRs are intended to help readers to find the results of research quickly, and to assess the validity, applicability and implications of these results [113]. Furthermore, SLRs should help people make practical decisions on healthcare. They are a good starting point for developing a health economic analysis [36,88].

When conducting a SLR, the first thing is to formulate a research question that a review will address [113]. The research question should specify the types of participants, interventions, comparisons, and outcomes in which they are interested. A well-formulated research question will guide many aspects of the review process such as the criteria for inclusion and exclusion criteria, which are set before the systematic search.

One of the features that distinguishes an SLR from a traditional literature review is a comprehensive search for relevant literature [88,113]. The aim of a literature search is to identify as many relevant studies as possible [113]. This literature search should be performed using all pertinent databases,

e.g. Medline and EMBASE. Additional relevant studies including unpublished sources can be found from reference lists of identified literature or by discussions with experts in the field being reviewed.

The structure of a search strategy should be based on the main aspects of the SLR [113]. Therefore, pre-defined inclusion and exclusion criteria will inform how the search may be conducted. Inclusion and exclusion criteria will specify the types of participants, interventions, comparators, designs, and, in some cases, the types of outcome. Furthermore, the time period when any study has been published should be considered in the search strategy. The aim of search strategies is to be as wide-ranging as possible to find all relevant studies, and, therefore, it is necessary to include a broad range of different terms for each aspect of the SLR. However, the sensitivity of the search strategy will reduce its precision and will retrieve more non-relevant articles. Therefore, the key element of the search strategy development is to find balance between sensitivity and precision. Sensitivity is defined as the number of relevant studies identified divided by the total number of relevant studies in existence, whereas precision is defined as the number of relevant studies identified divided by the total number of studies identified. The search strategies are recommended to be conducted together with information specialist with experience of searching for SLRs.

Studies included in the SLR should be chosen based on the explicit and objective inclusion and exclusion criteria, which are set before the systematic search based on the research question [88,113]. The inclusion and the exclusion criteria may be formulated by the framework of PICOTS i.e., population, intervention, comparator, outcome, timing, and setting [114]. When selecting studies, titles and abstracts should be evaluated first to exclude obviously irrelevant reports, and, following this, full-text articles could be examined. The information that should be collected should at least include details of methods, participants, interventions, comparators, outcomes, settings, contexts, results and investigators, and the use of a data collection form is recommended. SLRs may also contain the quality assessment of the reviewed literature. The assessment of methodological quality of relevant articles can also be included in the SLR using different tools. Selection of potential studies, data extraction, and quality assessment should be performed at least by two people independently to decrease the risk of bias. SLRs that are not maintained may become out of date or misleading.

3. AIMS OF THE STUDY

The aim of this study was to evaluate the costs, effectiveness, and cost-effectiveness of biological drugs in the treatment of RA and IBD using a SLR, a prospective observational study, and a patient-level simulation model as research methods. The results of this study may be used healthcare decision making.

Specific aims of this study were:

1. To identify, evaluate and summarise the relevant, published data on the cost-effectiveness of biological drugs for RA and IBD (Study I and Study II)
2. To assess the cost-effectiveness of biological drugs for the second-line treatment of RA based on the Finnish registry data (Study III)
3. To assess the costs, efficacy and effectiveness of the IFX biosimilar for in the maintenance treatment of IBD patients based on the Finnish real-world data (Study IV)

4. MATERIALS AND METHODS

4.1. Materials and methods of systematic literature reviews (I and II)

4.1.1. Literature search (I and II)

A comprehensive literature search on the cost-effectiveness of biological drugs for the treatment of RA and IBD was performed using Medline (Ovid), Cochrane Library (Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects, Cochrane Central Register of Controlled Trials, Cochrane Methodology Register, Heath Technology Assessment Database, and NHS Economic Evaluation Database), and SCOPUS (including Embase). Furthermore, ACP Journal Club and Web of Science were used in the search concerning RA. Literature searches were performed in March 2013 (RA) and in June 2014 (IBD). The reference lists of relevant articles were scrutinised. Furthermore, the grey literature and other relevant websites and databases (Centre for Reviews and Dissemination, Current Controlled Trials, Clinical Trials.gov, and PROSPERO) were hand-searched for relevant studies. The electronic search strategy was based on patients (RA, IBD, CD, or UC), intervention (biological drugs), outcomes (ICER), and study design (CEA) in different spellings. The biological drugs granted marketing authorisation by the EMA or the US Food and Drug Administration (FDA) before March 2013 (RA) and May 2014 (IBD) were included in the literature search strategy [115,116]. The search strategies were developed with a librarian. No time or language restrictions were made for the literature search.

4.1.2. Study Selection (I and II)

The study selection was based on the inclusion and the exclusion criteria formulated by the framework of PICOTS [114]. The study selection procedure encompassed three main stages. In the first stage, hits from the electronic databases were imported into reference management software (RefWorks). After removing duplicate citations, the second stage focused on the evaluation of the remaining studies based on their titles and abstracts. Studies clearly indicated as irrelevant to the study subject were excluded. The full articles retrieved that met the inclusion criteria are included in the current review. In the study concerning RA, the evaluation for inclusion was conducted independently by two persons (JJ and KA) first by title and afterwards by full-text. In case of disagreement, a third opinion (MB) was requested. In the study concerning IBD, the identified abstracts and full texts were screened for eligibility by one reviewer (SH) and the second reviewer (MB) was consulted.

Table 3. Inclusion and exclusion criteria in systematic literature reviews (I and II).

	Inclusion criteria	Exclusion criteria
Systematic literature review (I) of cost-effectiveness of rheumatoid arthritis		
Patients (P)	Rheumatoid arthritis	
Intervention (I)	Biological drugs (ABA, ADA, ANA, CTZ, ETA, GOL, IFX, RTX, TOC) as a monotherapy or combined with csDMARDs	
Control (C)	csDMARD(s) or other biological drug(s)	No treatment or placebo
Outcome (O)	QALYs At least direct healthcare costs ICER (if applicable)	No QALYs reported No costs reported
Study (S)	Cost-effectiveness analysis Modelling, empiric or observational analysis	CEA without QALY as the effectiveness measures Other study designs Published only as an abstract No English full-text
Systematic literature review (II) of cost-effectiveness of inflammatory bowel diseases		
Patients (P)	≥ 16-year old patients with moderate-to-severe CD or UC	< 16-year old patients Diagnosed mild CD or UC No diagnosed CD or UC
Intervention (I)	Biological drug treatment alone or together with conventional treatment or surgery	No biologic treatment
Control (C)	Conventional drug treatment, surgery, biological drug treatment or placebo treatment	No comparative treatment
Outcome (O)	ICER	Only costs or effectiveness
Time horizon (T)	≥ 12 months	< 12 moths
Study design (S)	Cost-effectiveness analysis Cost-effectiveness analysis by modelling	Cost-minimization analysis Cost-benefit analysis No health economic evaluation Published only as an abstract No English full-text

ABA = abatacept, ADA = adalimumab, ANA = anakinra, csDMARD = synthetic disease-modifying antirheumatic drugs, CEA = cost-effectiveness analysis, csDMARD = conventional synthetic disease-modifying anti-rheumatic drug, CTZ = certolizumab pegol, CD = Crohn´s disease, ETA = etanercept, GOL = golimumab, ICER = incremental cost-effectiveness ratio, IFX = infliximab, QALY = quality-adjusted life year, RTX = rituximab, TOC = tocilizumab, UC = ulcerative colitis

4.1.3. Data Extraction (I and II)

The data extraction form was based on the Cochrane Handbook for Systematic Reviews of Intervention and the abstract form of the NHS Economic Evaluation Database [117,118]. The following items were extracted: patients, interventions, controls, study design (the type of economic evaluation and modelling, perspective, time horizon, country, included costs, the methods of measuring and valuing outcomes and benefits, discount rate, currency, price year, and the type of

sensitivity analysis) and outcomes (total costs and benefits, ICER, and the results of sensitivity analysis). In order to facilitate the comparison of estimates collected from different studies, all costs were converted to 2013 (RA) or 2014 (IBD) euro using the exchange rate of the European Central Bank and the price indices of Statistics Finland [119–121]. In the RA study (I), two assessors (JJ and SH) independently extracted the data and discrepancies were resolved by consulting the third investigator (MB). In the IBD study (II), the data extraction was performed by one assessor (SH) and ambiguities were solved by another assessor (MB) for accuracy.

4.1.4. Quality Assessment (I and II)

As currently recommended, the quality of economic evaluations included was assessed using the Drummond checklist [117,122]. In addition, the Phillips checklist was used for modelling studies [123]. Furthermore, the reporting quality of the studies was assessed using the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) guidelines in the SLR concerning IBD [124]. In SLR concerning RA, two investigators (JJ and SH) independently extracted the data and discrepancies were resolved by consulting the third investigator (MB), whereas the quality assessment was conducted by one assessor (SH) and ambiguities were resolved by consulting another assessor (MB) in the SLR concerning IBD. The Drummond checklist, Phillips checklist and CHEERS checklist involve 35, 57, and 24 items, respectively. Quality scores based on fulfilment of items and average percentages of the applicable criteria met were calculated. To assess the relative quality of the studies, they were divided into three categories (good, adequate, and poor quality) ranking them by using the average percentages.

4.1.5. Synthesising Data (I and II)

The results of the included CEAs were stratified subgroups by the type of drug used, previous drug treatments and response to them, the comparator treatment, and previous surgery. ICERs were presented as principal outcomes. ICERS including only direct costs were considered primary results due to differences in the ways indirect costs (e.g. productivity losses) were calculated in the studies. In addition, ICERs including both direct and indirect costs were presented as secondary outcomes, if reported in the original studies. A quantitative synthesis of the study results was not possible because of the heterogeneity in participants, interventions and study designs.

4.2. Materials and methods of patient-level simulation model (III)

4.2.1. Patients and model (III)

The population consisted of RA patients who had previously used a TNF inhibitor as their first bDMARD and were about to begin their second bDMARD. A patient-level simulation model was developed to predict costs and outcomes associated with four alternative treatment regimens: ABA, RTX, TOC and a second TNF inhibitor. In this simulation TNF inhibitors were considered together as a single group rather than as individual drugs due to the same mechanism of action and similar effectiveness [125,126]. Every treatment regimen was simulated by identical cohorts of 1,000 patients. In case the simulated bDMARD treatment was discontinued either due to lack of efficacy or adverse events, patients were switched to another bDMARD in the beginning of the next cycle until

the patient had exhausted all four treatment options (Figure 3) [2,127,128]. Following this, patients were assumed to be treated with a 6th line treatment until death. The 6th line treatment represents a future treatment for rheumatoid arthritis, and based on the expert opinion, the treatment response to the 6th line treatment option was assumed to be the same as averaged treatment response to all biological treatments in the model. Patients were assumed to remain on any given treatment for at least 6 months. At the end of each 6-month period, the model individually evaluated for each person whether he or she would continue treatment, discontinue it or die.

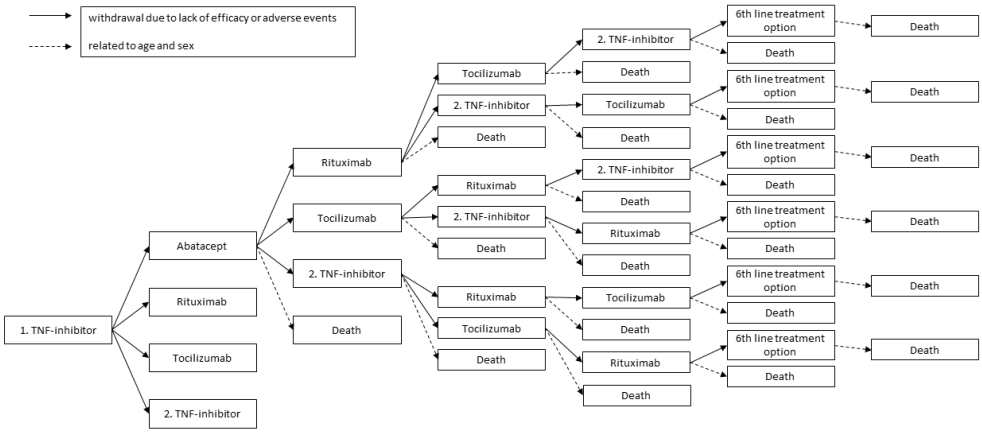

Figure 3. Treatment pathways included in the model. The pathways for rituximab, tocilizumab and TNF-inhibitors follow identical logic as for abatacept.
TNF inhibitor = Tumour Necrosis Factor Alpha inhibitor

The simulation used regression models to predict outcomes and costs for each patient individually in each period. Each patient's characteristics, history of drug use and past treatment responses were recorded in the model and utilised as predictors for future outcomes and costs. Regression models used in the simulation are described in the Appendix 1. The analysis using lifetime horizon was conducted from a societal perspective as the study included both direct and indirect costs, which were analysed separately [129]. However, out-of-pocket costs, including e.g. time and travelling, were not included in the analysis. Health outcomes also were expressed as QALYs. All costs and benefits were discounted at 3.0% annually [129]. A patient-level simulation model was conducted using R statistical programming language 3.2.2. The model was stochastic in nature and the 1,000 unique model runs with different seeds for random number generator quantified the variability in the results. Several subgroup and deterministic sensitivity analyses were carried out based on 300 model runs to explore the uncertainty and heterogeneity of the model results. Primary outcome of the simulation was ICER per QALY including only direct costs.

The primary data source for the model was the national register for biologic treatment in rheumatic diseases (ROB-FIN) and all assumptions were based on observed data unless otherwise mentioned. ROB-FIN is a longitudinal observational cohort study established in 1999 to monitor effectiveness and safety of biologic drugs in the treatment of RA and was originally based on structured data collection forms submitted by rheumatologists on patients´ routine care visits to outpatient specialized

healthcare. Starting in 2007, most of the data have been retrieved from electronic patient monitoring systems. Data on the patient´s hospitalization and outpatient visits were obtained from the Care Registers for Social Welfare and Health Care (HILMO) of National Institute for Health and Welfare (covering years 1999-2014). Data on sick leaves was acquired from the registers of Social Insurance Institution of Finland (covering years 2007-2012), whereas data on disability pensions were obtained from the registers of Social Insurance Institution of Finland (covering years 2007-2012) and the Finnish Centre for Pensions (covering years 2007-2012). Furthermore, the dates of deaths were obtained from the register of the Population Register Centre (data until 2012). These national healthcare registers included data on 2,567 RA patients, and they were linked to ROB-FIN using social security numbers.

Observed ROB-FIN data were used to construct the regression models later used to predict patients' treatment response, utility and costs in the simulation (Appendix 1). The model population was sampled with replacement among the patients included in ROB-FIN about to start their second bDMARD therapy, thus preserving any potential correlation between the variables. The baseline variables included in the model comprised age, sex, weight, Body Mass Index (BMI), HAQ, DAS28, time from diagnosis of rheumatic disease, Rheumatoid Factor (RF) status, and concomitant use of MTX, SSZ and HCQ along with the patients' outpatient and inpatient care costs during the past 12 months. The patients´ weight, BMI and RF status were fixed at the baseline values.

Treatment effectiveness was defined as an achievement of at least American College of Rheumatology (ACR) 20% improvement, a moderate EULAR response, or a DAS28 value of less than 3.2 [2,127,128]. The actual observed data were used to construct regression models, which in turn were used to predict the responses in the simulation (Appendix 1). Any effect the treatment could have on these disease activity parameters was assumed to be temporary and re-evaluated in the next period. In addition to lack of efficacy, treatment might be discontinued due to adverse events and other reasons. QALYs were calculated corresponding to EQ-5D-3L utilities predicted from the HAQ scores utilising a multinomial logistic regression model. The regression model was based on data from a survey including both HAQ and EQ-5D-3L conducted in Finland in 2009 [130]. Mortality rate adjusted by age and sex for patient-level data was based on the life table in 2017 published by Statistics Finland [131].

Direct costs comprised drug costs, administration costs of infusions, costs of switching, and outpatient and inpatient care, while indirect costs included early retirement due to RA and sick leave. Costs of drugs were based on the Finnish price list including the retail price without value added tax (VAT) of drugs and the dose in the label [132]. The costs for infusion drugs were the wholesale prices of Helsinki and Uusimaa Hospital District (Aaltonen T, personal communication, April 20, 2016). The prices of biosimilar IFX, ETA, and ADA were used in the base case analysis, whereas the price of biosimilar RTX was taken into account in sensitivity analysis. Drugs in outpatient care were in 2019 euros and all other costs were converted to 2017 euros using the price indices of Statistics Finland [120].

4.2.2. Ethical considerations (III)

Ethical approval for this study was granted by the Helsinki University Central Hospital ethical committee (73/13/03/00/14). The study permits the use of the patient records and cost data was granted by the Finnish National Institute for Health and Welfare (THL/1497/5.05.00/2013), the Finnish Population Register Centre (262/410/16) and the Social Insurance Institution of Finland (Kela 7/522/2016). Informed patient consents were acquired from patients who had been included in ROB-FIN prior to the introduction of the electronic patient monitoring systems.

4.3. Materials and methods of prospective observational study (IV)

4.3.1. Study design (IV)

In this investigator-initiated, prospective, observational, single-centre study, all adult IBD patients (≥18 years) receiving maintenance IFX (Remicade™, Janssen Biotech, Inc/ Schering-Plough, EU) therapy at Helsinki University Hospital were switched to biosimilar IFX (Remsima™, Celltrion Pharm, Inc**.,** South Korea) in the beginning of 2016. Before the administration of the first biosimilar IFX in the day-care unit, all IBD patients with IFX treatment were asked to participate in the study. Whether patients chose to participate in the study or not, all adult IBD patients (≥18 years) receiving maintenance IFX therapy were switched to a biosimilar one, and they received all the services they usually did. At the time of administration of the first biosimilar IFX, IBD patients were asked to complete a questionnaire concerning HRQoL and disease activity. Patients who had returned the first questionnaire and the informed consent form were asked to answer follow-up questionnaires at 3 and 12 months after switching. One reminder was sent to patients who had not returned the follow-up questionnaires.

HRQoL was measured using the generic 15D utility instrument [101,102] and disease-specific IBDQ [133]. Clinical disease activity assessment was based on the CDAI [54] in CD and on the pMayo in UC [56]. FC served for objective measurement of disease activity and was measured by a quantitative enzyme immunoassay (PhiCal Test, Calpro AS, Oslo, Norway). The FC values quoted as normal were <100 µg/g of stool [134]. The patients' clinical background information regarding the disease state and the treatments given were collected from the hospital records. IBD at diagnosis were classified using the Montreal classification, which assesses the extent of disease and severity of symptoms [135]. The Montreal classification for Crohn´s disease considers age of onset (A1 below 16 years, A2 between 17 and 40 years and A3 above 40 years), disease location (L1 ileal, L2 colonic, L3 ileocolonic, L4 isolated upper disease) and disease behaviour (B1 non-stricturing, non-penetrating, B2 stricturing, B3 penetrating, p perianal disease modifier). The extent of UC is classified as mucosal changes on endoscopy limited to the rectum (E1), the left side of the colon (E2), and beyond the splenic flexure (E3), whereas the symptom severity score ranges from none (S0) to severe systemic manifestations (S3).

The study was conducted from the healthcare provider perspective in the special healthcare setting. The costs of production of the services were obtained from the hospital accounting records of the HUS District, where all costs of specialised health care of individual patients were stored on a routine basis [136–139]. The total cost data covered all costs related to the secondary healthcare provider (intervention, ward, ambulatory visits, laboratory, radiology, pathology, outpatient visits). No

productivity costs or outpatient drug costs were included. Costs of IFX were calculated based on the hospital records. Discounting was not considered in the study as the data were based only on years 2015 and 2016. All costs were converted to 2017 euros using the healthcare price index of Statistics Finland [120]. The primary outcomes of the study were the changes in HRQoL, disease activity, and costs during the follow-up up.

4.3.2. Statistical analyses (IV)

The statistical significance of the difference in mean 15D scores and FC during follow-up was tested with paired samples *t* test. As the 15D and FC variables were not normally distributed and the patient size was relatively small, the Wilcoxon Signed Rank test as non-parametric test was also applied. Aside from minor differences in the level of statistical significance, the results of parametric and non-parametric tests were similar. Therefore, only results of parametric tests are reported for the 15D and FC. The Wilcoxon Signed Rank test was used to test the statistical significance between variables in IBDQ, CDAI, and pMayo. The statistical significance of the differences in health service use and costs during the follow-up were tested with paired samples *t* test. The Mann-Whitney U Test was used to examine differences between patients included and excluded from the study. The results are given as mean and standard deviation (SD) or as median and interquartile range (IQR). Values less than 0.05 were considered statistically significant. Statistical analyses were performed for CD and UC patients, and patients with IBDU were included in the UC group. The data were analysed using IBM SPSS Statistics 24 (SPSS, Inc.)

4.3.3. Ethical considerations (IV)

Ethical approval was granted by the Ethics Committee of Medicine of HUS (32/13/03/01/2016). The research permit was given by the HUS (HUS-170-2016-2 and HUS-333-2019-23). All patients gave informed written consent for participation in the study.

5. RESULTS

5.1. Results of systematic literature reviews (I and II)

5.1.1. Literature search and study selection (I and II)

Rheumatoid arthritis

In total, 4,653 non-duplicate references were identified with the literature search, of which 3,113 were excluded during title and abstract screening in the SLR of cost-effectiveness of biological drugs in the treatment of RA. After the assessment of 237 full-text articles, 41 studies were included in the current review. Patients, interventions, controls, outcomes or design of the studies did not meet the inclusion criteria of the SLR in 105 studies. Moreover, 71 studies were published only as conference abstracts, and, therefore, they were excluded from the study. A flowchart of the study selection in the SLR of process is presented in Figure 4. From the 41 studies included in the SLR, one study was based on empirical cost and effectiveness data from a randomised controlled trial (RCT) [140], two on observational data [141,142] while the remaining 38 studies used a modelling approach with multiple data sources [143–180].

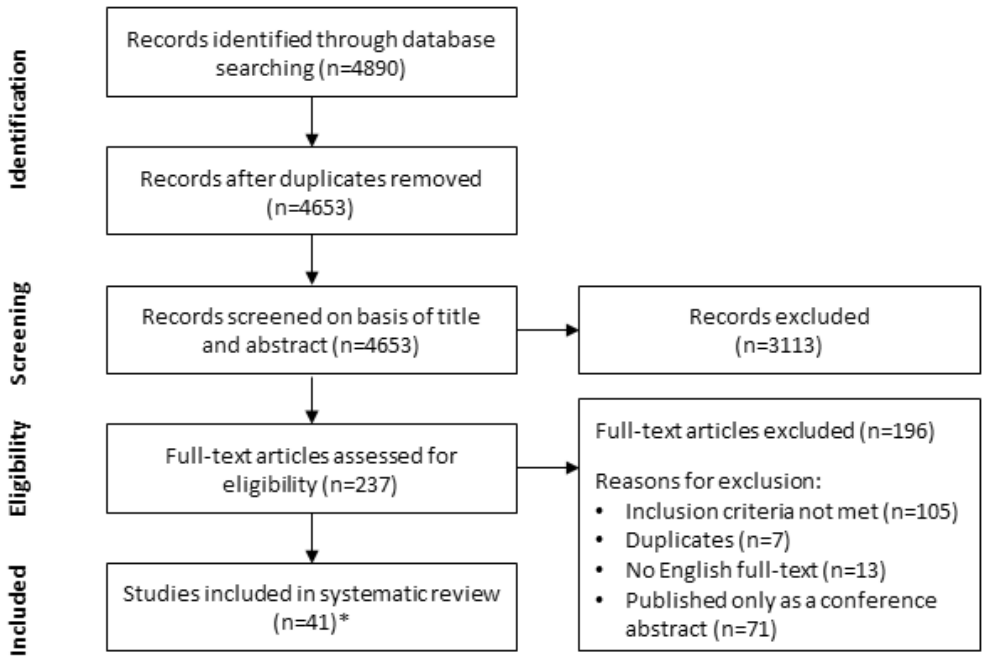

Figure 4. Flowchart of the study selection in systematic literature review of cost-effectiveness of rheumatoid arthritis (I).

**Studies included in the systematic literature review (I) have been made bold in the reference list.*

Inflammatory bowel diseases

In the SLR of cost-effectiveness of biological drugs in the treatment of IBD, the database search identified 1,828 references, of which 461 were removed as duplicates, leaving 1,367 studies to be screened by abstracts and titles for further evaluation. After the assessment of abstracts and titles, 50 full-text articles were evaluated. Additionally, six full-text articles were included, of which two were found from the bibliographies of already included studies [181,182] and four from the structured abstracts identified by the literature search [183–186]. In total, 25 studies were included in the review [181–205]. Study selection is presented in a flow diagram in Figure 5. All CEAs involved economic evaluation modelling, of which 17 and 7 were focused on CD and UC, respectively, while one study featured both diagnoses.

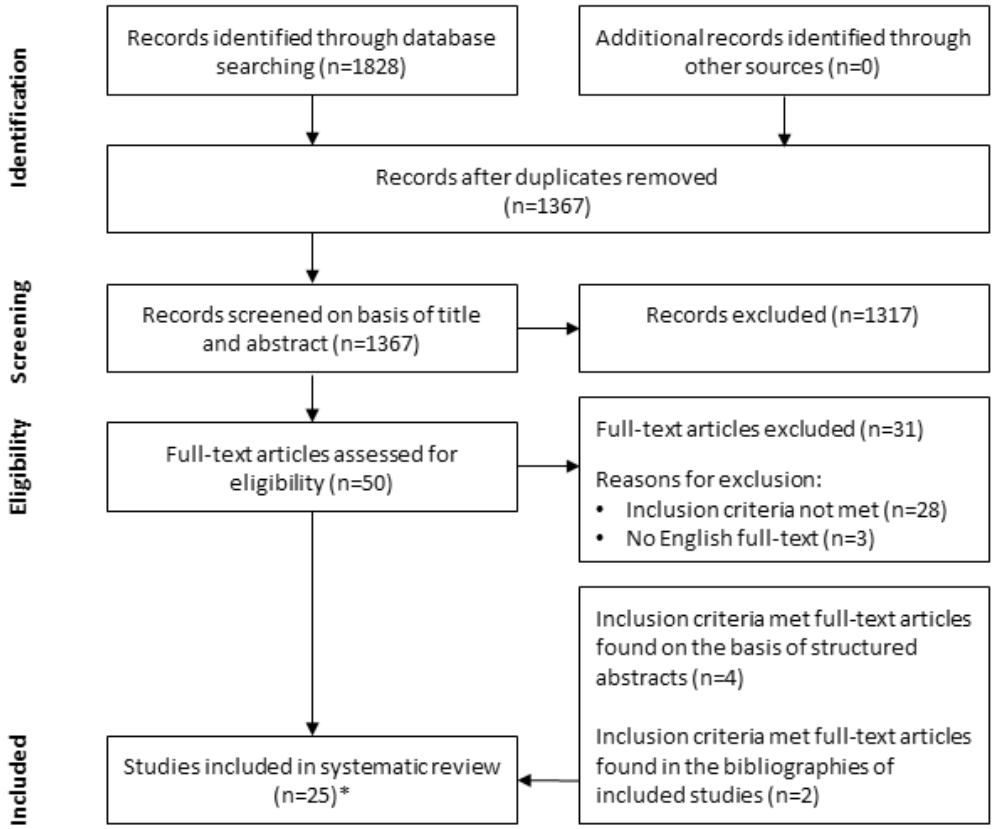

Figure 5. Flowchart of the study selection in systematic literature review of cost-effectiveness of inflammatory bowel diseases (II).

**Studies included in the systematic literature review (II) have been made italicised in the reference list.*

5.1.2. Cost-effectiveness (I and II)

Rheumatoid arthritis

The cost-effectiveness of biological drugs for patients with early RA and naïve to csDMARDs were analysed in seven studies. Four studies performed a comparison between biological drugs and csDMARDs [148,152,157,167]. The ICERs of TNF inhibitor in comparison to csDMARDs ranged from 39,000 to 1,273,000 €/QALY when only direct costs were considered. IFX was associated with the highest ICERs, ranging from 422,000 to 1,273,000 €/QALY, while ICERs for ETA and ADA as a monotherapy were below 100,000 €/QALY. As a combination therapy with MTX, ICERs for ETA and ADA were substantially higher. If both direct and indirect costs were considered, ICERs for biological drugs were slightly more favourable.

There were 21 studies comparing the biological drugs and csDMARDs in patients with an insufficient response to csDMARDs. When only direct costs were considered ICERs for IFX, ADA and ETA were 12,000–282,000; 44,000–274,000 and 40,000–708,000, respectively. ABT and TOC were associated with narrower ranges of ICERs (42,000 to 47,000 and 19,000 to 21,000, respectively). ICERs below 35,000 €/QALY were found in three studies [166,174,177] and below 50,000 €/QALY in ten studies [143–145,148,171,173,178]. Six studies performed comparisons between different biological drugs used in patients with an inadequate response to csDMARDs [148,153,155,164,166,176]. The results of these studies were contradictory. Two studies [164,166] found ETA to be dominant over IFX and ADA, while three of the other studies [148,155,176] reported ICERs ranging from 23,000 to 109,000 €/QALY for ETA when only direct costs were included. Two studies comparing TOC and ETA found TOC to be the dominant strategy.

Eight CEAs compared biological drugs and csDMARDs in patients who had had an insufficient response to at least one TNF inhibitor [146,150,156,160,172,175,179,180]. RTX was associated with the lowest ICERs, ranging from 26,000 to 48,000 €/QALY. Three of four studies evaluating RTX provided ICERs below 35,000 €/QALY and none of the studies reported ICERs more than 50,000 €/QALY. ICERs for the other agents ranged from 41,000 to 143,000 €/QALY. The results of the four studies comparing one biologic to another [146,156,163,179] indicated RTX as the most cost-effective biologic among patients with an insufficient response to a TNF inhibitor.

Inflammatory bowel diseases

In two studies, the cost-effectiveness of biological drugs was evaluated in CD patients with no previous treatment [189,199]. In comparison with conventional drugs for the treatment of fistulising CD, ICERs ascended in excess of 400,000 €/QALY [189] while for newly diagnosed luminal CD IFX was dominant [199]. No CEAs of biological drugs in UC patients without earlier treatment were found.

The cost-effectiveness of biological drugs in CD patients with previous conventional medical treatment was investigated in 12 studies [183,184,190–192,194,195,197,198,200,201,205]. For CD, ICERs for the biological drugs ranged from dominance to 549,335 €/QALY when compared with those of conventional medical treatment [183,184,190,191,194,197,198]. ADA as an intervention treatment resulted in more frequently lower ICERs than did IFX in comparison with conventional medical treatment [183,190,191,194]. IFX in comparison with surgery was not found to be cost-effective, with ICERs in excess of 77,000 €/QALY [195]. Between biological drugs´ cost-effectiveness

was investigated in four studies [183,190,201,205]. ICERs above 300,000 €/QALY were seen when comparing IFX with ADA [183,190], while ADA maintenance treatment appeared to be dominant in comparison with IFX maintenance treatment [205].

Two studies evaluated the cost-effectiveness of biological drugs for different activity levels of CD resulting in more favourable ICERs for severe CD than for moderate CD [194,198]. Biological induction treatment resulted in lower ICERs than the maintenance treatment [194]. In one study, IFX and corticosteroid combination treatment was shown to be cost-effective in comparison with IFX monotherapy [200].

Eight CEAs evaluated the cost-effectiveness of biological drugs in UC patients with previous conventional medical treatment [181–183,185,186,202–204]. ICER remained below 35,000 €/QALY when comparing IFX with either conventional medical treatment, surgery, or placebo treatment for UC patients with acute exacerbation requiring hospitalisation [181,182,185]. When investigating the cost-effectiveness of IFX for patients with moderate-to-severe UC, ICER ranged from 33,067 €/QALY to 407,499 €/QALY [183,186,202–204].

5.1.3. Quality assessment (I and II)

Rheumatoid arthritis

The average quality scores of the 41 studies included in SLR were 25.7 out of 35 (range 17 to 31) and 32.3 out of 57 (range 16 to 46) when evaluated using the Drummond checklist and Phillips checklist, respectively. The corresponding average percentages of the applicable items fulfilled were 81 (range 31 to 90) for the Drummons checklist and Phillips checklist, respectively. The most frequent quality issues were the incomplete reporting of the data sources, inappropriate comparator treatments, defects in the sensitivity analysis and the lack of quality assessment of data used.

Inflammatory bowel diseases

The mean amount of fulfilled criteria were 24.9 out of 35 (median 26, range 14–30), 29.6 out of 57 (median 29, range 14–46), and 18.2 out of 24 (median 18, range 10–23) for the Drummond checklist, Phillips checklist, and the CHEERS guideline, respectively. Studies by Assasi et al., Bryan et al., and Dretzke et al., which are all Health Technology Assessment (HTA) reports, fulfilled most criteria of the applicable items [183,185,194]. The quality elements most commonly omitted from the economic analyses were information on adjustments for data identification, baseline data, treatment effects, data incorporation, and assessment of uncertainty. The results of the quality assessment are shown in Figure 6.

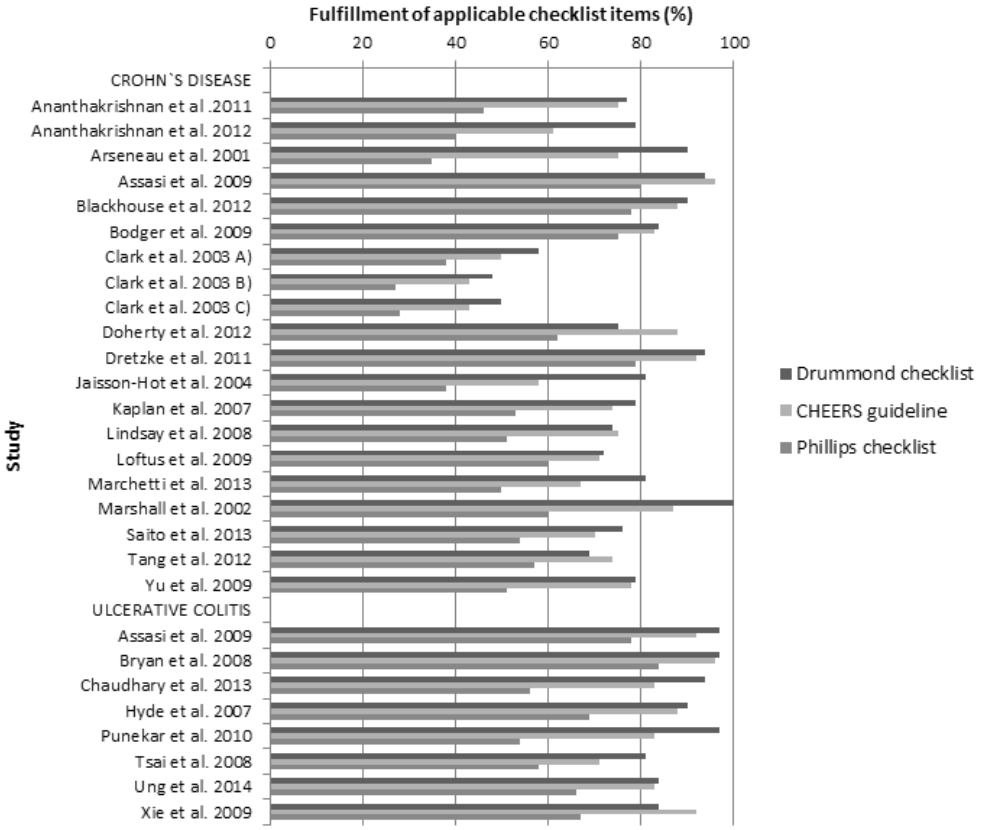

Figure 6. Quality assessment of the included studies (n=25) in the SLR of cost-effectiveness of biological drugs in the treatment of inflammatory bowel diseases (II).

5.2. Results of patient-level simulation model (III)

5.2.1. Rheumatoid Arthritis patients (III)

This study was based on the data on 2,567 RA patients. At baseline, the median age of patients included in the study was 56 years. 75% of patients were female. Median HAQ score was 1.1 (IQR 0.6-1.6), whereas median DAS28 was 4.6 (IQR 3.5-5.7). More than half of the patients had a treatment response to the first TNF inhibitor.

5.2.2. Base case analysis (III)

Lifetime drug costs without administration costs and costs of switching were the lowest for RTX, but when administration costs and costs of switching were included, drug costs were the lowest for TNF inhibitors (Table 3 and Figure 7). ABA had the highest drug costs. However, ABA had the lowest outpatient and inpatient care costs, while RTX had the highest outpatient and inpatient care costs. In total, the lowest and highest direct costs were associated with the TNF inhibitors and RTX, respectively. Indirect costs ranged from 148,718 € for TNF inhibitors to 165,300 € for RTX. Drug costs including administration costs and costs of switching represented over half of the total costs. QALYs

ranged from 9.41 of RTX to 9.66 of TNF inhibitors. In our model, patients died on average at the age of 85.6 (standard deviation 10.0). When the societal perspective was used, TNF inhibitors, ABA, and TOC had lower costs and higher QALYs than RTX, and, therefore, they were dominant in comparison to RTX. TNF inhibitors are the most cost-effective treatment option, as they have the lowest costs and the highest lifetime QALYs.

Table 4. Lifetime costs and Quality Adjusted Life Years (QALYs) of biological disease-modifying anti-rheumatic drugs per patient as a second-line biologic therapy in rheumatoid arthritis (III).

	Abatacept	Tocilizumab	TNF inhibitors	Rituximab
Drug costs, €	211,384	211,071	201,436	201,407
Administration costs, €	57,799	56,983	47,656	48,908
Drug costs including administration costs and costs of switching, €	270,028	268,928	249,937	251,291
Outpatient and inpatient care costs, €	25,805	32,749	26,968	69,681
Direct costs, €	295,833	301,677	276,905	320,972
Indirect costs, €	154,293	159,480	148,718	165,300
Total costs, €	450,126	461,157	425,623	486,272
Life years	19.27	19.27	19.27	19.27
QALYs	9.48	9.41	9.66	9.41

All costs and QALYs were discounted at 3 % per year.

bDMARD=biological disease-modifying anti-rheumatic drug, QALY=Quality-adjusted life year, TNF inhibitor=Tumour Necrosis Factor Alpha inhibitor

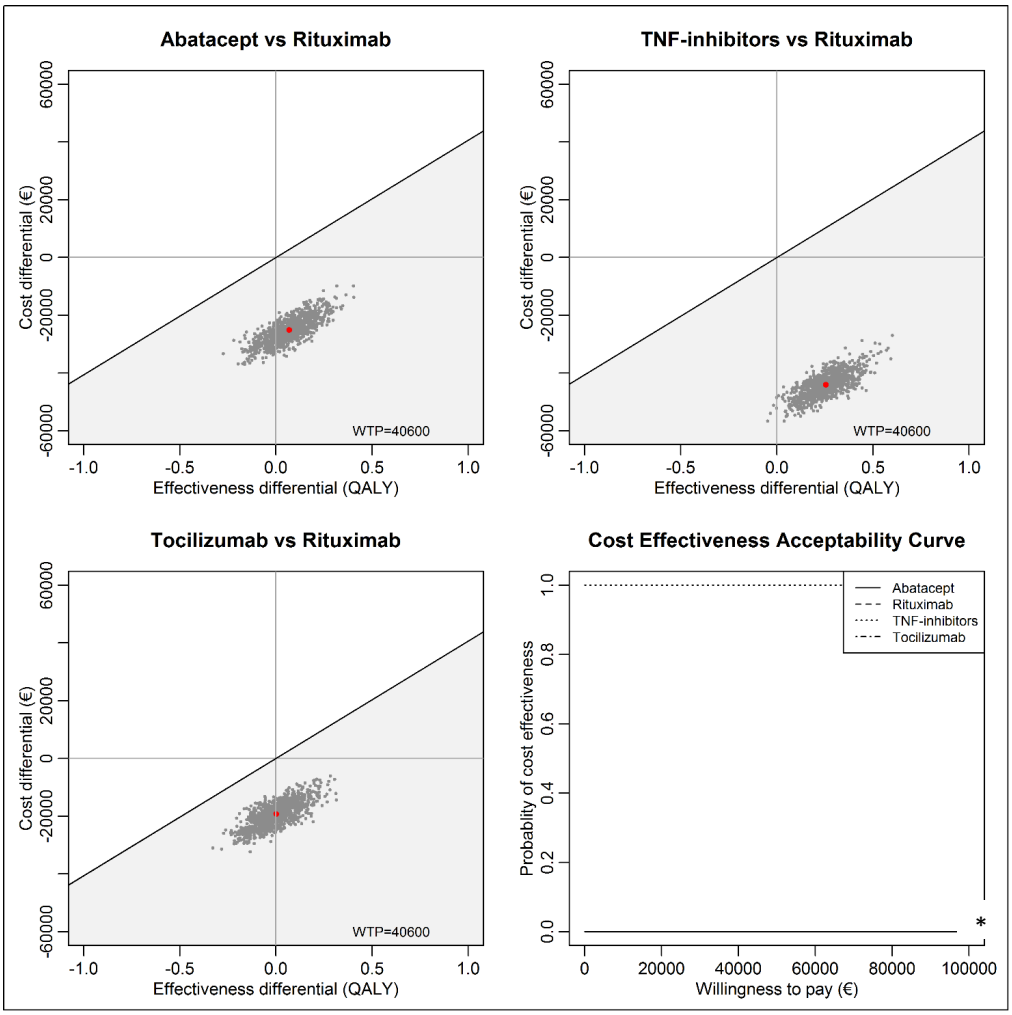

Figure 7. Incremental cost-effectiveness planes and cost-effectiveness acceptability curve for abatacept, TNF inhibitors, and tocilizumab in comparison to rituximab for the treatment of rheumatoid arthritis as a second-line therapy in a lifetime scenario (III).
QALY=quality-adjusted life year, TNF-inhibitors=Tumour Necrosis Factor Alpha inhibitors
*includes abatacept, rituximab and tocilizumab

5.2.3. Sensitivity analysis (III)

RTX had the highest direct and indirect costs and the lowest QALYs when they were discounted at 0%, but when the discounting rate of 6% was used, TOC had the lowest QALYs. When the time horizon of 10 years was used, RTX had the lowest drug costs including the costs of switching and the administration costs, while TOC was associated with the lowest QALYs. As compared with RTX, TNF inhibitors were dominant, whereas the ICER for ABA was 144,213 €/QALY when the time horizon of 10 years and both direct and indirect costs were considered. RTX as a second-line treatment option had the highest direct costs even when the price discount of 30% for the RTX biosimilar was used, owing to the highest outpatient and inpatient care costs for RTX. Removing half-cycle correction had

little effect on the results. QALYs decreased when the health stages were valued with the British tariff. Both direct and indirect costs were higher and QALYs were lower for women than for men. When compared with patients with no response to the first TNF inhibitor, primary responders had slightly higher direct and indirect costs and QALYs. The QALYs ranged from 11.96 to 12.37 for patients with negative RF status, while QALYs ranged from 9.16 to 9.42 for patients with positive RF status. In addition, both direct and indirect costs were higher among patients with negative RF status as compared to RF-positive patients. Furthermore, concomitant use of MTX or other non-biologic therapies led to increased QALYs in comparison to non-use of MTX or biologic monotherapy, respectively.

5.3. Results of prospective observational study (IV)

5.3.1. Inflammatory Bowel Disease patients (IV)

Of the 252 eligible IBD patients, 75 were willing to participate and returned their informed consent and questionnaire at the time of switching (Figure 8). A total of 21 patients were excluded from the study, and, consequently, 54 patients were included in the final analysis. Of these 54 patients, 48 (88.9 %) and 43 (79.6 %) replied to the questionnaire at 3 and 12 months after the switching. Patient characteristics were similar between patients included (n=54) and excluded (n=21) from the final analysis, except in the duration of IFX treatment (p=0.017) and the location of CD according to the Montreal classification (p=0.007) in CD. The median duration of IFX treatment was 7 months (IQR 0.8-6.3 year) and 4 year (IQR 1.6-7.8 year) in CD patients included and excluded from the study, respectively. The location of CD was colonic in most patients included in the study (61.5%), whereas the location was ileocolonic in most patients excluded from the study (57.7%).

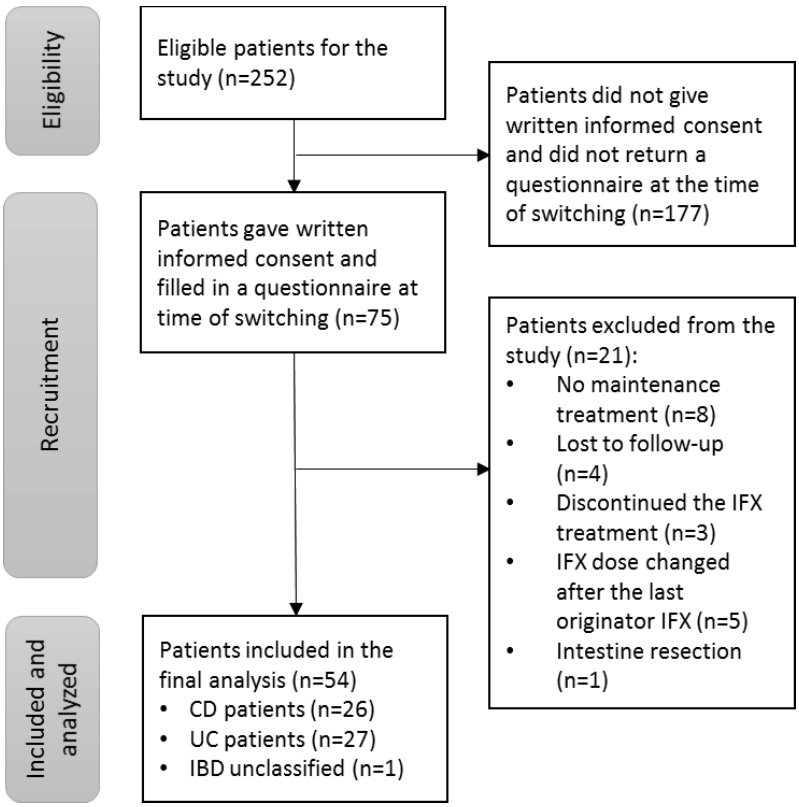

Figure 8. Flowchart of the patients included in the study (IV).
CD=Crohn´s disease, UC=ulcerative colitis, IBD=inflammatory bowel disease, IFX=infliximab

5.3.2. Health-related quality of life (IV)

At the same points of measurement, full health (the 15D score = 1) was reported by 12, 20, and 15% of CD patients, respectively, and by 7, 7, and 17% of UC patients, respectively. Compared to the time of switching, the mean 15D scores in CD (p=0.310 and p=0.129) and in UC patients (p=0.470 and p=0.319) did not differ at 3 and 12 months, respectively. A clinically important difference was not observed in UC during one-year follow-up, whereas in CD patients the change in the total 15D scores between 3 and 12 months was clinically important. However, the difference was not clinically important when compared to the time of switching in CD patients. The proportion of patients that experienced at least a minimum clinically important change in HRQoL 12 months after the switching was 40% for improvement and 31% for deterioration in the whole study group. Regarding the different dimensions, statistically significant difference was observed in excretion (p=0.042) and in breathing (p=0.021) in CD as compared to the time of switching, whereas in UC no statistically significant differences (all p>0.05) on any dimension were observed.

At the time of switching and 3 and 12 months later, IBDQ score ≥170 (considered remission) was reported by 73, 85, and 70% of CD patients, respectively, and by 64, 69, and 70% of UC patients, respectively. Statistically significant improvement (p=0.018) was observed in IBDQ scores at 3 months

after switching in CD. The percentages of patients who met an IBDQ change ≥16 (considered clinically important difference) was 5% (n=1) in CD and 17% (n=4) in UC 12 months after switching. The total IBDQ score decreased by more than 32 points (considered relapse) in one UC patient 12 months after switching.

5.3.3. Disease activity (IV)

At the time of switching and at 3 and 12 months later, a CDAI less than 150 (considered remission) was reported by 92, 89, and 63% of CD patients, respectively. pMayo score of <2 (considered remission) was reported by 63, 63, and 76% of UC patients, respectively. At respective points of measurement, median FC concentration was 82 (IQR 13-312), 83 (IQR 26-300), and 33 (IQR 10-186) in the whole study group. Compared to the time of switching, changes in the CDAI (p=0.227 and p=0.756), pMayo (p=0.971 and p=0.829), and FC concentration (CD: p=0.640 and 0.397; UC: p=0.666 and 0.785) showed no difference at 3 and 12 months, respectively.

5.3.4. Health service use and costs (IV)

The number of IFX administration visits and IFX doses between 2015 (IFX originator used) and 2016 (IFX biosimilar used) showed neither in CD (p=0.795 and p=0.139) nor in UC (p=0.113 and 0.097) a statistically significant difference. When the healthcare provider perspective in the special healthcare setting was used, costs of IFX were significantly higher (p<0.001) in 2015 than in 2016. Costs of IFX in 2016 were 35% of costs of IFX in 2015. The mean total costs covering all costs related to the secondary healthcare provider (intervention, ward, ambulatory visits, laboratory, radiology, pathology, outpatient visits, and excluding the costs of IFX) were 4,405 € (SD 4,132) per patient in the whole study group in 2015, while costs were 3,830 € (SD 2,573) in 2016. When patients who started IFX treatment in 2015 (4 CD patients and 10 UC/IBDU patients) were excluded, total costs were 3,804€ (SD 3,771) per patient in 2015 and 3,886 € (SD 2,597) per patient in 2016. Total costs related to secondary healthcare (excluding the costs of IFX) between 2015 and 2016 showed a difference neither in the whole study group (p=0.355) nor in patients who had started IFX treatment before 2015 (p=0.871).

6. DISCUSSION

6.1. Discussion on results

6.1.1. Discussion on costs, effectiveness and cost-effectiveness of biological drugs in the treatment of rheumatoid arthritis

Based on this study, the cost-effectiveness of biological drugs as a second-line biologic treatment in the treatment of RA is conflicting. SLR (I) revealed that RTX appeared to be the most cost-effective biological drug among patients with a previous exposure to TNF inhibitors, whereas TNF inhibitors, ABA, and TCZ as second-line biologic treatments for RA were dominant compared with RTX according to the patient-level simulation model (III). Consistent with the results of patient-level simulation model (III), previous studies have shown similar effectiveness between bDMARDs in patients with RA failing on TNF inhibitor [206,207], whereas other studies suggest that changing to RTX is more effective than switching to an alternative TNF inhibitor [208–210]. In contrast to the results of patient-level simulation model (III), RTX was associated with both the lowest costs and the highest QALY gain in a head-to-head RCT between RTX, TNF inhibitors, ABA and TCZ in the study published in 2015 [211]. Compared with other biological drugs, RTX has a unique mode of action and long dosing interval. In maintenance treatment, RTX infusions are often administered on demand in Finland. In the patient-level simulation model (III), the patients treated with RTX came to visit the rheumatologist only after the effect of the previous infusion began to wear off, which is very likely to lead to an underestimation of the effectiveness of RTX in our data, and, therefore, lead to overestimation of healthcare costs. Based on the registry data used in the simulation (III), RTX was administered every eight months in maintenance treatment. Similar dosing interval of RTX was reported by Keystone et al. [212], whereas the mean dosing interval of RTX varied between 11 and 13 months in daily clinical practice in Finland according to the study by Valleala et al. [213]. Therefore, a relatively short dosing interval used in the simulation might also be one reason to cause high costs of RTX treatment.

6.1.2. Discussion on costs, effectiveness and cost-effectiveness of biological drugs in the treatment of inflammatory bowel disease

Costs, effectiveness and cost-effectiveness of the biological drugs in the treatment of IBD was evaluated using the SLR (II) and prospective observational study (IV) in this study. In the SLR (II) biological drugs in comparison with conventional medical treatment were found to be cost-effective in the treatment of severe IBD on the basis of the cost-effectiveness threshold of 35,000 €/QALY. However, the cost-effectiveness of maintenance treatment remained unclear, and biological drugs did not seem to be cost-effective in moderate IBD. Similarly, SLRs published after 2014 have found that biological drugs are not cost-effective or the cost-effectiveness remains unclear in the maintenance treatment of IBD [214,215]. According to the SLR by Pillai et al. (2017), IFX and ADA are cost-effective in moderate to severe CD, whereas they are not cost-effective in UC, but VED is associated with favourable ICER in UC patients refractory to conventional treatment [215]. In contrast, biological drugs in IBD patients with severe disease and inadequate response to conventional drugs were particularly cost-effective, at the cost-effectiveness threshold of $CAD100,000 based on a literature review published in 2018 [214]. Based on the SLR (II) of this study, the cost-effectiveness between individual biological drugs remained unclear in the treatment of IBD,

although ADA was shown to be a more cost-effective biological treatment alternative than IFX. According to the recent SLR, ADA has been shown to be more cost-effective than originator IFX in moderate to severe CD, but after the onset of the IFX biosimilar, IFX seems to be more cost-effective than ADA [216]. In moderate to severe UC, IFX has been more cost-effective than ADA already before the IFX biosimilar. HRQoL, disease activity, and costs of switching originator IFX to biosimilar one in the maintenance treatment of Finnish IBD patients were evaluated in the prospective observational study (IV). Consistent with the results of the observational study (IV), previous studies showed comparable disease activity between originator IFX and biosimilar one [62,70–74]. In contrast to the previous studies, our study showed a statistically significant improvement in IBDQ scores 3 months after the switching in CD as compared with the time of switching. However, a statistically significant difference was no longer present at 12 months after the switching. Furthermore, the generic HRQoL measure, the 15D, suggests that the IFX biosimilar is comparable to originator one, and, therefore, the results of IBDQ should be interpreted with caution. It is unclear whether the change in IBDQ scores is due to the switching to the IFX biosimilar or due to other patient dependent or pharmacological factors.

In the prospective observational study (IV), patients received maintenance IFX treatment, and most patients included in the study were in remission based on the HRQoL and disease activity measured in the study. The mean 15D and IBDQ scores of IBD patients during one-year follow-up were slightly higher indicating better HRQoL than the mean 15D score of 0.874 and the mean IBDQ score of 163 in Finnish IBD patients reported by Haapamäki et al. [96]. Additionally, the mean 15D score was 0.868 for the Finnish IBD patients of the Health 2000 survey [100]. Based on the NOR-SWITCH study, the mean IBDQ score in IBD was 187-190, which is comparable to the mean IBDQ score of this study [74]. The 15D score has shown to be strongly related to the total IBDQ score and disease activity [96]. According to the study by Haapamäki et al., the total 15D scores of IBD patients in clinical remission can be estimated to be about 0.89 or higher [96]. In the prospective observational study (IV), the 15D score of 0.89 or higher was observed by 65, 75, and 60% of CD patients and by 57, 68, and 65% of UC patients at time of switching and 3 and 12 months later, respectively. This finding was in line with IBDQ, CDAI, and pMayo, as most IBD patients in this study were in remission. The study suggested that in maintenance therapy of IBD, biosimilar IFX was comparable to originator one during one-year study follow-up. This finding based on Finnish real-world data supports the opinion of the Fimea that biosimilars are interchangeable with the originator biological drugs under the supervision of a healthcare worker [85,86]. Based on the prospective observational study (IV), the costs of biosimilar IFX were around one third of the costs of originator one, whereas costs related to secondary healthcare (excluding the costs of IFX) were similar in 2015 (originator IFX used) and 2016 (biosimilar IFX used). Although IFX is used in hospitals, biosimilars have the potential to provide remarkable cost-savings for healthcare.

6.1.3. Discussion on results of systematic literature reviews

The uncertainty in economic evaluations can arise from several methodological disagreements among CEAs. For example, the source of effectiveness data has a substantial influence on ICER. In most studies included in the SLRs (I and II), the effectiveness estimates were based on one or several RCTs. Although the efficacy evidence is extremely necessary in the field of medicine, it has some limitations when applied as source of effectiveness in economic evaluations. Several factors, such as

access to care, cost, compliance and persistence, are not addressed in RCTs, and, as a consequence, the results of RCTs may cause a risk of overestimating effectiveness in comparison with the treatment in routine healthcare. Therefore, it may be that the CEAs using RCTs as a source of effectiveness produce lower ICERs than real-world data. The study by Aaltonen et al. showed that 7.6-44% of the patients included in the ROB-FIN register and treated with TNF inhibitors in routine clinical practice in Finland between 2000 and 2014 would have been potentially eligible for RCTs conducted between 2012 and 2017 [217]. Furthemore, the study showed that the patients eligible to RCTs had better treatment responses compared with the non-eligible patients. Another limitation of the use of RCTs as efficacy estimates is that they often use a placebo as a control treatment, while the aim of CEA is to compare active treatments in real-life practice.

In most studies included in the SLRs, the source of utility data was reported inadequately, and considerable variation existed in the instruments used to collect it. Similar to the patient simulation model (III), the utility scores of generic HRQoL instruments, which most frequently was EQ-5D, were obtained by determining the relationship between values on a disease-specific measure to a generic quality of life measure. This is necessary because of the fact that the generic HRQoL measures have been applied in only a few RCTs, while disease-specific measures are commonly used in RCTs. In the studies included in the SLR concerning RA, utility scores of generic HRQoL were generally derived from the HAQ, whereas CDAI was commonly used in IBD-related studies. Direct valuation methods (e.g., the standard gamble, the time trade-off) were used more frequently than indirect methods (e.g., EQ-5D) in IBD studies. The application of different algorithms for conversions creates a further source of heterogeneity in ICER estimates. Because of the variation in the methods used and in the preferences across individuals, the QALYs may vary widely between the studies and this affects the results of the CEAs. Moreover, extrapolation beyond the time horizon of the study involving the use of assumptions may create a further source of uncertainty. As biological drugs improve patients´ health status [218], they have the potential to yield gain in terms of reductions in hospitalisation, surgeries, and incapacity in future.

Among the studies included in the SLRs, the amount of the fulfilled items according to the Drummond checklist and the CHEERS guideline was higher than using the Phillips checklist. The reasons may be the aims of the checklists and the extensiveness of the Phillips checklist, which includes several topics relevant to modelling studies not considered in the Drummond checklist and the CHEERS guideline. On average, the same CEAs fulfilled the highest amount of the applicable items according to all three checklists. Most of the studies, which fulfilled most criteria of quality assessment checklists, were HTA reports. In the SLR concerning IBD (II), almost half of the included CEAs were funded by the pharmaceutical company or authors had received funding from the pharmaceutical company during the research project. Many of the studies funded by the pharmaceutical company produced favourable ICERs. However, it remained unclear whether the source of funding had an effect on the study results. In addition, the relation between the studies funded by a pharmaceutical company and fulfilment of applicable quality assessment criteria was found to be unclear. The quality assessment revealed several problems, namely insufficient reporting of data sources and problematic methodological details, which possibly reduce the validity of the results. Furthermore, variability in data inputs and heterogeneity in study designs made it challenging to compare the studies reliably. This finding also proved that there are many ways to conduct CEAs, and their comparison is challenging due to heterogeneous study designs, which create challenges for decision-makers.

6.2. Discussion on materials and methods

The aims of the SLRs (I and II) were to evaluate the published data on the cost-effectiveness of biological drugs in the treatment of RA and IBD internationally. SLR is a method of research that identifies, selects and critically appraises existing published literature using a pre-set criteria and protocol [36,88]. As standardised methodology is required to ensure the validity and reliability, the SLRs were performed following current recommendations for SLR of economic evaluations [113]. The comprehensive literature searches were utilised to minimise the risk of bias. The literature searches in SLR (I) and SLR (II) were mainly performed using the same databases (e.g. Medline, EMBASE and Cochrane Library). ACP Journal Club and Web of Science were used in the search concerning RA (SLR I), but based on the results of literature search (SLR I), it was not seen necessary to include these databases in the search concerning IBD (SLR II). The literature searches identified about 4,900 and 1,800 studies on the cost-effectiveness of biological drugs in the treatment of RA and IBD, respectively. As most of the studies identified were excluded from the SLR, and only 41 RA-related and 25 IBD-related studies were included in the final SLRs, literature searches seemed to be relatively sensitive rather precision. It was also notable that the amount of CEAs was relatively small. The studies included in the SLR were restricted to CUAs, instead of all CEAs, because QALY as a single measure of the effectiveness enabled a comparison of studies and the classification into different subgroups based on the patients´ previous treatments and comparator treatments. Such a classification seems almost essential because the patient history is a key factor while assessing the external validity and trying to generalise the results. Furthermore, comparator treatment has a great impact on ICERs. In both RA- and IBD-related SLRs, the quality of CEA was assessed using the Drummond and Phillips checklists, which are used to evaluate the methodological quality of economic evaluations. In addition, the CHEERS guideline was used in IBD-related SLR to evaluate the reporting of the included studies.

The aim of the patient-level simulation model (III) was to assess the cost-effectiveness of the second-line treatment of RA in a Finnish healthcare setting, whereas the aim of prospective observational study (IV) was to assess costs and effectiveness of the IFX biosimilar in the maintenance treatment of IBD patients in a Finnish healthcare setting. To avoid the quality issues of individual CEAs observed in SLRs (I and II), the patient-level simulation model (III) was conducted following the recommendations of Drummond and Phillips checklists, and reported using the CHEERS checklist, whereas prospective observational study (IV) was performed using the STROBE Statement for cohort studies [122–124,219].

In the patient-level simulation model on cost-effectiveness of biological drugs in RA (III), the real-world data on costs and effectiveness was based on registry data, and baseline characteristics of the model and population and the assumptions used in the model were primarily based on ROB-FIN data representing routine clinical practice. In addition, cost data derived from comprehensive Finnish national registers were employed whenever possible in the patient-level simulation model (III). The registry of the Social Insurance Institution of Finland covers extensively e.g. sickness allowance and disability pensions in Finland [220]. The Care Registers for Social Welfare and Health Care (HILMO) of National Institute for Health and Welfare collects data on the activities of health centres, hospitals and other institutions providing inpatient care and on the clients treated in them for the purposes of

statistics and research [221], whereas the Population Register Centre maintains and develop the Population Information System [222]. Data on patients included in the ROB-FIN (n=2,567) were retrieved from aforementioned registers. All these national registries were linked to ROB-FIN using social security numbers providing extensive and reliable data on Finnish citizens in the real world setting. However, it is notable that study population is based on the ROB-FIN, which is a prospective cohort study designated to monitor effectiveness and safety of biological drugs in the treatment of rheumatic diseases. In 2010, it was estimated that the coverage of RA patients treated with bDMARDs in Finland is 60% in the ROB-FIN register [223]. When the RA patients who started their first, second or third TNF treatment between 2004 and 2014 were considered in the ROB-FIN register, the proportion of patients lost to follow-up within six months was 12%, whereas the proportion within 3 years was 30 % [224]. To eliminate the bias caused by confounders in the observational data, several regression models were used to predict the patients' treatment response, utility and costs in the simulation.

Another strength of the observational study (IV) was its prospective nature and that all adult IBD patients receiving maintenance IFX therapy were systemically switched to a biosimilar one whether they participated in the study or not. Prospective studies involve the planning of the study, and, therefore, they enable the collection of more detailed information, such as generic HRQoL measures. In contrast, retrospective studies use existing data, and the data have been designed in many cases for different purposes than the objectives of the study in question. This is also the case in the patient-level simulation model (III), and the QALYs were calculated corresponding to EQ-5D-3L utilities predicted from the HAQ scores obtained from the ROB-FIN registry data. Although prospective observational studies are more sensitive to bias than RCTs, they may provide valuable information for cost-effectiveness analyses and decision-makers [225,226]. Another advantage of the prospective observational study was its relatively long follow-up as both HRQoL and disease activity were measured at the time of switching and at 3 and 12 months later. Furthermore, both clinical and objective disease-specific measures were used to evaluate disease activity. It is also notable that study population in the prospective observational study consisted of IBD patients treated in a tertiary clinic, representing IBD patients most difficult to treat.

The patient-level simulation model (III) memorised changes in patient characteristics over time and enabled simulation based on the individual patient's history. The history of what had taken place was an important aspect of the model because it affected the occurrence of future events, their consequences and valuations, and many other aspects of the simulation. The simulation followed up patients for their entire lifetime, because RA is a chronic disorder that progresses over time. As such, the long-term consequences of any differences in disease progression, effect on life expectancy, or drug discontinuation rates were assessed. The first TNF inhibitor was not included in the patient-level simulation model (III) as it was assumed to be identical between the comparators and would not affect the results.

Because of the high costs of original bDMARDs, interest has grown in biosimilars that are comparable to the reference medicinal product in terms of efficacy and safety. Many original biological drugs have reached, or are approaching, patent expiry. This will lead to the increasing development and use of biosimilar drugs in the future, offering considerable savings in comparison with the reference medicinal product. Price competition after patent expiry may also reduce the price of reference

medicinal product, leading to remarkable cost savings. In the prospective observational study (IV), the aim was to assess the costs and effectiveness of the IFX biosimilar in the treatment of IBD patients in Finnish healthcare, whereas the biosimilars of ETA, IFX, and ADA were considered in the patient level simulation model (III). The patent of RTX has expired but the RTX biosimilar for the treatment of RA was not on the market in Finland at the time of writing the manuscript. However, the RTX biosimilar for RA is supposed to be on the market in Finland in the near future, and, therefore, the impact of the RTX biosimilar was evaluated on the results in the sensitivity analysis. In the sensitivity analysis, a price discount of 30% for the RTX biosimilar based on the Finnish legislation concerning the confirming a reasonable wholesale price for medicinal products was used [227], but the price discount may be even higher in the future.

6.3. Limitations of this study

A key limitation of the SLRs is that they were conducted in 2013/2014, and the field of biological drugs in the treatment of RA and IBD has changed remarkably since then. Therefore, the results of SLRs should be interpreted with caution. The intervention treatments included in the search strategy were limited to biological drugs that had been granted marketing authorisation by the EMA or FDA for the treatment of RA in March 2013 and for IBD in June 2014. However, it is notable that many biological drugs have reached marketing authorisation for the treatment of RA or IBD after the search strategies were completed. Therefore, the results of SLRs are not reliable in all respects today, and they do not give a comprehensive evaluation on the cost-effectiveness of biological drugs in the treatment of RA and IBD. The literature searches were updated in April 2019, and they identified 2,620 RA-related (I) and 1,860 IBD-related (II) articles published after the completion of original literature searches. However, it is obvious that all identified articles do not fulfil the inclusion criteria of SLRs. Although patients were stratified into several subgroups in the SLRs (I and II), methodological differences, such as heterogeneity in time horizons, discount rates, and perspectives, make a comparison of different CEAs difficult. It is also notable that the studies included in the SLR are conducted internationally, and, therefore, they may not be generalisable to the Finnish healthcare system.

According to the guideline of SLRs, selection of potential studies, data extraction, and quality assessment should be performed at least by two people independently. The SLR concerning RA (II) was performed by two independent assessors, whereas only one assessor was used in IBD-related SLR (II) and any ambiguity was resolved with a second assessor to avoid human mistakes and to improve the reliability of the study. However, it is obvious that a satisfactory technique for assessing risk of bias in individual studies included in SLR (II) was not used, and therefore, the SLR (II) does not fully meet the SLR criteria. However, the bias caused by the use of only one assessor was minimized as all ambiquities were resolved by consulting another assessor in SLR (II).

Although the main advantage of our patient-level simulation model (III) was that data on costs and effectiveness were based on the registry data, some limitations were related to the registry data used. Reasons for the discontinuation of RTX treatment were severely underreported in ROB-FIN data, and, therefore, the risk of adverse events was assumed to be equal across all treatment regimens. Moreover, the discontinuation probabilities for non-biological co-therapies were assumed to be similar between the users of different biological drugs. Patients' erosive progression could not be taken into account as data on this subject were not available in ROB-FIN. The effect could be mitigated by the inclusion of HAQ scores, which have been shown to be correlated with the presence

of joint erosions [228]. In comparison to the prospective observational study (IV), the lack of a generic HRQoL instrument could cause some bias in the patient-level simulation model (III). To see whether results were sensitive to the method of utility conversion in the patient-level simulation model (III), another conversion algorithm and valuation method were employed in the sensitivity analyses. As a result, the choice of algorithm had no effect on the results, whereas the QALYs decreased when health stages were valued with the British tariff.

In the patient-level simulation model (III), RA was associated with mortality of the general population. According to the study by Kroot et al., mortality of RA patients was comparable with the expected mortality of the general population of the Netherlands up to 10 years of RA [229]. This finding was in line with the study by Lindqvist and Eberhardt et al. [230]. Furthermore, Lacaille et al. found that the mortality gap between RA and the general population in the first 5 years was not observed in people with RA onset after year 2000 [231]. However, it is notable that the patient populations in these studies comprised patients with a recent onset of RA. Although mortality has decreased among RA patients over the past few decades, the general belief is that patients with RA, especially the more severe cases, have a shortened life expectancy compared with the general population [10,46]. It is assumed that the order of these results would have been the same, if the association between disease activity and mortality in RA patients had been considered in the model.

The most important limitation of the prospective observational study (IV) was a lack of a control group continuing originator IFX. Of the 252 eligible IBD patients, only 54 patients were included in the final analysis, and, therefore, another limitation of the study was a relatively small patient number. Although patient characteristics were similar between patients included and excluded from the final analysis, a weakness of this study was the unknown difference between non-participants (i.e. patients who did not return their informed consent and questionnaire at the time of switching) and participants. As patients did not return the informed consent, it was not possible to collect their clinical background information from the hospital records. Those who did not take part in the study may have been unaware of their symptoms and their impact on HRQoL. No productivity costs or outpatient drug costs were analysed in this study. The status of working and number of sickness leave days were not analysed in the study due to defective data.

7. CONCLUSIONS AND FUTURE RESEARCH

The aim of this study was to evaluate the costs, effectiveness, and cost-effectiveness of biological drugs in the treatment of RA and IBD. Based on this study, the following conclusions can be drawn:

Cost-effectiveness of biological drugs in the treatment of RA:

- When the analysis based on the Finnish observational data was conducted from the societal perspective, TNF inhibitors, ABA, and TOC were dominant in comparison to RTX in RA patients, who had been previously been treated with TNF inhibitors. No significant differences were observed in effectiveness between biological drugs. TNF inhibitors had the lowest costs and highest QALYs, and, therefore, they were the most cost-effective treatment option. In contrast, RTX was the most cost-effective treatment option among RA patients with an inadequate response to TNF inhibitors according to the SLR.
- Based on the SLR, biological drugs did not seem to be cost-effective among csDMARD naïve or csDMARD resistant RA patients with the cost-effectiveness threshold of 35,000 €/QALY, but they might be cost-effective among csDMARD resistant patients with the threshold of 50,000-100,000 €/QALY.

Cost-effectiveness of biological drugs in the treatment of IBD:

- Based on the SLR, biological drugs seemed to be cost-effective in the treatment of active and severe IBD.
- The Finnish observational data suggested that switching from originator IFX to a biosimilar one had no impact on HRQoL and disease activity in the maintenance treatment of IBD. When the healthcare provider perspective in the special healthcare setting was conducted, the costs of biosimilar IFX were significantly lower than the costs of originator one, and switching from originator IFX to a biosimilar one had no effect on costs related to secondary healthcare (excluding the costs of IFX).

Medical treatment, especially in the field of biological drugs, is changing fast in RA and IBD. Therefore, further research is needed to confirm the cost-effectiveness of all available biological drugs, including biosimilars, in the treatment of RA and IBD utilising real-world data. In addition, CEAs between different biological drugs are required to find the most cost-effective treatment strategy reflecting routine clinical practice for RA and IBD patients. The validated methods for the use of generic HRQoL measures would enable better comparison between CEAs.

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Saara Huoponen

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Appendix 1. Regression models to predict the patient´s treatment response, utility and costs in the patient-level simulation model (III)

das28-change, linear regression

Adjusted R-square: 0.6027

Coefficients	**Estimate**	**Standard Error**	**p-value**
Abatacept	-0.85	0.63	0.1755
Tocilizumab	0.38	0.48	0.4285
Rituximab	-1.67	0.41	0.0004 ***
Age	-0.01	0.00	<0.0001 ***
Sex	0.21	0.05	0.0001 ***
das28(baseline)	0.67	0.02	<0.0001 ***
HAQ(baseline)	-0.09	0.04	0.0422 *
Methotrexate	0.13	0.05	0.0054 **
Sulfasalazine	0.03	0.07	0.6162
Hydroxycloroquine	-0.01	0.06	0.8141
RF	0.01	0.06	0.8334
Time from diagnosis	-0.00	0.00	0.6287
Number of the biological drug	-0.14	0.04	0.0011 **
Primary responder	0.13	0.05	0.0076 **
BMI	-0.01	0.00	0.0129 *
No previous EULAR response	-0.47	0.08	<0.0001 ***
Previous EULAR moderate response	0.01	0.08	0.9263
Previous EULAR good response	0.71	0.08	<0.0001 ***
Visit time	0.08	0.02	<0.0001 ***
Abatacept:Age	0.01	0.01	0.0261 *
Tocilizumab:Age	-0.00	0.01	0.5814
Rituximab:Age	0.01	0.00	0.0108 *
Abatacept:Sex	0.02	0.17	0.8942
Tocilizumab:Sex	0.08	0.16	0.6366
Rituximab:Sex	-0.03	0.11	0.7796
Abatacept:das28(baseline)	0.09	0.06	0.0961 .
Tocilizumab:das28(baseline)	0.15	0.06	0.0079 **
Rituximab:das28(baseline)	0.08	0.03	0.0131 *
Abatacept:HAQ(baseline)	-0.03	0.11	0.7490
Tocilizumab:HAQ(baseline)	-0.01	0.12	0.9133
Rituximab:HAQ(baseline)	-0.03	0.08	0.7041
Abatacept:Methotrexate	-0.02	0.13	0.8836
Tocilizumab:Methotrexate	-0.30	0.14	0.0370 *
Rituximab:Methotrexate	-0.09	0.09	0.3098
Abatacept:Sulfasalazine	0.36	0.29	0.2228
Tocilizumab:Sulfasalazine	-0.00	0.16	0.9855
Rituximab:Sulfasalazine	-0.03	0.13	0.8211
Abatacept: Hydroxycloroquine	-0.30	0.15	0.0472 *
Tocilizumab: Hydroxycloroquine	0.22	0.16	0.1794
Rituximab: Hydroxycloroquine	-0.07	0.10	0.4927
Abatacept:RF	0.15	0.21	0.4593
Tocilizumab:RF	-0.05	0.15	0.7268
Rituximab:RF	0.04	0.17	0.8385
Abatacept: Time from diagnosis	-0.03	0.01	0.0002 ***
Tocilizumab: Time from diagnosis	0.01	0.01	0.3206
Rituximab: Time from diagnosis	0.00	0.01	0.3677
Abatacept:Number of the biological drug	0.10	0.09	0.2552
Tocilizumab:Number of the biological drug	0.03	0.08	0.7369
Rituximab:Number of the biological drug	-0.04	0.06	0.5539
Abatacept:Primary responder	-0.01	0.13	0.9448
Tocilizumab:Primary responder	0.02	0.15	0.8940
Rituximab:Primary responder	-0.00	0.09	0.9833
Abatacept:BMI	0.01	0.01	0.6564

Tocilizumab:BMI	-0.00	0.01	0.8376
Rituximab:BMI	0.03	0.01	0.0013 **
Abatacept: No previous EULAR response	0.39	0.22	0.0685 .
Tocilizumab: No previous EULAR response	-0.13	0.26	0.6148
Rituximab: No previous EULAR response	0.19	0.15	0.1865
Abatacept: Previous EULAR moderate response	0.26	0.20	0.2023
Tocilizumab: Previous EULAR moderate response	-0.31	0.24	0.2062
Rituximab: Previous EULAR moderate response	-0.09	0.15	0.5342
Abatacept: Previous EULAR good response	-0.13	0.19	0.5082
Tocilizumab: Previous EULAR good response	-0.68	0.19	0.0004 ***
Rituximab: Previous EULAR good response	-0.32	0.14	0.0259 *
Abatacept:Visit time	-0.03	0.05	0.5634
Tocilizumab:Visit time	0.007	0.05	0.8887
Rituximab:Visit time	0.05	0.04	0.1600

das28-change in the 6th line treatment, linear regression

Adjusted R-square: 0.5869

Coefficients	**Estimate**	**Standard Error**	**p-value**
Age	-0.01	0.00	<0.0001 ***
Sex	0.24	0.04	<0.0001 ***
das28(baseline)	0.70	0.01	<0.0001 ***
HAQ(baseline)	-0.11	0.03	0.0005 ***
Methotrexate	0.03	0.04	0.4285
Sulfasalazine	0.07	0.05	0.1450
Hydroxycloroquine	-0.04	0.04	0.3038
RF	-0.03	0.05	0.5639
Time from diagnosis	-0.00	0.00	0.2797
Primary responder	0.12	0.04	0.0011 **
BMI	-0.01	0.00	0.0182 *
No previous EULAR response	-0.43	0.06	<0.0001 ***
Previous EULAR moderate response	0.01	0.06	0.8467
Previous EULAR good response	0.67	0.06	<0.0001 ***
Visit time	0.07	0.01	<0.0001 ***

HAQ, linear regression

Adjusted R-square: 0.5231

Coefficients	**Estimate**	**Standard Error**	**p-value**
Abatacept	-1.65	0.50	0.0009 ***
Tocilizumab	-0.19	0.37	0.6046
Rituximab	1.10	0.40	0.0058 **
Age	-0.01	0.01	0.0353 *
Age^2	0.00	0.00	0.0022 **
Methotrexate	-0.02	0.02	0.3944
Sulfasalazine	-0.05	0.03	0.0885 .
Hydroxychloroquine	0.02	0.02	0.4416
Time from diagnosis	0.01	0.00	<0.0001 ***
RF	-0.03	0.03	0.2970
Sex	-0.09	0.02	0.0002 ***
HAQ(baseline)	0.46	0.02	<0.0001 ***
das28(baseline)	0.09	0.01	<0.0001 ***
das28-change	-0.06	0.01	<0.0001 ***
ACR 20 response	-0.22	0.03	<0.0001 ***
ACR 50 response	-0.37	0.03	<0.0001 ***
ACR 70 response	-0.61	0.04	<0.0001 ***
No previous ACR response	0.04	0.03	0.2852
Previous ACR 20 response	0.02	0.03	0.6202
Previous ACR 50 response	-0.06	0.04	0.1514
Previous ACR 70 response	-0.15	0.04	0.0003 ***
Primary responder	0.01	0.02	0.5108
BMI	0.01	0.00	<0.0001 ***
Visit time	0.02	0.01	0.0056 **
Abatacept:Age	0.05	0.02	0.0020 **
Tocilizumab:Age	0.04	0.01	0.0036 **

Rituximab:Age	-0.03	0.01	0.0128 *
Abatacept:Age^2	-0.00	0.00	0.0023 **
Tocilizumab:Age^2	-0.00	0.00	0.0084 **
Rituximab:Age^2	0.00	0.00	0.0163 *
Abatacept:Methotrexate	0.04	0.06	0.4948
Tocilizumab:Methotrexate	-0.23	0.06	0.0003 ***
Rituximab:Methotrexate	-0.02	0.04	0.6164
Abatacept:Sulfasalazine	0.35	0.13	0.0077 **
Tocilizumab:Sulfasalazine	0.31	0.07	<0.0001 ***
Rituximab:Sulfasalazine	-0.03	0.06	0.6367
Abatacept:Hydroxychloroquine	0.22	0.07	0.0010 **
Tocilizumab:Hydroxychloroquine	0.05	0.07	0.5013
Rituximab:Hydroxychloroquine	-0.02	0.05	0.6452
Abatacept: Time from diagnosis	-0.01	0.00	0.0636 .
Tocilizumab: Time from diagnosis	-0.00	0.00	0.2654
Rituximab: Time from diagnosis	0.00	0.00	0.8011
Abatacept:RF	0.02	0.09	0.8511
Tocilizumab:RF	0.06	0.07	0.3671
Rituximab:RF	0.20	0.08	0.0127 *
Abatacept:Sex	-0.01	0.07	0.9362
Tocilizumab:Sex	-0.25	0.07	0.0003 ***
Rituximab:Sex	-0.14	0.05	0.0045 **
Abatacept:HAQ(baseline)	0.04	0.05	0.2062
Tocilizumab:HAQ(baseline)	-0.27	0.05	<0.0001 ***
Rituximab:HAQ(baseline)	-0.03	0.03	0.4401
Abatacept:das28(baseline)	-0.01	0.03	0.8748
Tocilizumab:das28(baseline)	0.07	0.03	0.0394 *
Rituximab:das28(baseline)	0.00	0.02	0.8364
Abatacept:das28-change	-0.02	0.03	0.4724
Tocilizumab:das28-change	-0.03	0.03	0.3322
Rituximab:das28-change	-0.00	0.02	0.8957
Abatacept:ACR 20 response	0.06	0.08	0.4446
Tocilizumab:ACR 20 response	-0.03	0.08	0.6769
Rituximab:ACR 20 response	0.00	0.06	0.9463
Abatacept:ACR 50 response	0.21	0.09	0.0186 *
Tocilizumab:ACR 50 response	-0.22	0.08	0.0091 **
Rituximab:ACR 50 response	-0.03	0.06	0.6200
Abatacept:ACR 70 response	0.32	0.09	0.0005 ***
Tocilizumab:ACR 70 response	-0.10	0.10	0.3269
Rituximab:ACR 70 response	-0.06	0.07	0.3649
Abatacept:No previous ACR response	0.03	0.08	0.7430
Tocilizumab:No previous ACR response	0.07	0.09	0.3989
Rituximab:No previous ACR response	0.04	0.06	0.5516
Abatacept:Previous ACR 20 response	0.03	0.10	0.7874
Tocilizumab:Previous ACR 20 response	0.00	0.10	0.9688
Rituximab:Previous ACR 20 response	0.07	0.07	0.3263
Abatacept:Previous ACR 50 response	0.10	0.10	0.3483
Tocilizumab:Previous ACR 50 response	-0.08	0.10	0.4554
Rituximab:Previous ACR 50 response	0.02	0.08	0.7809
Abatacept:Previous ACR 70 response	0.16	0.10	0.1201
Tocilizumab:Previous ACR 70 response	0.08	0.12	0.4853
Rituximab:Previous ACR 70 response	0.02	0.82	0.7765
Abatacept:Primary responder	-0.08	0.06	0.1494
Tocilizumab:Primary responder	-0.35	0.07	<0.0001 ***
Rituximab:Primary responder	0.03	0.04	0.4020
Abatacept:BMI	0.01	0.01	0.0412 *
Tocilizumab:BMI	-0.01	0.00	0.2199
Rituximab:BMI	-0.01	0.00	0.1148
Abatacept:Visit time	-0.02	0.02	0.3719
Tocilizumab:Visit time	-0.01	0.02	0.6525
Rituximab:Visit time	-0.03	0.02	0.04572 *

HAQ in the 6th line treatment, linear regression

Adjusted R-square: 0.4883

Coefficients	**Estimate**	**Standard Error**	**p-value**
Age	-0.01	0.00	0.7642
Age^2	0.00	0.00	0.0961 .
Methotrexate	-0.04	0.02	0.0109 *
Sulfasalazine	0.02	0.02	0.4948
Hydroxycloroquine	0.05	0.02	0.0076 **
Time from diagnosis	0.01	0.00	<0.0001 ***
RF	-0.06	0.02	0.0050 **
Sex	-0.11	0.02	<0.0001 ***
HAQ(baseline)	0.45	0.01	<0.0001 ***
das28(baseline)	0.08	0.01	<0.0001 ***
das28-change	-0.04	0.01	<0.0001 ***
ACR 20 response	-0.22	0.02	<0.0001 ***
ACR 50 response	-0.41	0.03	<0.0001 ***
ACR 70 response	-0.64	0.03	<0.0001 ***
No previous ACR response	0.09	0.03	0.0001 ***
Previous ACR 20 response	0.09	0.03	0.0038 **
Previous ACR 50 response	-0.03	0.03	0.3499
Previous ACR 70 response	-0.10	0.03	0.0012 **
Primary responder	-0.02	0.02	0.1825
BMI	0.00	0.02	0.0023 **
Visit time	0.01	0.01	0.1093

ACR, ordered logistic regression

		95% CIs	
Coefficients	**Odds ratio**	**Lower**	**Upper**
Abatacept	0.19	0.01	2.30
Tocilizumab	1.129	0.19	6.96
Rituximab	0.019	0.00	0.07
Age	0.98	0.97	0.99
Sex	1.23	1.01	1.48
das28(baseline)	1.373	1.29	1.47
HAQ(baseline)	0.99	0.84	1.16
Methotrexate	1.06	0.90	1.25
Sulfasalazine	1.14	0.90	1.45
Hydroxychloroquine	1.03	0.84	1.26
RF	1.35	1.06	1.74
Time from diagnosis	0.99	0.98	1.00
Number of the biological drug	0.79	0.67	0.93
Primary responder	1.30	1.09	1.55
BMI	0.98	0.96	0.99
No previous ACR response	0.40	0.30	0.53
Previous ACR 20 response	1.38	1.03	1.84
Previous ACR 50 response	2.33	1.73	3.15
Previous ACR 70 response	6.26	4.53	8.67
Visit time	1.05	0.98	1.13
Abatacept:Age	1.02	1.00	1.05
Tocilizumab:Age	1.00	0.98	1.02
Rituximab:Age	1.02	1.01	1.04
Abatacept:Sex	0.94	0.50	1.76
Tocilizumab:Sex	0.18	0.66	2.13
Rituximab:Sex	1.29	0.86	1.92
Abatacept:das28(baseline)	1.11	0.90	1.37
Tocilizumab:das28(baseline)	1.02	0.83	1.25
Rituximab:das28(baseline)	1.12	0.99	1.26
Abatacept:HAQ(baseline)	0.94	0.64	1.39
Tocilizumab:HAQ(baseline)	1.21	0.77	1.90
Rituximab:HAQ(baseline)	0.90	0.68	1.20
Abatacept:Methotrexate	0.99	0.62	1.61
Tocilizumab:Methotrexate	0.91	0.53	1.56

Rituximab:Methotrexate	1.19	0.84	1.68
Abatacept:Sulfasalazine	0.98	0.31	2.93
Tocilizumab:Sulfasalazine	1.07	0.60	1.93
Rituximab:Sulfasalazine	0.50	0.31	0.80
Abatacept:Hydroxychloroquine	0.52	0.29	0.92
Tocilizumab:Hydroxychloroquine	0.87	0.48	1.58
Rituximab:Hydroxychloroquine	0.76	0.52	1.13
Abatacept:RF	2.77	1.15	7.07
Tocilizumab:RF	0.51	0.29	0.90
Rituximab:RF	1.50	0.74	3.20
Abatacept:Time from diagnosis	0.96	0.93	0.98
Tocilizumab:Time from diagnosis	1.01	0.98	1.04
Rituximab:Time from diagnosis	1.02	1.00	1.04
Abatacept:Number of the biological drug	1.26	0.94	1.70
Tocilizumab:Number of the biological drug	1.09	0.80	1.47
Rituximab:Number of the biological drug	1.10	0.88	1.39
Abatacept:Primary responder	1.08	0.68	1.73
Tocilizumab:Primary responder	0.81	0.46	1.41
Rituximab:Primary responder	0.95	0.67	1.35
Abatacept:BMI	0.97	0.92	1.03
Tocilizumab:BMI	1.01	0.96	1.05
Rituximab:BMI	1.05	1.02	1.08
Abatacept:No previous ACR response	1.78	0.85	3.72
Tocilizumab:No previous ACR response	0.66	0.32	1.35
Rituximab:No previous ACR response	1.08	0.65	1.80
Abatacept:Previous ACR 20 response	0.76	0.34	1.68
Tocilizumab:Previous ACR 20 response	0.38	0.18	0.79
Rituximab:Previous ACR 20 response	0.66	0.38	1.16
Abatacept:Previous ACR 50 response	1.13	0.50	2.55
Tocilizumab:Previous ACR 50 response	0.69	0.32	1.49
Rituximab:Previous ACR 50 response	0.45	0.25	0.81
Abatacept:Previous ACR 70 response	0.37	0.16	0.82
Tocilizumab:Previous ACR 70 response	0.49	0.20	1.21
Rituximab:Previous ACR 70 response	0.30	0.16	0.58
Abatacept:Visit time	1.16	0.97	1.39
Tocilizumab:Visit time	1.02	0.85	1.22
Rituximab:Visit time	1.10	0.96	1.26

ACR in the 6th line treatment, ordered logistic regression

		95% CIs	
Coefficients	**Odds Ratio**	**Lower**	**Upper**
Age	0.99	0.98	0.99
Sex	1.34	1.16	1.55
das28(baseline)	1.37	1.31	1.44
HAQ(baseline)	0.95	0.85	1.07
Methotrexate	1.05	0.93	1.19
Sulfasalazine	0.95	0.78	1.13
Hydroxychloroquine	0.92	0.79	1.07
RF	1.27	1.05	1.53
Time from diagnosis	0.99	0.98	1.00
Primary responder	1.21	1.06	1.38
BMI	0.99	0.97	1.00
No previous response	0.40	0.33	0.49
Previous ACR 20 response	1.14	0.92	1.42
Previous ACR 50 response	2.21	1.77	2.78
Previous ACR 70 response	5.07	3.97	6.49
Visit time	1.06	1.01	1.12

EQ-5D-3L, multinomial logistic regression

				95% CIs	
		Coefficients	**Odds Ratio**	**Lower**	**Upper**
Mobility	*No problems*		1		
	Some problems	Age	1.03	1.02	1.05
		Sex	0.83	0.61	1.13
		HAQ	59.76	30.93	115.43
		HAQ^2	0.41	0.28	0.60
	Extreme problems	Age	1.06	0.99	1.13
		Sex	0.371	0.07	1.86
		HAQ	324.09	0.16	658781.60
		HAQ^2	0.64	0.11	3.83
Self-care	*No problems*		1		
	Some problems	Age	1.00	0.99	1.02
		Sex	0.33	0.21	0.52
		HAQ	541.90	0.01	2051.60
		HAQ^2	0.33	0.19	0.57
	Extreme problems	Age	1.05	1.00	1.11
		Sex	0.14	0.04	0.49
		HAQ	132.26	2.33	7496.22
		HAQ^2	0.94	0.31	2.81
Usual activities	*No problems*		1		
	Some problems	Age	1.00	0.99	1.01
		Sex	0.79	0.56	1.13
		HAQ	131.77	62.99	275.67
		HAQ^2	0.36	0.23	0.56
	Extreme problems	Age	1.01	0.98	1.04
		Sex	0.54	0.24	1.21
		HAQ	748.22	94.63	5916.21
		HAQ^2	0.40	0.20	0.78
Pain/discomfort	*No problems*		1		
	Some problems	Age	1.01	0.99	1.02
		Sex	0.92	0.67	1.27
		HAQ	95.98	45.64	201.86
		HAQ^2	0.26	0.19	0.35
	Extreme problems	Age	0.97	0.95	0.10
		Sex	0.47	0.23	0.96
		HAQ	2977.60	537.86	16484.00
		HAQ^2	0.16	0.10	0.28
Anxiety/depression					
	No problems		1		
	Some problems	Age	0.99	0.98	1.00
		Sex	0.90	0.658	1.25
		HAQ	4.61	2.75	7.70
		HAQ^2	0.78	0.65	0.95
	Extreme problems	Age	0.93	0.89	0.97
		Sex	0.37	0.12	1.22
		HAQ	5.51	0.65	46.99
		HAQ^2	1.14	0.58	2.22

Outpatient and inpatient costs, linear regression

Adjusted R-square: 0.3455

Coefficients	**Estimate**	**Standard Error**	**p-value**
Age	-3.80	19.71	0.8470
Age^2	0.04	0.19	0.8366
RF	-191.88	113.40	0.0906
Sex	654.14	213.50	0.0022 **
HAQ	1262.39	424.91	0.0030 **
das28	-32.48e	201.43	0.8719
BMI	24.08	8.08	0.0029 **
Outpatient and inpatient costs during the last 12 months	0.44	0.05	<0.0001 ***

Outpatient and inpatient costs during the last 12 months^2	-0.00	0.00	0.0096 **
Age:HAQ	-41.65	14.93	0.0053 **
Age:das28	12.27	7.65	0.1087
Age: Outpatient and inpatient costs during the last 12 months	-0.00	0.00	0.0010 ***
Age: Outpatient and inpatient costs during the last 12 months^2	0.00	0.00	0.0009 ***
Age^2:HAQ	0.03	0.13	0.0177 *
Age^2:das28	-0.13	0.07	0.0637 .
Age^2: Outpatient and inpatient costs during the last 12 months^2	-0.00	0.00	0.0016 **
RF:das28	106.12	41.68	0.0109 *
RF: Outpatient and inpatient costs during the last 12 months	0.04	0.01	0.0004 ***
Sex:HAQ	93.28	57.36	0.1039
Sex:BMI	-20.65	7.72	0.0075 **
Sex: Outpatient and inpatient costs during the last 12 months	-0.06	0.02	0.0002 ***
Sex: Outpatient and inpatient costs during the last 12 months^2	0.00	0.00	0.0017 **
HAQ:das28	95.85	18.90	<0.0001 ***
HAQ: Outpatient and inpatient costs during the last 12 months	-0.02	0.00	0.0006 ***
das28:BMI	-5.88	2.51	0.0190 *
das28: Outpatient and inpatient costs during the last 12 months	0.03	0.01	<0.0001 ***
das28: Outpatient and inpatient costs during the last 12 months^2	-0.00	0.00	<0.0001 ***
BMI: Outpatient and inpatient costs during the last 12 months	-0.00	0.00	0.0003 ***
BMI: Outpatient and inpatient costs during the last 12 months^2	0.00	0.00	0.0006 ***

Indirect costs, linear regression

Adjusted R-square: 0.2865

Coefficients	**Estimate**	**Standard Error**	**p-value**
Age	-2282.37	461.60	<0.0001 ***
Age^2	51.00	10.93	<0.0001 ***
RF	-4787.43	1766.04	0.0068 **
Sex	328.52	1157.20	0.7765
HAQ	-12970.19	4451.32	0.0036 **
das28	1039.96	361.02	0.0040 **
BMI	97.16	84.75	0.2517
Outpatient and inpatient costs during the last 12 months	-1.60	0.70	0.0226 *
Outpatient and inpatient costs during the last 12 months^2	-0.00	0.00	0.6271
Age: Age^2	-0.30	0.08	0.0003 ***
Age:HAQ	701.03	184.30	0.0001 ***
Age: Outpatient and inpatient costs during the last 12 months	0.08	0.03	0.0050 **
Age^2:Sex	0.85	0.37	0.0209 *
Age^2:HAQ	-6.46	1.90	0.0007 ***
Age^2:das28	-0.23	0.12	0.0487 *
Age^2:BMI	-0.08	0.03	0.0068 **
Age^2: Outpatient and inpatient costs during the last 12 months	-0.00	0.00	0.0060 **
RF:Sex	-2816.79	929.60	0.0025 **
RF:BMI	208.17	66.20	0.0017 **
HAQ:das28	-277.07	159.02	0.0816 .
HAQ: Outpatient and inpatient costs during the last 12 months^2	-0.00	0.00	0.0019 **
das28: Outpatient and inpatient costs during the last 12 months	-0.09	0.05	0.0471 *
das28: Outpatient and inpatient costs during the last 12 months^2	0.00	0.00	0.0008 ***
BMI: Outpatient and inpatient costs during the last 12 months	0.02	0.01	0.0492 *
BMI: Outpatient and inpatient costs during the last 12 months^2	-0.00	0.00	0.0180 *
Outpatient and inpatient costs during the last 12 months: Outpatient and inpatient costs during the last 12 months^2	0.00	0.00	0.0113 *

ACR=American College of Rheumatology, BMI= Body Mass Index, das28=Disease Activity Score 28, EULAR= European League Against Rheumatism, HAQ= Health Assessment Questionnaire, RF=Rheumatoid Factor

Signifance codes: *** < 0.001, ** < 0.01, * < 0.05, . < 0.1