Comparative Effectiveness of Pharmacological Therapies for the Treatment of Moderate to Severe Crohn's Disease

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DEDICATION

I dedicate this work to my beloved mother, Isabelle Abboud, who showed me the way and who was a model of strength, courage, determination and an endless source of unconditional love.

Je dédie ce travail à ma mère chérie, Isabelle Abboud, qui m'a montré le chemin et qui a été un modèle de force, de courage, de détermination et surtout une source inépuisable d'amour inconditionnel.

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ABSTRACT

Background and aims:

Network meta-analysis allows to draw inferences about the relative efficacy of different agents, even in the absence of head-to-head clinical trials. The purpose of this research was to assess the comparative effectiveness of therapies used for the induction of remission in adult patients with moderate to severe Crohn's disease based on a network meta-analysis.

Methods:

A systematic review (SR) of MEDLINE, EMBASE, Cochrane Central Register of RCT/ SR, and Clinicaltrials.gov was performed from 1990 to October 2015. Twenty-eight randomized controlled trials were identified comparing corticosteroids, immuno-suppressants and biologic agents either with an active comparator or with placebo. Relative treatment effects were estimated using a Bayesian random-effects network meta-analysis and were reported as odds-ratio (OR) with 95% credible interval (CrI).

Results:

Aadalimumab, the combination of infliximab and azathioprine (IFX_AZA), budesonide, infliximab, natalizumab, prednisone, vedolizumab and the combination of infliximab and natalizumab (NTZ_IFX) were superior to placebo for induction of remission. On the other hand, immunosppressants (azathioprine, 6-mercaptopurine, methotrexate), the combination of infliximab and methotrexate (IFX_MTX) and two biologic agents, certolizumab and ustekinumab did not show a statistically significant difference when compared to placebo. Results for ustekinumab, NTZ_IFX and IFX_MTX are based on one trial and should be considered with caution.

The combination of IFX_AZA was the most effective treatment with statistically significant results when compared to immuno-suppressants (6-mercaptopurine, azathioprine and methotrexate) and to the biologic agents certolizumab and natalizumab. Among monotherapies, prednisone was superior to 6-MP, CTZ, MTX, NTZ; infliximab

was superior to AZA, CTZ, MTX; adalimumab was superior to CTZ, MTX, NTZ and finally, budesonide was superior to CTZ and MTX.

The ranking showed IFX_AZA to have the highest probability of being ranked best treatment (36%) followed by NTZ_IFX (33.6%) and by prednisone (16.5%). The surface under the cumulative ranking curve also showed IFX_AZA to be best overall with a SUCRA value of 91.89%, NTZ_IFX to be second best (83.51%) and prednisone third best (82.12%). The results of NTZ_IFX should be considered with caution given they were based on one trial with a small number of patients, totaling 79.

Conclusion:

Based on this network meta-analysis the combination of infliximab and azathioprine was the most effective therapy for inducing remission in patients with moderate to severe Crohn's disease.

ABRÉGÉ

Contexte et objectifs :

La méta-analyse en réseau permet de tirer des conclusions sur l'efficacité relative de différents agents, même en l'absence d'essais cliniques en tête à tête. Le but de cette recherche était d'évaluer l'efficacité relative des thérapies utilisées pour l'induction de la rémission chez des patients adultes atteints d'une maladie de Cohn modérée à sévère, selon une méta-analyse en réseau.

Méthodes :

Une revue systématique (SR) de MEDLINE, EMBASE, Cochrane Central Register of RCT/SR et Clinicaltrials.gov a été réalisée de 1990 à octobre 2015. Vingt-huit essais contrôlés randomisés ont été identifiés comparant des stéroïdes, des immunosuppresseurs et des agents biologiques avec un comparateur actif ou avec placebo. Les effets relatifs des traitements ont été estimés à l'aide d'une méta-analyse en réseau bayésienne avec système d'effets aléatoires et ont été rapportés comme rapport de cotes (OR) avec 95% d'intervalle plausible (CrI).

Résultats :

Adalimumab (ADA), la combinaison d'infliximab et d'azathioprine (IFX_AZA), budésonide (BUD), infliximab (IFX), natalizumab (NTZ), prednisone (PRED), vedolizumab (VDZ) et la combinaison de l'infliximab et du natalizumab (NTZ_IFX) étaient supérieurs au placebo pour l'induction de la rémission. Par contre, les immuno-supppresseurs (azathioprine (AZA), 6-mercaptopurine (6-MP), méthotrexate(MTX)), la combinaison de l'infliximab et du méthotrexate (IFX_MTX) et les agents biologiques, certolizumab (CTZ) et ustekinumab (UST) n'ont démontré aucune différence statistiquement significative en comparaison au placebo. Les résultats pour l'ustekinumab, NTZ_IFX et IFX_MTX sont basés sur un essai clinique et doivent être considérés avec prudence.

IFX_AZA a été le traitement le plus efficace avec une supériorité statistiquement significative comparée aux immunosuppresseurs (6-MP, AZA et MTX) et aux deux agents biologiques, CTZ et NTZ. Parmi les monothérapies, la prednisone était supérieure au 6-MP, CTZ, MTX, et NTZ; l'infliximab était supérieur au AZA, CTZ, et MTX; l'adalimumab était supérieur au CTZ, MTX, et NTZ et le budesonide était supérieur au CTZ et MTX.

Le classement a montré que la combinaison IFX_AZA avait la plus grande probabilité d'être classé le meilleur traitement (36%) suivi de la combinaison NTZ_IFX (33,6%) et de la prednisone (16.5%). La surface sous la courbe de classement cumulatif a également montré que IFX_AZA était au premier rang du classement avec une valeur SUCRA de 91.89%, la combinaison du NTZ_IFX était au deuxième rang (83.51%) et la prédnisone au troisième rang (82.12%). Les résultats de la combinaison du NTZ_IFX doivent être considérés avec prudence étant donné qu'ils sont basés sur un essai clinique avec un petit nombre de patients (total de 79).

Conclusion :

Sur la base de cette méta-analyse en réseau, la combinaison de l'infliximab et de l'azathioprine était la thérapie la plus efficace pour induire la rémission chez les patients atteints de maladie de Crohn modérée à sévère.

PREFACE

FORMAT OF THE THESIS

This thesis in the traditional style comprises the following sections: an introduction, a review of key aspects of Crohn's disease, a background on systematic review and network meta-analysis, the results of the data analysis with a final discussion and conclusion, and all cited publications and appendices.

CONTRIBUTION OF AUTHORS

The original idea of using a network meta-analysis (NMA) for this thesis was introduced by my supervisor Dr. John Sampalis. I built on this idea and explored its application to Crohn's disease, given a personal interest in autoimmune diseases. The research protocol was developed with input from Dr. John Sampalis and from the Research Advisory Committee members: Dr. Jacques Lapointe, Dr. Moishe Liberman, Dr. Sender Liberman and Dr. Georges Tsoukas.

From the beginning of my research, I designed automated, ongoing literature searches to keep abreast of relevant NMA concepts and developments throughout my thesis years. This allowed me to acquire the statistical knowledge needed in this area to design the statistical methodology for my research. Mrs. Nazi Torabi, McGill Library, helped in the development of the search strategy for the systematic review. I performed the studies' selection, data abstraction and quality assessment. Mrs. Lin Yang, JSS Medical Research, created the SAS program for the Generalized Estimation Equation technique and the R (gemtc) programs for the NMA statistics. I took a course in R programming with the department of family medicine, McGill University, which allowed me to write the R routines for the pairwise and sensitivity analyses for the research. Dr. John Sampalis, provided technical guidance for the statistical analysis and feedback throughout the process.

I performed the interpretation of the results and I am the single author of all chapters in this thesis. Dr. John Sampalis reviewed and provided comments on the thesis document.

STATEMENT OF ORIGINALITY

To my knowledge, this is the first work to compare all pharmacological agents indicated for the treatment of adult patients with moderate to severe Crohn's disease in a network meta-analysis. Despite the advancement in the knowledge of Crohn's disease and the considerable improvement

in the clinical management of patients, a question remains today as to which pharmacological strategy, a step-up or a top-down, is best for the patient. By including all agents in one analysis, this research contributes to the knowledge regarding the positioning of the different agents according to their relative efficacy in inducing remission in those patients and hence, to answer a public health care need that has not yet been clearly answered.

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LIST OF ABBREVIATIONS

$\bar{D}_{res}$	Mean residual deviance
5-ASA	5-aminosalicylates
6MP	6-mercaptopurine
ACG	American College of Gastroenterology
ACTH	Adrenocorticotropic hormone
ADA	Adalimumab
AGA	American Gastroenterology Association
AHRQ	Agency for Healthcare Research and Quality
anti-TNF∝	anti-tumor necrosis factor
ASCA	Saccharomyces cerevisiae antibodies
AZA	Azathioprine
AZA_IFX	Combination of azathioprine and infliximab
BSG	British Society of Gastroenterology
BUD	Budesonide
CAG	Canadian Association of Gastroenterology
CBirl	Flagellin
CD	Crohn disease
CDAI	Crohn disease activity index
CDAS	Crohn's disease activity score
CDEIS	Crohn's Disease Endoscopic Index of Severity
CI	Confidence interval (s)
CrI	Credible interval (s)
CRP	C-reactive protein
CS	Corticosteroids
CT	Computed tomography
CTZ	Certolizumab
DIC	Deviance information criterion
DNA	Deoxyribonucleic acid
ECCO	European Crohn's and Colitis Organization

EMBASE	Excerpta Medica dataBASE
EMTREE	Elsevier's biomedical expert subject headings
ESR	Erythrocyte sedimentation rate
FC	Fecal lactoferrin
FDA	U.S. Food and Drug Administration
GEE	Generalized estimating equation
GeMTC	Graphical user interface for network meta-analysis with R
GLM	Generalized linear model
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HBI	Harvey Bradshaw index
IBD	Inflammatory bowel disease
IFX	Infliximab
IFX_MTX	Combination of infliximab and methotrexate
IS	Immuno-suppressants
IV	intravenous
MA	Pairwise meta-analysis (es)
MaRIA	Magnetic resonance index of activity
MCMC	Markov Chain Monte-Carlo
MEDLINE	Medical Literature Analysis and Retrieval System Online
MEGS	MRE global score
MeSH	Medical Subject Headings
miRNA	Micro ribonucleic acid
MRE	Magnetic resonance enterography
mRNA	Messenger ribonucleic acid
MTX	Methotrexate
NICE	National Institute for Health and Care Excellence
NMA	Network meta-analysis (es)
NTZ	Natalizumab
NTZ_IFX	Combination of natalizumab and infliximab
OmpC	Other membrane protein C
OR	Odds ratio (s)

OVID	Grey literature database
P	Placebo
pANCA	Perinuclear anti-neutrophil cytoplasmic antibodies
PICO	Participants, intervention, comparator, outcome
PICOS	Participants, intervention, comparator, outcome, study design
PML	Progressive multifocal leukoencephalopathy
PRED	Prednisone
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analysis
PRO	Patient-reported outcomes
psrf	Potential scale reduction factor
PubMed	Publisher/public MEDLINE
QoL	Quality of life
R	Open source programming language and software environment
RCT	Randomized controlled trials
rjags	Just Another Gibbs Sampler
ROB	Risk of bias
RR	Risk ratio (s)
SAS	Statistical Analysis Software
SES	Simple Endoscopic Score
SES-CD	Simple Endoscopic Score in Crohn's disease
SIGN	Scottish Intercollegiate Guidelines Network
SR	Systematic review (s)
SUCRA	Surface under the cumulative ranking curve
UC	Ulcerative colitis
UME	Unrelated mean effects
UST	Ustekinumab
VDZ	Vedolizumab

INTRODUCTION

Crohn's disease (CD) is a chronic, inflammatory, multifactorial disease whose symptoms and complications lead to significant morbidity, mortality and impact on patient's social, personal and professional quality of life. CD is difficult to diagnose as it presents with clinical symptoms like diarrhea, fatigue, weight loss, abdominal and stomach pain that are common to other conditions such as irritable bowel syndrome, celiac disease, ulcerative colitis, or infection.

Once the appropriate exams and tests are made and a definitive diagnosis is placed, the treating physician is faced with the challenge of finding the medication(s) that will help induce remission, and keep the patient's symptoms under control while ensuring a good benefit/risk ratio with the right balance between the drug's side effects and its efficacy in controlling the patient's symptoms.

Since CD is heterogeneous, involving different etiology/pathology characteristics in individuals, the patient's response to treatment and the disease's progression are today unpredictable, an obstacle that future advances in genomic and in other "Omics" research areas are expected to resolve. Nevertheless, physicians rely on identified patterns which consider the patient's age at diagnosis and the disease location, severity and behavior to determine the best therapeutic treatment. Generally, physicians and patients may have to go through trials of medications or a "combination of" to control the disease's symptoms and to achieve mucosal healing. Even when remission is achieved, "flare-ups" or complications may happen as the disease progresses, necessitating changes to the treatment plan or surgeries.

With the introduction of biologics for the treatment of CD, physicians have today a multitude of drug options to choose from to help patients live without symptoms. However, despite the clinical evidence that is already available, many questions remain as to what is the optimal treatment and to which patient, as a monotherapy or in combination with other drugs, and when to initiate a treatment or to introduce a change. Another question physicians are faced with is whether a step-up treatment plan, i.e. starting with less costly and toxic drugs, then adding or changing the treatment if the symptoms are not controlled, or a top-down therapy plan, i.e. starting with biologics and immune-modulators, would be a more beneficial approach for a given patient.

The lack of head-to-head trials adds to the challenge physicians face in identifying the

optimal treatment for a given patient. Pairwise meta-analyses (MA) are generally used to help in the decision-making process. Nevertheless, a limitation of these analyses is their inability to compare more than two treatments at a time (pairwise comparisons) and therefore they do not help answer the question of how all treatments compare to each other and which one is the best.

More recently, "network meta-analyses" (NMA) (also called "mixed-treatment comparisons" or "indirect treatment comparisons") have been developed to enable comparison of multiple interventions in a single statistical model. By pooling both direct and indirect evidence from trials that include a common comparator, NMA provide estimates of the differences in treatment effects among the competing drugs whether they have been compared in head-to-head trials or not. With the appropriate assumptions, NMA can strengthen inference by borrowing strength from indirect evidence to produce more precise estimates of treatment effects than standard pairwise MA. NMA also enable the ranking of the treatment options based on probabilities' estimate of one treatment being the best or second etc. for a given outcome.

Thirteen NMA[1-13] have already been conducted to assess the comparative efficacy or safety of different agents for the treatment of Crohn's disease, seven in patients with moderate to severe CD and six in patients mild to moderate CD or post-surgery. Of those published in 2017, one evaluated the efficacy of amino-salicylates vs corticosteroids[1] in mild to moderate CD and the second assessed mucosal healing with biologic drugs in patients with moderate to severe CD[8]. However, none of the NMA has evaluated, in a single analysis, the efficacy of all agents that are recommended for the treatment of moderate to severe CD.

This research, conducted as part of a Ph.D. program with the department of Experimental Surgery at McGill University, includes a review of the evolution of CD therapeutic management as well as a systematic review and NMA of trials published between 1990 and October 2015 of all agents used for the treatment of adult patients with moderate to severe CD. This research is today unique in that it is a comprehensive analysis of all recommended treatments for moderate to severe CD based on the available evidence during the search period.

OBJECTIVES

The specific objectives are:

I. To conduct a comparative effectiveness research on pharmacological agents used to treat adult patients with moderate to severe CD. This research will include the following steps:
   I.1. A systematic review of the literature to identify randomized controlled trials of pharmacologic drugs in patients with moderate to severe CD that were published between 1990 and December 2015
   I.2. To use NMA methodologies to calculate the relative effect estimates of all pharmacological drugs used for the treatment of adult patients with moderate to severe CD. The objectives are the following:
      I.2.1. To compare the effectiveness of treatments in inducing remission in active CD
      I.2.2. To attribute a ranking to each treatment by calculating the probability that each treatment is the best among the other treatments included in the network

1. REVIEW OF CROHN'S DISEASE AND ITS THERAPEUTIC MANAGEMENT

1.1. Crohn's Disease as a Subtype of IBD

Inflammatory bowel disease (IBD) comprises a group of conditions with two major subtypes: Crohn's disease (CD) and ulcerative colitis (UC). Both diseases are characterized by chronic, progressive and relapsing intestinal inflammation[14-16]. The pathogenesis of IBD is multifactorial and involves interactions between unknown environmental triggers, the gut microbiota and the patient's DNA[17,18]. IBD is a lifelong disease, that may occur between childhood and late adulthood although it affects primarily young people, with 80% of cases being diagnosed in patients 20-30 years of age[19]. Although CD and UC have many clinical and pathological features in common, they differ in terms of behavior, location and histological findings[14-16].

CD, as opposed to UC, may affect any part of the gastrointestinal tract, from the mouth to the anus, but is often located in the terminal ileum (40% to 70%)[19]. In CD, the inflammation is characterized by isolated, patchy lesions and can extend from the inner to the outer lining of the intestinal wall. UC presents as continuous inflammation (as opposed to patches) and only affects portions of the large intestine (colon), including the rectum and the anus. In UC, the inflammation is generally confined to the mucosa[19]. Patients with more severe IBD, may also have extra-intestinal manifestations affecting mainly the joints, skin, eyes, mouth as well as the liver or bile ducts.

1.2. Disease Classification

Disease classification is an important step in the identification of differences in the characteristics and behavior of CD. The Montreal classification[20] (Table 1), issued by the Working Party of investigators at the World Congress of Gastroenterology in 2005, classified CD based on age at onset, disease location and disease behavior. This classification, which was a revision to the Vienna classification, has allowed a subcategory for patients whose age at diagnosis is 16 years or less, to reflect available evidence on different serotypes or genotypes in early onset CD. It has also added a subcategory for isolated upper gastrointestinal disease, making the other categories (L1 – L3) non-exclusives and accounting for the fact that upper disease can coexist with other disease locations. This classification has also created a new subcategory for perianal disease within the category "behavior" to account for data showing that perianal fistulas can exist without intestinal fistulas. These changes were thought to reflect findings from new studies, from clinical observations and from new investigational techniques[21]. The Montreal classification is advocated by current guidelines while acknowledging its limitations.

Table 1: Montreal Classification of Crohn's Disease

Age at diagnosis	- A1 < 16 y - A2 17 y to 40 y - A3 > 40 y
Location	- L1 ileal - L2 colonic - L3 ileocolonic - L4 isolated upper disease
Behavior	- B1 non-stricturing, non-penetrating - B2 stricturing - B3 penetrating - P perianal disease modifier

L4 can be added to L1 - L3 when both present
p can be added to B1 - B3 when both present

1.3. Disease Natural Course

The natural course of CD may involve lesions, symptoms with increasing severity, complications such as abscesses, fistulas and strictures, surgery, increasing disability and mortality[19]. Different studies have shown that age and phenotype at diagnosis are important predictors of disease course[14,19,22-25].

In general, it has been shown that ileitis or ileocolic disease, upper gastrointestinal involvement, age< 40 years, perianal lesions and need for corticosteroids at diagnosis were major predictors for a disabling course of disease involving the development of complications and need for surgery[19,22-24,26,27].

1.3.1 Disease Location

At the time of diagnosis, 30% of patients with CD have either ileitis or colonic disease and 40% have ileocolic disease. Five to fifteen percent have associated upper gastrointestinal lesions and 20-30% have perianal lesions[14,19]. The location of disease remains generally stable with only 10-15% of patients experiencing a change in their lesions' location after 10-years of follow-up[28]. In a prospective population-based study of a cohort of 200 patients with CD from Norway, 27% had ileitis, 45% had colitis, 26% had ileocolic and 4% had upper gastrointestinal disease at the time of diagnosis. After five years of follow-up, 14% had a change in their disease location with 23% having ileitis, 37% having colitis, 38% having ileocolic and 6% having upper gastrointestinal disease[23]. A certain number of patients with CD end up developing perianal lesions and fistula. Perianal lesions were observed in 20%-30% and fistula in 15%-20% of patients with CD[29-31].

1.3.2 Disease Behavior

At time of diagnosis, patients will generally not have a penetrating disease or strictures but most will develop strictures and penetrating lesions during follow-up. It was noted that 50% of patients will have a stable course of disease, whereas the remaining will suffer from complications often requiring hospitalization and surgery[23,26]. This evolution towards more

complications has been linked to the lesion's initial localization, with small bowel lesions being more associated with abscesses, fistula and strictures than colonic lesions which remain uncomplicated for several years[19].

This was observed in a population-based study from Olmstead County, Minnesota, where ileitis and ileocolic lesions at diagnosis were 5 to 7 times more likely than colonic disease to evolve from non-penetrating/non-fistulizing diseases to diseases with fistula, abscess or stricture[29]. The risk of fistula development has been estimated to range from 20 to 40 % during the lifetime of patients with CD[32].

The population-based study from Norway has also shown that terminal ileum and upper gastrointestinal locations at diagnosis correlated with higher risk of strictures during follow-up, whereas penetrating complications were associated with age < 40 at diagnosis. In this study, 53% of the patients had developed strictures or penetrating disease at 10-year follow-up. Ileum location, strictures or penetrating behavior and age < 40 at diagnosis were also found to be independent risk factors for bowel surgery during follow-up[23].

In another European population-based study (EC-IBD) of a cohort of 358 patients with CD, those with upper gastrointestinal disease at diagnosis had an increased risk of relapse, whereas age > 40 and colonic disease were associated with a lower risk of complications[24].

1.3.3 Disease Complications

CD is associated with a high rate of hospitalization and surgery. In the Olmstead County population-based study of a cohort of 211 patients with CD, diagnosed between 1970-1997, 129 patients (57%) were hospitalized at least once and the cumulative risk of any hospitalization for CD were 32%, 52% and 62% at 1 year, 5 years and 10 years, respectively[33].

In the Copenhagen County population-based study of CD patients diagnosed between 1962 and 1987, 83% of the patients were hospitalized at least once within the first year of diagnosis but this rate declined to a constant 20% each year during the subsequent 5 years[34].

Studies conducted over different time periods covering the pre-biological era and the post-biological era have indicated a decrease in the rates of hospitalizations and surgeries. A population-based study from Canada[35] , has reported a decline in the hospitalization rate from 29.2 per 100,000 population in 1994-1995 to 26.9 per 100,000 population in 2000-2001. However, the impact of medications on the rate of CD hospitalization was not part of the study

analyses.

As for surgeries, in Norway, the South-Eastern study[23] of a cohort of 197 patients with CD has reported a cumulative probability of surgery of 13.6%, 27% and 37.9% at 1, 5 and 10 years after diagnosis, respectively. In this study, surgery was strongly associated with a terminal ileum lesion, with strictures or penetrating disease and with age < 40 years at diagnosis. There was no association between surgery and colonic lesion or simple inflammatory disease. Of the 197 patients in this cohort, 38% had required at least one surgery and 9% had required 2 or more during the 10-year follow-up[23].

Slightly higher rates were reported in the Olmstead County study[36] and in a study from Denmark[37] where the surgical rates observed were 58% after a median time of 13.2 years and of 55% after 10 years, respectively. The overall cumulative risk for surgery reported in a Europe-wide population- based study[38] was of 40-55% 10 years after diagnosis. The risk of a second or more operations reported in the Norway[23] and Denmark[37] population-based studies were 9% and 13%, respectively 10 years after diagnosis. Recurrence of disease or relapse has been observed in a high number of patients who underwent surgeries. A Scandinavian population-based study[34] has reported disease recurrence and a need for second operation in 30% of patients 10 years after their first surgery. The postoperative recurrence rates observed in a retrospective population-based study[39] of a cohort of 1936 patients with CD in Sweden were 33% and 44% at 5 and 10 years after resection and these post-operative relapse rates remained unchanged over time.

1.3.4 Disease Mortality

A meta-analysis[40] has shown that CD was associated with an increased risk of death compared to the general population with a pooled estimate for the standardized mortality ratio of 1.52. The analysis has also shown that the risk of mortality has decreased over the last 30 years; however, this decrease was not statistically significant. These results have suggested that advances in medical and surgical treatments have not resulted in a significant impact on the prognosis of CD[19].

1.4. Treatment Goals and Disease Activity Assessment

With the increasing evidence that inflammation in the bowels persists even in the absence of

gastrointestinal symptoms and the introduction of drugs proven to heal the mucosa, the goals of treating patients with CD has evolved over the years from controlling clinical symptoms to mucosal healing and more recently to deep remission, defined empirically as a steroid-free clinical remission (CDAI < 150), a biological remission (CRP < 5.0 mg/L) and a complete mucosal healing (absence of ulcers)[41]. This definition has been challenged on the basis that mucosal healing or absence of ulcers by itself is not indicative of absence of inflammation and that histological healing may be necessary to confirm deep remission.

1.4.1 Symptoms Assessment

Symptomatic remission is usually measured using either the Crohn Disease Activity Index (CDAI) or the Harvey Bradshaw Index (HBI). The CDAI was developed in 1970's[42] to assess disease severity in patients with CD mainly in clinical trials setting. The HBI[43] was designed in the 1980's with the idea of simplifying data collection and computation found to be quite complicated using the CDAI. The CDAI is still the index most used in clinical trials and for regulatory approval of pharmacologic agents. It includes 8 variables three of which are based on a 1-week patient diary (pain, stool frequency, well-being). The CDAI total score is calculated by adding the score of each variable after adjustment with a weighting factor and for the presence of complications[42]. Its values range from 0 to 600. In clinical trials, remission or quiescent disease is defined as a CDAI score < 150 and relapse refers to a CDAI value of ≥ 150. Response to treatment is measured as either a 70-point or 100-point decrease in CDAI score from baseline.

The CDAI score is also used to classify the severity of disease where a value of 150-219 is mild disease, 220 – 450 is moderate to severe and > 450 is extremely severe disease. As for the HBI, it includes 5 clinical parameters (general well-being, complications, abdominal mass, abdominal pain and number of liquid stools for the previous day) with an adjustment of the score in the presence of complications. A score of < 5 represent clinical remission[43]. A correlation was found between the CDAI and the HBI scores, with an HBI ≤ 4 being equivalent to a CDAI score ≤ 150[44].

1.4.2 Biomarkers Assessment

Few serologic and stool biomarkers have been identified as being useful indicators for disease activity and progression including C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), fecal calprotectin (FC), and fecal lactoferrin (FL)[45]. CRP and ESR are non-specific markers of inflammation that can be elevated in patients with IBD as well as in patients with other conditions[46-48].

CRP was shown to be indicative of severe CD when level is >12 mg/L[45]. However, ~~but~~ certain patients with endoscopically active CD may show low CRP levels including those with ileitis CD or a low body mass index[49]. As for the fecal biomarkers, FC and FL, they both measure protein levels in the feces. They are more specific than serologic biomarkers and high levels of these two markers has been considered as indicative of IBD[45,50].

A recent MA[51] of 19 studies including 2500 participants showed pooled sensitivity estimates of 0.49, 0.92 and 0.88 for CRP, FC and FL, respectively and pooled specificities estimates of 0.73, 0.82 and 0.79 for CRP, FC and FL, respectively. The study also showed that FC was more sensitive in UC patients but overall was more sensitive than CRP for both CD and UC[51]. Although CRP, FC and FL have been shown to be good predictors of disease course and of response to therapy, they are not good markers for distinguishing UC from CD[52].

Saccharomyces cerevisiae antibodies (ASCA), antibodies to bacterial proteins such as other membrane protein C (OmpC) and flagellin (CBirl) as well as perinuclear anti-neutrophil cytoplasmic antibodies (pANCA) are being assessed as a stand-alone or in combination for their association with CD[52]. ASCA has been shown to have high specificity but low sensitivity to CD[53] and in a MA, the combination ASCA+/pANCA- to have a sensitivity of 55% and a specificity of 93% for the evaluation of CD[54]. However, more studies are needed to determine their definitive value in differentiating the phenotypes of IBD.

Laboratory tests combined with the patients' clinical evaluation were estimated to provide diagnosis in approximately 50% of patients. Current research is investigating new approaches to biomarkers whereby a group of biomarkers would have a pattern of operation or signature that can be useful from a diagnostic perspective[52]. Among those approaches are the gene expression profiling techniques which can be based on profiling of messenger ribonucleic acid (mRNA) extracted from either whole blood[55,56], or peripheral blood mononuclear cell RNA[57,58], or mucosal biopsies[59,60]. These techniques have been shown to have the ability to differentiate between CD, UC and other non-inflammatory diseases[61] and to predict disease activity in

patients with UC and CD[62]. Another approach is evaluating microRNA (miRNA) levels as a potential marker of disease activity in patients with IBD. Studies of peripheral blood miRNA[63,64] and tissue miRNA[65-67] are showing promising results in identifying patients with IBD and distinguishing UC from CD. The goals of this research area are to identify biomarkers or biomarker signature which will be more sensitive and more specific than current serologic and stool tests to identify IBD phenotypes and to predict the course of disease and patients' response to treatment.

1.4.3 Mucosal Assessment

Although both the CDAI and HBI continue to be used in clinical trials and practice settings to assess induction and maintenance of remission, the medical community and regulatory agencies[68] acknowledge their shortcomings from being restricted to the assessment of patients' clinical symptoms and their lack of evaluation of structural intestinal damage. It has been proposed to use composite indices where remission is based not only on a CDAI score, shown to poorly correlate with endoscopic inflammation[69] and serum and fecal biomarkers[69,70], but also on objective measures of disease activity using endoscopy, cross-sectional imaging and laboratory biomarkers[71,72].

Two endoscopic indices, the Crohn's Disease Endoscopic Index of Severity (CDEIS) and the Simple Endoscopic Score in Crohn's disease (SES-CD) have been used in clinical trials to assess patients' eligibility and response to treatment[73]. However, despite recent evidence showing that treating to mucosal healing is associated with improved clinical outcomes, the invasive aspect of the endoscopic assessment has limited its routine use in clinical practice[74].

Magnetic resonance enterography (MRE) on the other hand, offers the advantages of being non-invasive and free of ionizing radiation, as opposed to computed tomography (CT) scans where the risk associated with radiations has been a concern particularly for CD patients where multiple imaging exams are needed over the course of their disease[74]. Few MRE indices have been developed based on various imaging features to measure disease activity and patients' response to treatment including the magnetic resonance index of activity (MaRIA)[75], the Crohn's disease activity score (CDAS)[76] and a modified version of the CDAS, the MRE global score (MEGS)[77]. MRE has been shown to enable the evaluation of areas of the small bowel that cannot be accessed with standard ileo-colonoscopy, to help determine the presence of disease

complications as well as to assess disease activity[78]. However, more studies are needed to determine the additive value it offers over other assessment methods in terms of patients' clinical outcomes and cost.

Also, in line with the concept of treating beyond endoscopic healing to histological healing, two histological indices, the global histological activity score[79] and the Naini Cortina score[80], were developed to enable measurement of histological inflammation. More studies are needed to validate these indices and to determine their predictive values in the assessment of disease progression and complications.

In general, studies are still needed to assess the feasibility, cost-effectiveness and the necessity of combining clinical evaluation, biomarkers, endoscopic and histological measures as treatment goals and to prove that treating to target or treating to "deep remission" will have an impact on the natural course of disease i.e. on the patients' long-term outcomes[71,72].

1.5. Treatment Options and Guidelines

1.5.1 Prior to Biologics Era

The first mention of strictures and enlargement of the ileum as well as lesions in the colon date back to 1809 in a description of one case read by William Saunders at a meeting of the Royal College of Physicians in London[81]. Other rare descriptions of similar cases followed during the century as well as early in the 1900, until a British physician, Dr. Kennedy Dalziel, in 1913 described 8 cases with "chronic interstitial enteritis" indicating it was a prime mention and excluding any evidence of tuberculosis[81].

In 1932, Dr. Burrill Crohn and colleagues, from the Mount Sinai Hospital in New York, identified 14 patients with clinical symptoms and intestinal abnormalities observed during surgery that did not correspond to any known disease and gave the name of "regional ileitis" to the disease of the terminal ileum[81]. Their discovery was published in the Journal of the American Medical Association in October 1932 under the title of "Regional Ileitis: A Pathologic and Clinical Entity". Since then, the disease bears the name of Dr. Crohn. Back then, resection was thought to be the treatment of choice restoring complete health in most patients and the debate in this field was about one-stage resection versus two-stage resection and in which patients[81]. A publication on this topic from 1952, has indicated that there was no effective medical therapy for

this condition and if the surgeon was reluctant to operate then bed rest, a proper diet and the use of adrenocorticotropic hormone (ACTH) and cortisone were appropriate to reduce patients' symptoms[82].

A review of the therapeutic management of "regional enteritis", published in 1957[83], had acknowledged that not all patients are good candidates for surgery and that some patients without complications may be managed in a similar way to any chronic debilitating infection. The recommended therapeutic management then included a protein-rich diet, rest and drugs such as antibiotics and Sulfasalazine. This therapeutic plan could be combined with tranquilizing agents and with radiation as an adjunct therapy[83]. As for patients with complications, repeated blood administration was advised as a major therapeutic measure to correct the state of deficiency seen in this type of patients and steroids for patients with syndrome resembling sprue, secondary uveitis or pyoderma[83]. By the end of 1950's "regional ileitis" was recognized as a diffuse, widespread disorder that cannot be completely extirpated and cured by surgery of the diseased tissues, and there was acknowledgement of the available medical treatments as supportive symptomatic measures with definitive limitations[84].

The subsequent decades led to an increased clinical experience and understanding of the pathogenesis of IBD as well as to the development of new formulations of existing drugs with improved delivery systems and reduced toxicity for application to IBD. This included topically active steroids, coated slow-release 5-aminosalicylates (5-ASA), immuno-suppressants (IS), and the introduction of biological drugs in the late 1990s. Those agents have offered physicians more treatment options to control patients' symptoms, to limit the disease progression and to improve the disease's long-term prognosis.

Although no practice guidelines for the management of patients with Crohn's disease were developed in the period 1990 – 1999, several papers on the medical management of this condition based either on the authors' clinical experience or as a summary of the existing clinical evidence were published during this period. Sulfasalazine was established as the most widely prescribed drug for the treatment of IBD since the 1940s, mainly due to Dr. Nana Svartz's success in treating patients with colitis using this agent which was originally developed to treat rheumatoid arthritis[85,86]. Despite its widespread acceptance, the clinical evidence showed that this drug had high incidence of adverse reactions[87] and limited effectiveness, being useful in treating prophylactically active ulcerative colitis and Crohn colitis but not Crohn ileitis[88]. This

led to the development of a new generation of drugs, derived from Sulfasalazine, the "amino-salicylates", which lack the sulfa portion identified as responsible for the toxicity of the parent drug. Topical, suppository and slow release coated oral 5-ASA were since then used as an alternative treatment in patients with Crohn disease intolerant to sulfasalazine[85]. These new formulations offered distinct release profiles and were used to target the inflammation in a specific area of the gastrointestinal tract. The slow-release formulations, like mesalamine, offered a new option for patients with mild to moderate Crohn's disease of the small intestine. Studies conducted in the 1990s[89-92], as opposed to those conducted in the 1970s and 1980s with sulfasalazine[93-95], showed the efficacy of 5-ASAs and stressed the importance of using higher doses for short-term treatment and for maintenance of remission[96]. A meta-analysis of the data on 5-ASA[97], confirmed the efficacy of this class of drugs for the maintenance of remission in patients with CD.

Nevertheless, corticosteroids (CS) retained their place as the mainstay of treatment for active or acute relapses of Crohn's disease and newer topical and oral formulations, like budesonide, were developed with reduced systemic absorption and extensive first-pass metabolism with a view to minimize systemic toxicity[98]. However, corticosteroids were not retained as an option for the maintenance of remission in Crohn's disease.

As for IS, the use of Azathioprine and 6-Mercaptopurine for the treatment of Crohn's disease was delayed by the negative results shown in the National Cooperative Crohn's Disease Study[94], which did not account for the fact that these drugs were slow-acting agents requiring longer time before showing efficacy. The published data by Present et al. in 1980[99] confirmed the efficacy of these agents and were mainly behind the increased use of these agents to treat Crohn's disease. Other studies[100,101], published in the early 1990s, have also shown the efficacy of these agents in maintaining long-term remission in patients with CD. Other IS with faster onset of action were also trialed in patients with Crohn's disease including methotrexate and cyclosporine. A major concern with these drugs has been their potential association with rare but serious adverse events, such as an increased risk of lymphoma and leucopenia particularly in patients with low levels of thiopurine methyltransferase (TPMT) enzyme; Adjusting the thiopurine dosage based on the level of this enzyme in patients with CD or switching to another agent if the level is too low has been advised since a deficiency of TPMT enzyme appears to account for some dose and metabolism toxicities[102,103]. Overall, IS were considered as having steroid-sparing effect and to

be effective in treating refractory disease, difficult to treat fistulas and as a long-term prophylaxis treatment post-surgery and in patients with recurrent flares[104].

In summary, the medical management of Crohn's disease at the beginning of the 1990s[98,104-107] was based mainly on the use of CS for active CD in all disease locations. Sulfasalazine was considered an option for patients with Crohn colitis and mesalamine offered an option for Crohn ileitis. Azathioprine and 6-mercaptopurine, were used in patients not responding to corticosteroids, in those who relapsed when the CS dose was reduced or in those intolerant to corticosteroids. If the longer onset of action of those agents was a concern, methotrexate and cyclosporine were considered good alternatives. Antibiotics, such as metronidazole and ciprofloxacin, were recommended for the treatment of perineal disease and fistulas and parenteral nutrition for patients uncontrolled with conventional therapy. The prophylaxis regimen consisted of sulfasalazine or a 5-ASA, alone or with a low-dose or an alternate-day regimen of a corticosteroid, or an immunosuppressant, or parenteral nutrition or surgery for fistulas and strictures.

1.5.2 Biologics Era

The late part of the decade saw the introduction of the first anti-tumor necrosis factor (anti-TNFα), infliximab, which was launched in the U.S. in late 1998 and in Canada in 2001 for the treatment of CD. In general, the medical plan for treating Crohn's disease continued to be based primarily on the conventional therapy which included oral and intravenous (IV) CS, sulfasalazine or 5-ASA with a choice based on the target site of inflammation, azathioprine or 6-mercaptopurine with methotrexate and cyclosporine as an alternative therapy, metronidazole and ciprofloxacin for cases of perianal disease or fistulas and nutritional therapy, parenteral or enteral diet. However, infliximab was integrated in the armamentarium of drug therapies, but given uncertainties about its long-term efficacy and safety, was considered an option for patients with active disease who were refractory to other treatments[108-113].

Over the last 10 to 15 years, the advances in the understanding of Crohn's disease pathophysiology and natural course as well as the piling evidence from controlled trials of pharmacological drugs have helped decision-making and the development of consensus regarding the best medical management of the disease. It is noteworthy that, even in the era of biologics, corticosteroids remained the mainstay of initial treatment of active CD in all intestinal

locations. However, it is well recognized that these agents should not be considered for maintenance of remission given their toxicity profile and limited efficacy over the long-term. The guidelines encourage the establishment of a long-term therapeutic plan using other agents with a selection based on disease level of activity, site and behavior as well as any previous response to treatment and the presence of complications or extra-intestinal manifestations[114].

Amino-salicylates were not shown to offer any benefits over placebo or budesonide in several meta-analyses[115,116]. In recent guidelines, they are not recommended anymore[114] or their use has been limited to mild CD when patients decline, cannot tolerate or where CS are contraindicated[117] or to colonic CD in absence of disease complications[118].

Accounting for the importance of mucosal healing and the benefits anti-TNFα and IS offer in terms of histological remission, the guidelines are recommending the use of these agents as add-on therapy to CS and their early introduction, alone or in combination, for the treatment of extensive small bowel disease. The European Crohn's and Colitis Organization (ECCO) 2016 guidelines[114] have added Vedolizumab, an anti-adhesion molecule, as a good alternative for patients with moderate to severe disease who are refractory to anti-TNFα. Nutritional therapy is considered an important supportive care and total parenteral nutrition a good adjunctive therapy for patients with fistulas and complex diseases[114]. These guidelines recommend maintenance of remission with thiopurines, methotrexate, an anti-TNFα or Vedolizumab if remission was induced with this agent, with relapses managed with either a dose optimization or a change of therapy[114]. Surgery remains an option for all refractory patients and an alternative to medical treatment in patients with disease limited to the distal ileum[117].

The comparative tables shown below (Tables 2 and 3) summarize the key recommendations issued by three European groups for the treatment of patients with CD.

Table 2: European Guidelines for Induction of Remission in Patients with CD

	ECCO 2016	BSG 2011	NICE 2012
Induction of Remission			
Mild to moderate ileocaecal CD	Oral budesonide	- Oral CS - TNF-antagonist therapy if refractory to CS	- Conventional glucocorticoids (CG) - Budesonide (Bud) if CG declined, contraindicated, or cause intolerance (not for severe cases) - 5-ASA if CG or Bud inappropriate (not for severe cases)
Moderate to severe ileocaecal CD	- Systemic CS - Anti-TNFa for refractory/intolerant to CS - or CS + IS - or Vedolizumab for refractory/intolerant to CS and/or anti-TNFa	- Oral corticosteroids - TNF-antagonist therapy if refractory to corticosteroids - AZA or 6-MP	**Add-on Therapy to CS:** - AZA or 6-MP if dose of CS cannot be tapered or > 2 inflammatory exacerbations in 12 months - MTX if intolerant to AZA or 6-MP - IFX and ADA for severe CD in those non-responsive, intolerant to CS and/or IS or if contraindicated, as part of a treatment plan until failure or for up to 12 months whichever is shorter – Reassessment afterward needed - IFX for fistulas in those non-responsive, intolerant to CS and/or IS or where contraindicated - If IFX or ADA given monotherapy or in combination with IS, patients should be informed of uncertainty of comparative effectiveness and long-term SEs of mono vs combination therapy (2016 update)
Colonic CD	- Systemic CS - Anti-TNFa for relapses - Vedolizumab for refractory/intolerant to CS and/or anti-TNFa	- Oral CS - TNF-antagonist therapy if refractory to CS - AZA or 6-MP **For Perianal:** - AZA or 6-MP - TNF-antagonist therapy if refractory to other treatments	**Same as Add-on Therapy to CS**
Extensive small bowel disease	- Systemic CS - early anti-TNFa and/or IS	- Oral CS - TNF-antagonist therapy if refractory to CS - AZA or 6-MP	**Same as Add-on Therapy to CS**
Oesophageal or gastroduodenal CD	- Mild: Proton pump inhibitor - Severe: SCS or anti-TNFa - Symptomatic strictures: dilatation or surgery		
- CS = Corticosteroids; SCS = systemic corticosteroid; 5-ASA = 5-aminosalicylates; IS = immunosuppressant; AZA = azathioprine; 6-MP = 6-mercaptopurine; MTX = methotrexate; IFX = infliximab; ADA = adalimumab;			

Table 3: European Guidelines for Maintenance of Remission in Patients with CD

	ECCO 2016	BSG 2011	NICE 2012
Maintenance of remission			
First presentation after CS	- Thiopurines or MTX - No treatment	- AZA or 6-MP or MTX - Infliximab or adalimumab (when resistant or intolerant of infliximab)	- AZA or 6-MP - MTX if used for induction with CS or if contraindication or intolerance to AZA or 6-MP - IFX and ADA if signs of active disease with reassessment every 12 months
Relapse of localized disease	- Escalation of maintenance treatment - Surgery		- Same Maintenance after surgery: - 5-ASA - or AZA/6-MP for patients with poor prognosis
Extensive disease	- Thiopurines - anti-TNFa for severe disease		Same as above
MTX = methotrexate; AZA = azathioprine; 6-MP = 6-mercaptopurine; CS = corticosteroid; IFX = infliximab; ADA = adalimumab; 5-ASA = 5-aminosalicylates;			

In Canada, the Canadian Association of Gastroenterology (CAG) has published in 2009 a consensus developed by a group of 25 participants for the use of tumor necrosis factor-alpha antagonist therapy in Crohn's disease[119]. These guidelines included multiple statements to address induction and maintenance therapies as well as safety issues with these agents. No comprehensive guidelines for the management of CD have been developed by CAG. In summary, all anti-TNFα agents available at the time (infliximab, adalimumab and certolizumab) are considered effective in inducing remission in patients with active disease despite conventional therapy and in maintaining remission in patients who have responded to an induction regimen[119]. However, a dose-escalation, a shorter dose interval or a switch to another anti-TNFα agent may be considered for patients with a partial response. In non-responders, therapy should be stopped and a switch to another anti-TNFα may be considered. The guidelines recommend the concomitant use of thiopurines to reduce hypersensitivity reactions and to increase the effectiveness of the anti-TNFα drug as well as their use alone to maintain remission after induction with anti-TNFα in selected patients[119]. Several contraindications were also issued by these guidelines based on the products monograph and the evidence from clinical trials. These

will not be a subject of discussion in this document given our focus on the effectiveness of pharmacological treatments.

In the United States, the American Gastroenterology Association (AGA) has issued in 2013 a guideline addressing the use of thiopurines, methotrexate and anti-TNFα drugs for the induction and maintenance of remission in patients with moderate to severe CD[120]. The American College of Gastroenterology (ACG) guidelines, on the other hand, date back to 2009. The latter are more comprehensive and address the management of CD in adult patients[121].

In summary, the 2013 AGA guidelines recommend the use of anti-TNFα agents monotherapy or the combination of anti-TNFα and a thiopurine to induce remission in patients with moderate to severe CD, the combination being considered more effective than anti-TNFα alone[120]. They also suggest against using thiopurine monotherapy or methotrexate for inducing remission in those patients. As indicated in the AGA technical review report[122], the conclusion to remove any role for the immuno-modulators in the induction of remission in corticosteroid treated patients is based on their analysis of the evidence which showed immuno-modulators are not more effective than placebo. This decision differs from the guidelines issued by the ACG, the ECCO and the BSG. The key recommendations issued by the ACG are summarized in table 4. Like the guidelines issued by other groups, corticosteroids are the cornerstone therapy for induction of remission in patients with mild, moderate and severe disease unless otherwise desired or indicated. The report highlights the lack of evidence to support the use of antibiotics or anti-mycobacterial agents in the setting of luminal disease. Azathioprine, 6-mercaptopurine and all anti-TNFα drugs were attributed a grade A and methotrexate a grade B for the treatment of moderate to severe CD after therapy with CS or in patients with inadequate response to CS. Also, natalizumab despite its association with increased risk of progressive multifocal leukoencephalopathy (PML) is recommended for patients who fail on or are intolerant to CS and anti-TNFα agents. This latter recommendation differs from other guidelines. Infliximab was issued a grade A level of recommendation for the treatment of non-suppurative perianal and fistulizing disease based on the existing evidence[123,124] whereas IS and antibiotics were granted a grade C level of recommendation based on the lack of controlled trials demonstrating their benefits in this patients' population[121].

Table 4: ACG Guidelines for the Management of CD in Adults

	ACG 2009	
Induction		
	Mild to moderate active CD	- CS or budesonide for ileum and/or right colon
	Moderate to severe CD	- CS - AZA or 6-MP for maintaining steroid induced remission - MTX for steroid-dependent or steroid-refractory CD - IFX, ADA, CTZ in patients who have not responded to CS or IS or as 1st line when CS are contraindicated or not desired - NTZ monotherapy for non-responders or intolerant to CS and anti-TNFa therapy
	Severe fulminant CD	- CS (parenteral) then equivalent oral at discharge - AZA or 6-MP for maintenance - Surgery for non-responders or if worsening of symptoms
	Perianal and fistulizing CD	- Antibiotics, IS or IFX for non-suppurative, chronic
Maintenance		- AZA, 6-MP, MTX - IFX, ADA, CTZ - IFX or IFX+AZA > AZA for patients with moderate to severe CD who failed to respond to 1st line therapy - NTZ
	After surgery	- AZA, 6-MP or IFX - Metronidazole - Mesalamine
CS = Corticosteroids; AZA = azathioprine; 6-MP = 6-mercaptopurine; MTX = methotrexate; IFX = infliximab; ADA = adalimumab; CTZ = certolizumab; NTZ = natalizumab;		

1.6 Transition Paragraph: Step-up vs Top-down Treatment Strategies

Current therapeutic guidelines for the clinical management of patients with moderate to severe Crohn's disease are, generally, recommending a "step-up" treatment approach (CS, IS, anti-TNF∝, anti-integrin antibodies) or an "accelerated" approach (CS + IS, anti-TNF∝, anti-integrin antibodies) as opposed to a "top-down" approach (IS + anti-TNF∝, anti-integrin antibodies) for the pharmacological management of the disease.

However, evidence from clinical trials has shown that both immunosuppressants[125-129] (azathioprine, 6-mercaptopurine and methotrexate) and biologic agents[130-137] act not only on patients' symptoms but also on the natural course of disease by inducing and maintaining mucosal healing in patients with CD. Data from the SONIC trial[132] have also shown that the combination of a thiopurine with an anti-TNF∝ not only provided greater efficacy in controlling patients' symptoms but also provided better healing of the mucosa than either one used alone. Mucosal healing has been linked to reductions in hospitalization, colectomy and surgery rates as well as to lowering steroid use[138-143].

Despite this evidence, but in line with current guidelines, CS continue to be heavily used in this patient population. Population-based studies conducted in Canada[144] and comparing prescribing prevalence over different time-periods (2002 – 2010 vs 1995 – 2001) and in the Netherlands[145] (2006 – 2011 vs 1991 – 1998) have shown that the use of CS continued to be high particularly in the first year after diagnosis. In addition, the Canadian study[144] has found no change in the cumulative exposure to corticosteroids between 1995 and 2010 but a relative increase in the cumulative use of 36immuno-suppressants (19.8% in 1995 – 2000 vs 31.7% in 2005 – 2009) and biologic agents (5.1% in 2001 – 2004 vs 12.7% in 2005 -2009). These data highlight a knowledge-to-action gap which may be attributed to the relatively high cost of biologic agents, to these agents being perceived as causing more adverse events, particularly serious infections and finally, the need for stronger evidence to support the superiority of a top-down approach in treating patients with moderate to severe CD.

NMA was developed as a statistical methodology to address the scarcity of head-to-head clinical trials and to provide clinicians and decision-makers with the means to draw conclusions on the comparative effectiveness of available agents. This methodology was used in this research to help answer the questions of what is the relative effect size of agents that are recommended

for the treatment of moderate to severe CD and how do they compare to each other, based on current evidence. By positioning the efficacy of the combination of biologic and IS therapy vs other biologics, IS and CS monotherapies, the results addressed the questions on whether there is value in a top-down treatment approach and the place of IS and CS in the management of these patients. However, as already recognized, these efficacy results need to be considered while accounting for other factors such as the risk/benefit ratio for a given patient and the cost of medication.

2. SYSTEMATIC REVIEW AND NETWORK META-ANALYSIS

2.1. BACKGROUND

Systematic review (SR) has emerged since the 1990s as a fundamental basis for comparative effectiveness research and evidence-based health-care decision-making. Its primary objective is to synthesize the available evidence and to communicate to the end-users either a qualitative, narrative description of the direction of effect and/or a quantitative estimate of effect and its related statistical inferences based on the results of meta-analyses[146]. SR involves an explicit, systematic, reproducible formal process to ensure a comprehensive search of the literature and a selection of the primary studies that answer a specific research question. The process is designed in a way to minimize subjectivity and bias, two pitfalls attributed to narrative reviews. The Cochrane Collaboration group has been instrumental in defining methodological guidance[147] for conducting SR. The steps involved in conducting a SR include:

- Setting clear objectives with a pre-defined eligibility criteria (search protocol): This helps define the focus of the research i.e. the questions that need to be answered and determine the criteria based on which the studies will be selected for inclusion in the review. The first framework to help structure and break down health-related questions into searchable keywords was developed by Richardson et al. in 1995[148]. This framework is based on 4 areas: participants (P), interventions (I), comparators (C), and outcomes (O). The acronym PICO is used as a reminder of those areas. Several variations of this framework were generated later, adapting it to specific research fields[148]. One of the variations also used in health-care settings is PICOS where "S" refers to the study design of interest and to other study-specific elements. An evaluation of PICO as a knowledge representation for clinical questions has found it to be mainly suited to therapy questions and less applicable to other clinical information needs but overall has ascertained its value in evidence-based medicine[149]. PICO is used as a framework for the conduct of SR by most expert guidance[147,150-152] and is part of the consensus statements issued by the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analysis) group for the reporting of systematic reviews and meta-analysis[153] or its extension incorporating network meta-analysis[154].

- Conducting a systematic search and selecting studies that meet the defined criteria: The reliability and validity of effect estimates resulting from a pair-wise MA or NMA rely on how thorough, objective and reproducible the SR was and whether all relevant studies were identified and included. Two key approaches were identified that help minimize the bias in the retrieval process: 1) using a variety of search methods: electronic, visual scanning of reference lists, hand-searching key journals and conference proceedings, contacting authors and manufacturers, citation searching, grey literature/unpublished papers and 2) searching multiple databases[147]. The decision of which database to use should be based on the research questions being addressed. There is currently no agreement on what constitutes an acceptable number of databases to be searched. However, the related cost and the time available to complete the search are two determinants and often limiting factors. MEDLINE, EMBASE, PubMed and Cochrane Central Register for Controlled Trials electronic databases are the most commonly used in medicine and health-care research. Search filters or "Hedges"[147] exist to facilitate retrieval of records from bibliographic databases and to reduce the number that the researcher needs to sift. They have been developed by combining controlled vocabulary terms, thesauri such as MeSH (Medical Subject Headings) for MEDLINE and EMTREE for EMBASE, with a series of key text words, Boolean operations and wildcard variants ("?" "#") to optimize retrieval[147,150]. Search filters may be interface-specific (OVID, PubMed), database-specific (MEDLINE, EMBASE) or focused on publication type (RCT, SR). However, not all databases provide a thesaurus and researchers may need to rely on synonyms and key terms to develop their search. Also, search filters are not a guarantee of optimal retrieval, hence, the importance of complementing any electronic search with other types of searches to increase the sensitivity and precision of the retrieval process. Guidelines on systematic reviews[147,150,151] recommend: 1) that the search be conducted with the help of an experienced librarian, 2) to download records into a reference management software or an equivalent, 3) to have the screening and selection of studies done by at least two reviewers independently with any discrepancies between the two resolved by consensus and finally, 4) to report the search results using a PRISMA flow-chart.

- Abstracting the data: the reliability of the synthesis of evidence relies heavily on the accuracy and the systematic extraction of data from the selected studies. The data will not only be used for the analysis but also for assessing the risk of bias and the quality of the studies. Several groups[147,150,151] have issued recommendations on the variables to consider when planning data extraction, which include: general information on the study, eligibility criteria, participants, interventions, and outcomes as well as any miscellaneous important information. Sufficient time needs to be dedicated to designing a data collection form, to developing clear instructions on how to extract and code the data and to piloting it using a small sample of the selected studies to help reduce data extraction errors. The data extraction form can be a basic paper or an electronic spreadsheet, a custom database or an online tool[147]. Each format has its own pros and cons and the choice of which one to use relies on a personal decision[147]. As with the selection process, it is advised that the data extraction process be performed by two reviewers to minimize errors and to have the discrepancies resolved by consensus or with the help of a third reviewer[147,150,151].
- Appraising the evidence: Expert guidance for the conduct of SR uses the term "risk of bias" for the assessment of individual studies and the term "quality" for the assessment of a body of evidence[147,150,151,155]. However, assessing the bias of individual studies is part of the evaluation of the strength of the body of evidence since high risk of bias in a study influences the credibility of the relative summary estimates. The process must be based on a systematic approach and criteria assessing risk of bias (ROB) of individual studies should be distinct from criteria assessing the precision, directness, applicability of the overall evidence[155]. The ROB assessment refers to the internal validity of individual studies and its purpose is to identify whether the conduct and the design of the study have compromised the confidence in the relation between the exposure and the outcome and consequently, the estimate of effect[155]. In a SR published in 2008, Armijo-Olivo et al.[156] identified 21 scales for assessing the ROB in RCTs and found that the majority were not "rigorously developed or tested for validity or reliability". Moher et al.[157] also reported that only 12% of the scales that were developed for the assessment of the methodological quality of RCT have been empirically evaluated. In general, the available scales were either design-specific or could be used across different designs[156,158-160]. Until recently,

the "Jadad Scale"[161,162] was the most commonly used for assessing the ROB in SR. It addresses three domains, namely randomization, blinding and handling of withdrawals/drop-outs but does not address bias in allocation concealment. This scale was found to have the strongest evidence of validity and reliability[156]. However, it has recently been criticized as it addresses the quality of reporting rather than the risk of bias[161,163]. In 2008, the Cochrane Collaboration group published a new tool for randomized trials, the "Risk of Bias Tool"[147] to address the inconsistent approaches in the assessment of ROB in different systematic reviews. This publication was released after the one by Armijo-Olivo et al. and consequently, the ROB tool was not part of this group's SR review. The tool[147,164] was updated in 2011 based on its validation with users. It addresses six specific domains, namely sequence generation, allocation concealment, blinding of participants, personnel and outcomes assessors, incomplete outcome data, selective outcome reporting and "other issues". Each domain includes one or more entries to allow the description of what was reported on the conduct of the study. As a result, studies are rated "low risk", "high risk" or "unclear risk" of bias. This tool is currently the most used in systematic reviews because of its transparency in implementation. Based on the Cochrane Collaboration group, when assessing the quality of trials included in a SR, it is recommended to choose a tool designed specifically for use in systematic reviews that addresses items related to internal validity, that is design-specific, and to avoid the use of a composite score i.e. an overall numeric rating of the study risk of bias across items[155]. This group has also recommended to use the results of the ROB assessment in the synthesis of the evidence and to report the process along with its limitations[155].
Once the ROB in each individual study has been assessed appropriately, the next steps involve the assessment of characteristics such as consistency, precision, directness and reporting bias, which serves to indicate to what extent one can be confident that the calculated relative estimate of effect is correct[151]. These characteristics are well-established concepts for the evaluation of quality, however, there is a lack of an evidence-based system for systematically applying these concepts[151]. The GRADE (Grading of Recommendations Assessment, Development and Evaluation) approach is based on these characteristics but has yet to be rigorously evaluated[151]. Meanwhile, it has been adopted by several groups, mainly by the GRADE group, the Cochrane Collaboration group and a

modified version by the AHRQ (Agency for Healthcare Research and Quality) Effective Health Care Program, where it is mainly used in the context of decision-making.
As for the quantitative synthesis (meta-analysis), it addresses the heterogeneity among study effects as well as the uncertainty (CI or CrI) and the sensitivity of the conclusions drawn (sensitivity analysis)[151]. Whether a pairwise meta-analysis (MA) or a network meta-analysis (NMA) is conducted, both methods combine the information collated from the selected studies with the objective of calculating precise estimates of effect. MA provides a pairwise comparison of estimates of effect between two interventions and yields one pooled effect estimate, whereas NMA provides estimates of effect for all possible comparisons in a body of evidence, combining head-to-head trials and indirect evidence, when appropriate, in one statistical model, yielding more than one pooled effect estimate. However, a point to consider is that quantitative synthesis is not a mandatory step in the conduct of a SR i.e. it may or may not follow SR.

2.2 Methods

2.2.1 Search Strategy

With the help of a librarian from McGill University, the following databases were searched for primary RCTs published between 1990 and October 2015: MEDLINE®(Ovid), Embase®(Ovid), Cochrane Central Register of Controlled trials as well as the trial registry www.clinicaltrials.gov. The electronic search was supplemented with a citation tracker using Scopus of relevant papers to identify additional studies as well as with a screening of all relevant guidelines, systematic reviews, and meta-analyses.

The search was performed using a SIGN (Scottish Intercollegiate Guidelines Network) filter for controlled trials, controlled vocabulary descriptors (Medical Subject Headings (MeSH) and EMTREE) and specific keywords to represent the concept of CD and its therapeutic management. The search strategies used for the different databases are listed in Appendix I. Articles published in English and French languages were selected and all references were imported to the EndNote Citation Management software where duplicated references were removed.

2.2.2 Study Selection

The search result was screened first by title and abstract and then by full text review. Since a second reviewer was not available to do the screening as recommended by the SR methodological guidelines[147,150,151], the same reviewer randomly selected 25% of the reports from the pool of studies and the screening process was repeated on two occasions for the title and abstract review. The number of reports for the random review and the decision to repeat the process twice were chosen arbitrarly. For the full text review, again since a second reviewer was not available, the trials selection was cross-checked with those of other systematic reviews and meta-analyses to ensure no studies were missed out during the selection process. The eligibility criteria of the research protocol, which were based on the PICO framework (Table 5) were used to guide the selection of studies.

Table 5: Protocol's Eligibility Criteria

CATEGORY	INCLUSION
Population	• human subjects, adults (>=18) with moderate to severe CD (CDAI[1] = 220 – 450 or HBI ≥ 8-16)
Intervention	• CD medication (approved for Rx of moderate to severe CD) or combination of active medications
Comparator	• CD medication (approved for Rx of moderate to severe CD), combination of medications or placebo
Outcomes	• Endpoint: • Induction of remission: defined as a CDAI less than 150 or HBI < 5 or the remission criteria of the study at the time of the primary endpoint measure or if not defined by the study at the last study point measurement
Studies	• only RCTS, written in English or French

For the outcome of interest, both placebo-controlled and head-to-head randomized controlled trials were selected. The outcome of interest was induction of remission as defined by a CDAI score of less than 150 or HBI less than 5 at the time of the primary endpoint measurement as defined by the study's methodology. If the time of the primary endpoint measurement was not clearly stated in the study's report, the last recorded measurement of the endpoint was abstracted.

The drugs considered were those recommended by the guidelines for the induction of remission in adult patients with moderate to severe CD. These included:

- Immuno-suppressants: azathioprine, 6-mercaptopurine, methotrexate
- Biologics:
    i. Anti-TNF therapies: infliximab, adalimumab, certolizumab pegol
    ii. Anti-integrin antibodies: vedolizumab, natalizumab
    iii. Interleukin receptor blocker: ustekinumab
- Corticosteroids: prednisone, prednisolone, 6-methylprednisolone, hydrocortisone, budesonide

The exclusion criteria included: trials studying agents not currently recommended for the treatment of moderate to severe CD, pediatric patients (age < 18yr), postoperative patients, single blind, observational, crossover trials or those that did not report induction of remission as an outcome as well as trials that could not be linked within the network through a shared comparator. Trials comparing the same medication at different dosages without the inclusion of a different comparator being a placebo or an active agent were also excluded.

2.2.3 Data Abstraction

For all reports, the following information was extracted: data relevant to the study, participants and disease baseline characteristics, as well as those relevant to eligibility criteria, interventions and outcome measures and results. The list of variables is shown in Appendix II. Data were extracted based on the intention-to-treat analysis of each trial with the outcome data extracted at the time of the primary end-point measure as specified by the trial, or at the longest time-point if not specified by the trial.

2.2.4 Quality Assessment

Bias in the included trials was assessed using the Cochrane Collaboration Risk of Bias tools[147]. The choice of this tool was based on it being specifically designed for use in SR of RCT, being transparent and not being based on a composite score, three criteria highly recommended by expert guidance[147,151]. Studies with high risk of bias were excluded from the analysis and since a second reviewer was not available to validate this assessment, the evaluation was cross-

checked against the ROB assessment conducted in other published SRs, where available. Any disagreement between the two was resolved based on the researcher own evaluation. The ROB assessment of studies evaluating the induction of remission was color-coded with green indicating "low risk" of bias, yellow indicating "unclear risk" of bias and red indicating "high risk" of bias (see Table 6 in the results section). A low overall risk of bias was defined as a low risk rating in at least four domains.

The quality of the network, or external validity of the trials was assessed through the validation of a key assumption that stands behind the validity of inferences drawn from a NMA[165]: that there are no important differences between the trials included in the network other than the treatments being compared. This validation encompassed an evaluation of the trials for clinical or methodological heterogeneity referred to as "transitivity" as well as examining the network for the presence of "inconsistency", also referred to as statistical heterogeneity which is an extension of transitivity across all indirect comparisons in the loop[165-167]. The terms similarity[168], transitivity[169] and exchangeability[170] have been interchangeably used in the literature to refer to the underlying assumption that the direct evidence from AC and BC trials, as an example, could be combined to learn indirectly about the AB comparison[166]. This implies that the distribution of effect modifiers in trials AC and BC is similar for the indirect comparison AB to be valid[165,166,171]. This assumption cannot be tested statistically, but its plausibility can be evaluated conceptually and epidemiologically[166,167]. One way of assessing its plausibility is to examine the studies for important differences in the distribution of effect modifiers[166]. However, the quality of this assessment and its feasibility depend on the availability of data on the effect modifiers as well as on the number of studies per treatment comparison[165,166]. Other formulations of the transitivity assumption have been presented where transitivity assumes that the choice of the comparator in the trials is independent, directly and indirectly, from the relative effectiveness of the interventions[166,167] or that included patients could have been randomized to any of the treatments included in the network[166,167].

On the other hand, consistency (or coherence) is considered as the statistical manifestation of transitivity[165,166] and can only be evaluated in the presence of a closed loop of evidence. It assesses whether the direct and indirect evidence for a given comparison agree i.e. the evidence from a head-to-head trial comparing A to B agree with the indirect evidence for AB that is drawn from the trials comparing A to C and B to C[165,166,172]. Several statistical methods have been

developed to assess consistency, some designed to identify the loops associated with inconsistency[173-175](local methods) and others designed to infer about consistency in the entire network[170,176-181](global methods). If there is no direct evidence for the relative effectiveness of two treatments, i.e. no closed loop, then consistency reduces to transitivity.

2.2.5 Data Synthesis

Data synthesis using NMA involves, in general, the following key steps:

- Assessing heterogeneity (transitivity/similarity) within and between the trials
- Deciding on the statistical approach and model: Bayesian or frequentist, fixed vs random
- Fitting the model chosen to the data and calculating relative effect estimates
- Assessing heterogeneity (inconsistency) between direct and indirect estimates

The R software version 3.3.3, the rjags "Just Another Gibbs Sampler" version 4-6 and the "GeMTC" packages in R were used for all statistics unless otherwise specified. The R studio version 1.0.136 was used for editing.

2.2.5.1 Assessing transitivity/similarity

- A traditional pairwise meta-analysis was used to estimate the studies' treatment effect by calculating the Risk Ratio (RR) and confidence intervals (CI) for each pairwise comparison based on the inverse variance weighting for pooling. Both fixed-effect and random-effect models were fitted and an I^2 (percent of variation due to heterogeneity and not to chance, 0 indicates no variation and 100 indicates significant variation) and σ^2 statistics (between-studies variance, > 1 indicates substantial variance) were calculated to estimate the heterogeneity between the studies. If a pairwise meta-analysis could not be performed, for instance in the case of a single RCT of two given treatments, only the RR, CI and p-value were calculated to measure the treatment effect size.
- A visual comparison of all the estimated trial-specific treatment effects using a forest plot displaying RR, CI, Weight, and p-values to assess the size, direction and precision of each treatment effect.

- A generalized estimating equation (GEE) model with repeated measures (binomial distribution with a link function = logit) was used to investigate the changes in the treatment effects while adjusting for different covariates. The procedure "PROC GENMOD" in SAS statistical software version 9.4 was used to run the model. The significance level was set at the 5% level with a p-value <0.05 indicating a significant difference in the treatment effect.

2.2.5.2 Choosing between Bayesian or frequentist and between fixed or random effects models

A Bayesian approach was chosen for the analysis to allow the calculation of probabilistic estimates and the ranking of treatments, advantages that are currently proper to this method. To model the relationship between the treatment (independent variable) and the outcome (induction of remission) a generalized linear model (logistic regression) with a binomial likelihood (binary outcome: remission or no remission), was fitted to the data.

The choice between fixed vs random effects models was made by assessing and comparing the goodness-of-fit of both models. The mean residual deviance $\bar{D}_{res}$ (mean estimate of the deviance of each data point from the fitted model) was calculated and used as an absolute measure of model fit with a $\bar{D}_{res}$ roughly equal to the total number of independent data points indicating an adequate model fit. The deviance information criterion DIC ($\bar{D}_{res} + P_D$ a measure of the model complexity) was also used to help in the selection process where a smaller DIC indicates a better model fit (a difference greater than 5 as a rule of thumb).

2.2.5.3 Building the model

For the calculation of the relative effect estimates, non-informative prior probability distribution (as opposed to informative priors based on current data beliefs) was chosen for the treatment effect measures to allow the observed data to dominate estimation and a Uniform (0, 2) prior probability distribution was chosen for between-study standard deviation given that the relative effect measures estimated in the MA did not vary much ($0 \leq Tau < 2$). The Markov Chain Monte-Carlo (MCMC) algorithm was used to generate posterior distributions of the model parameters, including the relative

treatment effects, the between-study variance and the corresponding credible intervals (CrI). All chains were run with a "burn-in" period of 5,000 (the first 5,000 samples returned from the MCMC algorithm were discarded) followed by 50,000 monitoring iterations and a thinning interval at the 50th MCMC (keeping values intermittently by accepting one in every 50) to ensure convergence of the MCMC sampling algorithm to the posterior distribution.

Convergence was tested by running 4 chains and by visually inspecting the sampling plot for each parameter as well as by using the Brooks-Gelman-Rubin (BGR) statistics. Convergence was deemed achieved if the potential scale reduction factor (psrf) in the BGR test was close to 1 with upper CI $\leq$ 1.05 for each parameter[182]. The posterior log OR and their CrI were calculated to estimate the treatments effects with a CrI not including the null value considered as significant.

2.2.5.4 Assessing inconsistency of the network

The statistical evaluation of heterogeneity (inconsistency) to assess agreement between direct and indirect evidence was done using a consistency model (local method) and an inconsistency model (global method). The first model assesses consistency between direct and indirect evidence at the loop level and the second model assesses this consistency in the whole network. In the consistency model[175], the direct evidence is compared with the indirect evidence calculated as a weighted difference between the NMA estimate and the direct estimate. In the inconsistency model, also called unrelated mean effects (UME)[170], no consistency constraints are placed in the model, and each mean treatment effect is treated as a separate parameter to be estimated, and all treatment effects are drawn from a normal distribution using non-informative priors and under the assumption of a common variance σ^{2}[170]. This model has been advocated when multiple-arm trials are included in the network[170].

Log OR and their CI were calculated for each comparison in each model and the heterogeneity between the results of the consistency model and those of the inconsistency model were measured by an I^2 statistic at the loop level as well as by a global I^2 statistic for the whole network.

2.2.5.5 Ranking of treatments

The Bayesian approach using the MCMC simulated samples allowed the calculation of the probabilities for a specific treatment to be in all possible ranks. Within each MCMC sample, treatments were ranked by their estimated effect sizes and then across all samples, averages to be in the first rank, second, third and so on, were calculated to obtain rank probabilities.

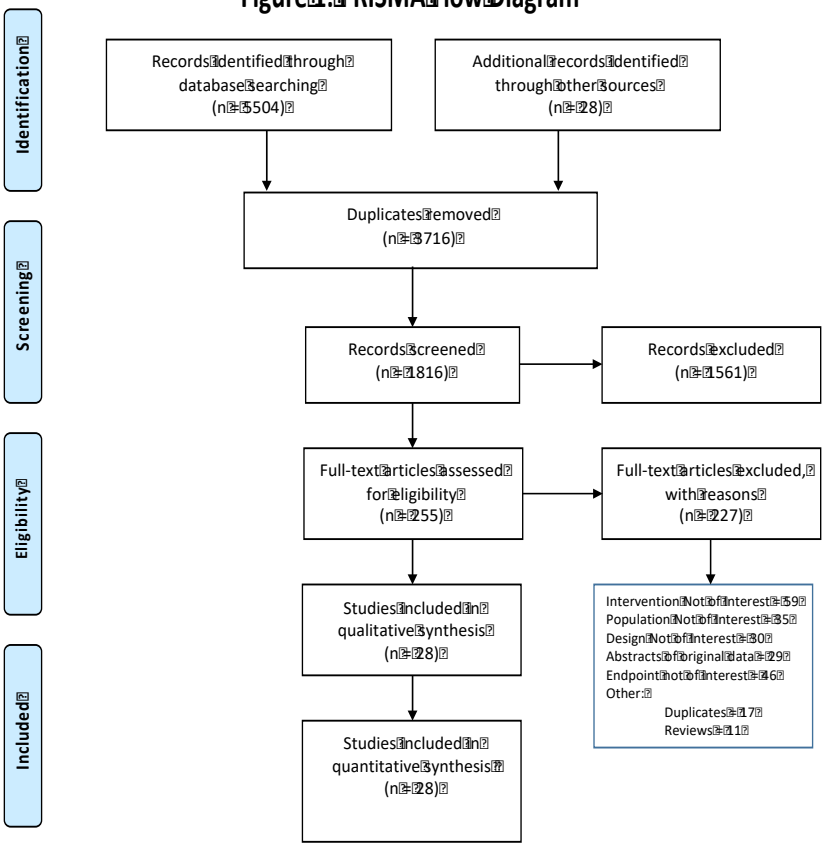
Cumulative rankograms were used to plot the cumulative probability of each treatment to be anywhere between the first and the last rank against the ranks. The surface under the cumulative ranking curve (SUCRA) was used to provide a hierarchy of the treatments. The larger the SUCRA value, the better the rank of the treatment, with SUCRA equal to 1 for the best treatment and to 0 for the worst treatment.

2.3 Results

2.3.1 Search results

The electronic search of databases identified 5504 records and twenty-eight more were identified through the screening of guidelines and meta-analyses. After duplicates were removed, a total of 1816 records remained for review of titles and abstracts, and of these, 255 were selected for full text review. Two hundred twenty-seven were excluded mainly for not meeting the protocol predefined inclusion criteria for patient population, interventions, outcomes or design and few more were duplicates (17) or reviews (11). Twenty-eight studies[183-210] remained and were included in the final analysis. The PRISMA flow diagram was used to report the search results and is shown in Figure 1. The trials' key characteristics have been summarized and are included in Appendix III.

Figure 1: PRISMA Flow Diagram



2.3.2 Risk of bias of included studies

Overall, the included studies were of low risk of bias for most assessed items including random sequence generation, allocation concealment, blinding, incomplete outcome reporting, selective reporting and other sources of bias. Blinding was rated as high risk of bias in two studies, but their overall bias was either low or fair. Most of the studies did not properly explain how they concealed the treatment's allocation but again, the overall risk of bias remained low. The risk of bias is summarized in Table 6.

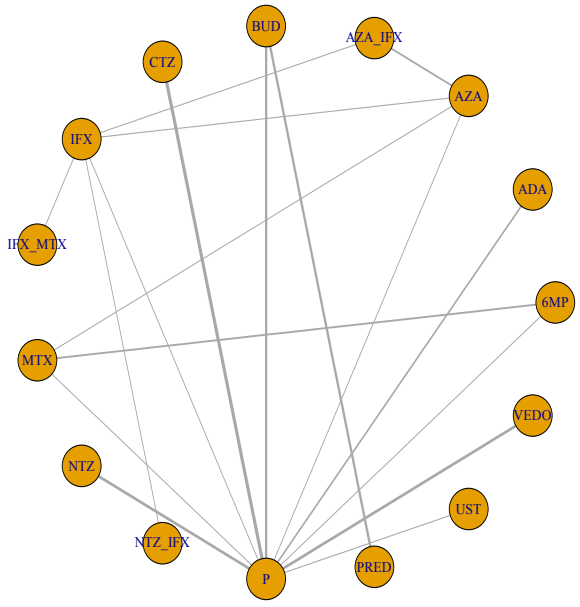
TABLE 6: RISK OF BIAS IN INCLUDED STUDIES FOR THE INDUCTION OF REMISSION ANALYSIS

STUDY		SELECTION BIAS		PERFORMANCE AND DETECTION BIAS	ATTRITION BIAS	REPORTING BIAS	OTHER BIAS	OVERALL RISK OF BIAS
Author	Year	Random Sequence Generation	Allocation Concealment	Blinding	Incomplete Outcome Reporting	Selective Reporting	Other Bias	Overall Risk
ARDIZZONE	2003	Computer generated list	Unclear	HIGH Investigator-blind only	No patients lost to F-up. Withdrawal considered treatment failure	All outcomes reported	No	LOW
Campieri	1997	Unclear (in report) Cochrane report: performed centrally by a computer (information obtained from authors)	Unclear	Double-blind, identical blister packages	Withdrawals and causes reported	All outcomes reported	No	LOW
Colombel	2010	Performed centrally	Perfomed centrally UNCLEAR How	Double-blind Placebo oral and Infusions	Patients lost to F-up considered not in remission	All outcomes reported	No	LOW
Feagan	2008	Random assignment 1:1:1 ratio	Unclear	Double-blind, identical placebo	Withdrawals and causes reported	All outcomes reported	No	LOW
Ghosh	2003	Computer generated list	Block randomization schedule	Double-blind, placebo controlled	Withdrawals and causes reported	All outcomes reported	No	LOW
Greenberg	1994	Centrally generated computer randomisation sequence. Cochrane report from sponsor	Unclear	Double-blind	Withdrawals and causes reported	All outcomes reported	No	LOW
Hanauer	2006	Computer generated list	Interactive voice-response system	Double-blind, placebo controlled	Withdrawals and causes reported	All outcomes reported	No	LOW
Lemann	2006	Computer generated list	Permutation table of size 2 or 4	Double-blind, placebo controlled	Withdrawals and causes reported	All outcomes reported	No	LOW
Mate-Jimenez	2000	Unclear	Unclear	Unclear	Reasons of patients withdrawal described. Worst outcome assumed	Primary outcome & post-hoc outcomes reported	No	FAIR
Rutgeerts	1994	Randomization at each site by block of 4	Unclear	Double-blind, double-dummy	Withdrawals and causes reported	All outcomes reported	No	LOW
Sandborn	2005	Centrally generated computer randomisation sequence	Unclear	Double-blind	Withdrawals and causes reported	All outcomes reported	No	LOW
Sandborn	2013	Computer generated list 3:2 ratio	Unclear	Double-blind, placebo controlled	Withdrawals and causes reported	All outcomes reported	No	LOW
Sandborn	2007	Random assignment 1:1:1 ratio	Unclear	Double-blind, placebo controlled	Withdrawals and causes reported	All outcomes reported	No	LOW
Sandborn	2012	Adaptive randomization performed centrally	Unclear	Double-blind, placebo controlled	Drop-outs/withdrawals and causes reported	All outcomes reported	No	LOW
Sandborn	2007	Centrally generated computer scheme by block of 4	Interactive voice-response system	Double-blind, placebo controlled	Withdrawals and causes reported	All outcomes reported	No	LOW
Sandborn	2011	Centrally generated computer randomisation sequence	Unclear	Double-blind, placebo controlled	Withdrawals and causes reported	All outcomes reported	No	LOW
Sands	2012	Centrally generated computer randomisation sequence by blocks of 16 patients	Interactive voice-response system	Double-blind, placebo controlled	Withdrawals and causes reported	All outcomes reported	No	LOW
Sands	2007	Unclear	Unclear	Double-blind, placebo controlled	Withdrawals and causes reported	All outcomes reported	No	LOW
Schreiber	2005	Prepared by a statistician	Interactive voice-response system	Injections given by a nurse not involved in the study. Investigator blinded	Withdrawals and causes reported	All outcomes reported	No	LOW
Suzuki	2013	Computer generated list	Unclear	Double-blind, placebo matching pills	Withdrawals and causes reported	All outcomes reported	No	LOW
Targan	2007	Centrally generated computer randomisation sequence	Unclear	Double-blind, placebo controlled	Withdrawals and causes reported	All outcomes reported	No	LOW
Targan	1997	Centrally prepared by an independent organisation	Solutions prepared by a pharmacist	Double-blind, placebo controlled	Withdrawals and causes reported	All outcomes reported	No	LOW
Tremaine	2002	Centrally generated computer randomisation sequence by blocks of 5 patients	Unclear	Double-blind	Withdrawals and causes reported	All outcomes reported	No	LOW
Winter	2004	Randomized but method UNCLEAR	Unclear	Double-blind, placebo controlled	Withdrawals and causes reported	All outcomes reported	No	LOW
d'Haens	1998	Randomized but method unclear	Unclear	HIGH	Drop-outs/withdrawals and causes reported	LOW	LOW	FAIR
Oren	1997	Unclear	Unclear	Double-blind. Investigators blinded to treatment assignment	ITT analysis and missing data handling described	All outcomes reported	No	LOW
Feagan	2014	Computer generated sequence based on 3:1:1 ratio	Unclear	Double-blind, placebo controlled	Withdrawals and causes reported	All outcomes reported	No	LOW
Reinisch	2008	Automated using Interactive Voice response randomization system	Automated using Interactive Voice response randomization system	Double-blind, double-dummy	Unclear	All outcomes reported	No	LOW

2.3.3 Network geometry

The network diagram of the trials included in the analysis is shown in Figure 2. It illustrates the direct comparisons among the different treatment agents, with the nodes representing the treatment and the width of the lines connecting them representing the number of trials. The network included 28[183-210] trials, of which 26 were two-arm trials and two were three-arm trials. The trials involved 15 agents or a combination of, including placebo, and 7319 study participants. As expected, most of the interventions were compared to placebo. However, the network does show 4 closed loops.

FIGURE 2: NETWORK CONFIGURATION FOR INDUCTION OF REMISSION DATA



2.3.4 Fixed vs random effects model

The pairwise meta-analyses showed that the interventions' relative effect size varies and that the amount of variation in the whole network as calculated by the I^2 statistic was equal to 62%, suggesting moderate heterogeneity[211]. I^2 is the proportion of

variation that is real and is expressed as a ratio with values between 0% and 100%, where an I^2 value between 50% and 75% indicates moderate heterogeneity. The results are shown in Appendix IV.

The generalized estimating equation (GEE) did not show any significant differences (p-value > 0.05) in the relative treatment effect between the trials when adjusting for key covariates. Those included: treatment duration, age, sex, disease duration, disease location, presence of fistulas, previous surgery, CDAI score at baseline, CRP value at baseline and prior use of anti-TNF∝. The results of the GEE analysis showed that those covariates did not differ between the trials in a way that would have impacted the treatment's effect and confirmed the similarity of the trials on those characteristics. The results of the GEE analyses are shown in Appendix V.

Finally, the posterior samples from the GLM with fixed effect returned a mean residual deviance of $\bar{D}_{res} = 50.68$ and a DIC = 92.93 whereas the samples from the random effects model returned a $\bar{D}_{res} = 51.18$ and a DIC = 95.03. A difference in DIC smaller than 5 suggests similar fit of both models, fixed and random.

However, since the pairwise analysis showed a variation in the whole network that was moderate ($I^2 = 62\%$), the random effects model was chosen for the data analyses.

2.3.5 Effectiveness of therapies to induce remission

To ensure the reliability of the model's effect estimates, convergence (no or minimal variation between the posterior samples and the posteriors to be used in the analysis) was confirmed by visual inspection of the MCMC trace plots for each parameter (Appendix VI) and with the Brooks-Gelman-Rubin (BGR) diagnostic test which showed a potential scale reduction factor (psrf) value of 1.02 with the upper CI value ≤ 1.05 for every parameter (Appendix VIII).

The pooled relative treatment effects, expressed as OR, and the CrI estimates were calculated by exponentiating the posterior means of the log odds ratio (lnOR) obtained from the Bayesian random effects model (Appendix VII), with OR > 1 favoring the drug listed in the column (Table 7).

Adalimumab (ADA), the combination of infliximab with azathioprine (AZA_IFX), budesonide (BUD), infliximab (IFX), natalizumab (NTZ), prednisone (PRED), vedolizumab (VDZ)) and the combination of natalizumab and infliximab (NTZ_IFX) were shown to have statistically significant relative odds of remission when compared to placebo. On the other-hand 6-mercaptopurine (6MP), azathioprine (AZA), certolizumab (CTZ), methotrexate (MTX), ustekinumab (UST) and the combination of infliximab and methotrexate (IFX_MTX) were not different from placebo. The results of UST, IFX_MTX and NTZ_IFX are based on one trial and should be considered with caution.

The combination AZA_IFX showed consistent higher odds in inducing remission when compared to all other treatments with results reaching statistical significance compared to:

- Immuno-suppressant monotherapy: 6MP (OR: 4.9, 95%CrI: 1.52 – 15.96), AZA (OR: 3.35, 95%CrI: 2.2 – 5.16), MTX (OR: 6.11, 95%CrI: 2.23-16.28)
- CTZ (OR: 4.18, 95%CrI: 1.62 – 10.49)
- NTZ (OR: 3.39, 95%CrI: 1.34 – 8.5)

As for anti-TNF$\propto$ monotherapies, infliximab was shown to have increasing odds of inducing remission when compared to AZA (OR: 2.14, 95%CrI: 1.36 – 3.56), to CTZ (OR: 2.66, 95%CrI: 1.12 – 6.62) and to MTX (OR: 3.94, 95%CRI: 1.48 – 11.02) and adalimumab was superior to CTZ (OR: 2.46, 95%CrI: 1.32 – 4.48), to MTX (OR: 3.63, 95%CrI: 1.26 – 9.87), and to NTZ (OR: 1.99, 95%CrI: 1.07 – 3.71).

Prednisone was superior to 6MP (OR: 3.56, 95%CrI: 1.11 – 11.47) and NTZ (OR: 2.44, 95%CrI: 1.19 – 4.95) and both prednisone and budesonide were superior to CTZ (PRED: OR: 3.0, 95% CrI: 1.49 – 6.11; BUD: OR: 2.05, 95% CrI: 1.17 – 3.56) and to MTX (PRED: OR: 4.44, 95% CrI: 1.42 – 12.94; BUD: OR: 3.03, 95% CrI: 1.12 – 8.25).

And finally, the combination of NTZ_IFX was superior to MTX (OR: 5.37, 95%CrI: 1.28 – 22.87). The results of NTZ_IFX are based on a single trial with small sample size and should be considered with caution given the uncertainty around the treatment effect.

TABLE 7: RELATIVE EFFECTS (OR AND CrI) OF PHARMACOLOGICAL AGENTS INCLUDED IN THE INDUCTION OF REMISSION ANALYSIS

	6MP	ADA	AZA	AZA_IFX	BUD	CTZ	IFX	IFX_MTX	MTX	NTZ	NTZ_IFX	P	PRED	UST	VDZ
6MP	6MP	2.86 (0.92, 9.12)	1.46 (0.49, 4.48)	**4.9 (1.52, 15.96)**	2.41 (0.8, 7.24)	1.16 (0.42, 3.19)	3.13 (1, 10.28)	2.86 (0.67, 12.3)	0.8 (0.33, 1.95)	1.48 (0.51, 3.97)	4.39 (0.89, 20.49)	0.94 (0.35, 2.44)	**3.56 (1.11, 11.47)**	1.79 (0.54, 5.58)	1.84 (0.63, 5.1)
ADA	0.35 (0.11, 1.08)	ADA	0.5 (0.19, 1.31)	1.7 (0.58, 4.76)	0.84 (0.41, 1.72)	0.41 (0.22, 0.76)	1.09 (0.39, 2.97)	1 (0.25, 3.97)	0.28 (0.1, 0.79)	0.5 (0.27, 0.93)	1.54 (0.35, 6.17)	0.33 (0.19, 0.55)	1.21 (0.54, 2.86)	0.61 (0.27, 1.42)	0.63 (0.32, 1.27)
AZA	0.68 (0.22, 2.05)	1.99 (0.76, 5.16)	AZA	**3.35 (2.2, 5.16)**	1.65 (0.66, 4.18)	0.8 (0.35, 1.86)	**2.14 (1.36, 3.56)**	1.97 (0.74, 5.42)	0.55 (0.22, 1.34)	0.99 (0.44, 2.36)	2.97 (0.95, 9.49)	0.64 (0.3, 1.42)	2.41 (0.85, 6.75)	1.21 (0.44, 3.46)	1.25 (0.53, 3.03)
AZA_IFX	0.2 (0.06, 0.66)	0.59 (0.21, 1.72)	0.3 (0.19, 0.45)	AZA_IFX	0.49 (0.18, 1.36)	0.24 (0.1, 0.62)	0.64 (0.4, 1.05)	0.59 (0.22, 1.63)	0.16 (0.06, 0.45)	0.3 (0.12, 0.75)	0.89 (0.27, 2.83)	0.19 (0.08, 0.46)	0.71 (0.23, 2.14)	0.36 (0.12, 1.09)	0.38 (0.15, 0.98)
BUD	0.41 (0.14, 1.25)	1.2 (0.58, 2.41)	0.61 (0.24, 1.51)	2.05 (0.73, 5.7)	BUD	0.49 (0.28, 0.85)	1.3 (0.5, 3.63)	1.17 (0.35, 4.62)	0.33 (0.12, 0.9)	0.61 (0.34, 1.04)	1.84 (0.43, 7.1)	0.39 (0.24, 0.62)	1.45 (0.95, 2.29)	0.73 (0.33, 1.67)	0.76 (0.4, 1.4)
CTZ	0.86 (0.31 2.39)	**2.46 (1.32, 4.48)**	1.25 (0.54, 2.83)	**4.18 (1.62, 10.49)**	**2.05 (1.17, 3.56)**	CTZ	**2.66 (1.12, 6.62)**	2.44 (0.7, 8.94)	0.68 (0.28, 1.73)	1.22 (0.84, 1.88)	3.74 (0.93, 14.01)	0.79 (0.6, 1.07)	**3 (1.49, 6.11)**	1.49 (0.75, 3.16)	1.55 (0.96, 2.56)
IFX	0.32 (0.1, 1)	0.91 (0.34, 2.53)	0.47 (0.28, 0.73)	1.55 (0.95, 2.51)	0.77 (0.28, 2.01)	0.38 (0.15, 0.9)	IFX	0.92 (0.38, 2.23)	0.25 (0.09, 0.68)	0.46 (0.19, 1.13)	1.38 (0.5, 4.1)	0.3 (0.13, 0.69)	1.14 (0.36, 3.16)	0.56 (0.19, 1.63)	0.58 (0.23, 1.49)
IFX_MTX	0.35 (0.08, 1.49)	1 (0.25, 3.94)	0.51 (0.18, 1.35)	1.68 (0.61, 4.62)	0.85 (0.22, 2.86)	0.41 (0.11, 1.42)	1.08 (0.45, 2.64)	IFX_MTX	0.28 (0.08, 1.05)	0.51 (0.14, 1.79)	1.49 (0.38, 6.05)	0.33 (0.1, 1.12)	1.23 (0.29, 4.71)	0.61 (0.16, 2.34)	0.63 (0.18, 2.2)
MTX	1.25 (0.51, 3.06)	**3.63 (1.26, 9.87)**	1.82 (0.75, 4.57)	**6.11 (2.23, 16.28)**	**3.03 (1.12, 8.25)**	1.48 (0.58, 3.6)	**3.94 (1.48, 11.02)**	3.63 (0.95, 13.33)	MTX	1.82 (0.73, 4.62)	**5.37 (1.28, 22.87)**	1.17 (0.49, 2.8)	**4.44 (1.42, 12.94)**	2.23 (0.76, 6.36)	2.32 (0.88, 5.93)
NTZ	0.68 (0.25, 1.97)	**1.99 (1.07, 3.71)**	1.01 (0.42, 2.27)	**3.39 (1.34, 8.5)**	1.65 (0.96, 2.92)	0.82 (0.53, 1.2)	2.16 (0.89, 5.21)	1.97 (0.56, 6.96)	0.55 (0.22, 1.38)	NTZ	3.03 (0.74, 10.91)	0.65 (0.48, 0.86)	**2.44 (1.19, 4.95)**	1.21 (0.61, 2.53)	1.26 (0.77, 2.08)
NTZ_IFX	0.23 (0.05, 1.13)	0.65 (0.16, 2.86)	0.34 (0.11, 1.05)	1.13 (0.35, 3.67)	0.54 (0.14, 2.32)	0.27 (0.07, 1.07)	0.73 (0.24, 1.99)	0.67 (0.17, 2.61)	0.19 (0.04, 0.78)	0.33 (0.09, 1.35)	NTZ_IFX	0.21 (0.06, 0.85)	0.81 (0.18, 3.56)	0.41 (0.1, 1.77)	0.42 (0.11, 1.7)
P	1.06 (0.41, 2.89)	**3.06 (1.8, 5.31)**	1.55 (0.7, 3.32)	**5.26 (2.18, 12.55)**	**2.59 (1.62, 4.18)**	1.26 (0.93, 1.67)	**3.32 (1.45, 7.69)**	3.06 (0.9, 10.49)	0.85 (0.36, 2.05)	**1.54 (1.16, 2.1)**	**4.66 (1.17, 16.61)**	P	**3.74 (1.99, 7.32)**	1.86 (1.01, 3.63)	**1.95 (1.31, 2.94)**
PRED	0.28 (0.09, 0.9)	0.83 (0.35, 1.86)	0.41 (0.15, 1.17)	1.4 (0.47, 4.35)	0.69 (0.44, 1.05)	0.33 (0.16, 0.67)	0.88 (0.32, 2.8)	0.81 (0.21, 3.42)	0.23 (0.08, 0.7)	0.41 (0.2, 0.84)	1.23 (0.28, 5.58)	0.27 (0.14, 0.5)	PRED	0.5 (0.2, 1.27)	0.52 (0.24, 1.12)
UST	0.56 (0.18, 1.84)	1.63 (0.7, 3.71)	0.83 (0.29, 2.27)	2.8 (0.91, 8.08)	1.38 (0.6, 3.03)	0.67 (0.32, 1.34)	1.79 (0.61, 5.16)	1.63 (0.43, 6.42)	0.45 (0.16, 1.31)	0.83 (0.39, 1.63)	2.44 (0.57, 10.07)	0.54 (0.28, 0.99)	1.99 (0.79, 4.9)	UST	1.04 (0.48, 2.16)
VDZ	0.54 (0.2, 1.58)	1.58 (0.79, 3.13)	0.8 (0.33, 1.88)	2.66 (1.02, 6.89)	1.32 (0.71, 2.48)	0.64 (0.39, 1.04)	1.72 (0.67, 4.35)	1.6 (0.45, 5.53)	0.43 (0.17, 1.14)	0.79 (0.48, 1.3)	2.39 (0.59, 9.12)	0.51 (0.34, 0.76)	1.93 (0.9, 4.22)	0.96 (0.46, 2.08)	VDZ

AGENTS IN COLUMNS ARE COMPARED TO AGENTS IN ROWS (REFERENCE) - SIGNIFICANT VALUES ARE IN BOLD AND "OR" UNDERLINED

2.3.6 Assessment of heterogeneity/inconsistency in the network

As stated in the methods section 2.2.5.4, two different statistical methods (UME, and consistency) were used to assess the inconsistency in the network.

The points estimate and CI for each comparison, in each of the UME and consistency models are shown in Appendix IX. The I^2 statistic comparing the results between these two models showed no evidence of inconsistency with a p-value > 0.05 for all comparisons within a given loop (Table 8). The global assessment of the heterogeneity

within the whole network also showed no inconsistency as per a global I^2 statistic equal to 0 for both the consistency and inconsistency models (Table 8).

TABLE 8: ANALYSIS OF HETEROGENEITY

Per-comparison I-squared:

	t1	t2	i2.pair	i2.cons	incons.p
1	6MP	MTX	2.107596	6.249207	NA
2	6MP	P	NA	0.000000	0.6603350
3	ADA	P	0.000000	0.000000	NA
4	AZA_IFX	IFX	NA	0.000000	0.6819529
5	AZA	AZA_IFX	0.000000	0.000000	NA
6	AZA	IFX	NA	0.000000	0.4483018
7	AZA	MTX	NA	0.000000	0.3581580
8	AZA	P	NA	0.000000	0.3602882
9	BUD	P	0.000000	0.000000	NA
10	BUD	PRED	0.000000	0.000000	NA
11	CTZ	P	0.000000	0.000000	NA
12	IFX	IFX_MTX	NA	NA	NA
13	IFX	NTZ_IFX	NA	NA	NA
14	IFX	P	NA	48.374097	0.2225084
15	MTX	P	NA	0.000000	0.7598991
16	NTZ	P	0.000000	0.000000	NA
17	P	UST	NA	NA	NA
18	P	VEDO	0.000000	0.000000	NA

Global I-squared:

	i2.pair	i2.cons
1	0	0

t1 = first treatment; t2 = second treatment; i2.pair = variance in the unrelated mean effect (UME) model; i2.cons = variance in the consistency model; incons.p = p value of comparison between UME and consistency model

2.3.7 Ranking of treatments

NMA offers the advantage of estimating the probability that each treatment is the best among all other treatments included in the analysis, for each outcome analyzed. The probability of each treatment to achieve each possible rank was calculated based on the MCMC simulated samples of posterior treatment effects. These probabilities are presented in Table 9 where the total of each column or row is equal to 100% and graphically, as a rankogram, in Figure 3.

The results showed that the combination of AZA_IFX had the highest probability of being in rank number 1 (36.0%) followed by the combination of NTZ_IFX (33.6%) and PRED (0.165). The results of NTZ_IFX are based on a single trial with small sample size and should be considered with caution given the uncertainty around the treatment

effect. Methotrexate and placebo had the highest probability of being in rank number 15 (worst among the 15 agents), 49% and 24%, respectively.

Also, the surface under the cumulative ranking curve (SUCRA) for each treatment, which accounts for the probabilities across the ranks, was calculated to identify the best overall, 2nd best overall and so forth with a value of 1 indicating the best overall and 0 for the worst. The SUCRA plots are shown in Figure 4. Once again, the combination of AZA_IFX was rated best overall with a SUCRA value of 91.89%, followed by the combination NTZ_IFX (SUCRA = 83.51%) and by PRED (SUCRA = 82.12%). On the other hand, placebo was rated among the worst with a SUCRA value of 15.93% followed by MTX (SUCRA = 15.06%). Again, the results of NTZ_IFX are based on a single trial with small sample size and should be considered with caution given the uncertainty around the treatment effect.

In general, ranking probabilities and SUCRA results should always be considered with the relative treatment effect and CI of an intervention given the uncertainty around the measurements when data are sparse.

TABLE 9: PROBABILTIES FOR EACH TREATMENT OF BEING THE MOST EFFECTIVE OR LEAST EFFECTIVE

Treatment	1st	2nd	3rd	4th	5th	6th	7th	8th	9th	10th	11th	12th	13th	14th	15th
6MP	0	0.002	0.004	0.005	0.01	0.014	0.021	0.03	0.056	0.069	0.094	0.111	0.129	0.247	0.206
ADA	0.054	0.102	0.121	0.127	0.177	0.179	0.12	0.066	0.027	0.015	0.006	0.002	0	0	0
AZA	0	0	0	0.003	0.023	0.045	0.076	0.124	0.133	0.123	0.144	0.128	0.094	0.074	0.032
AZA_IFX	0.36	0.337	0.156	0.074	0.04	0.019	0.008	0.004	0.001	0	0	0	0	0	0
BUD	0.002	0.022	0.064	0.114	0.128	0.188	0.212	0.14	0.078	0.036	0.013	0.004	0.001	0	0
CTZ	0	0	0	0	0	0.002	0.004	0.012	0.035	0.091	0.207	0.32	0.196	0.117	0.016
IFX	0.003	0.062	0.211	0.248	0.162	0.12	0.091	0.056	0.029	0.011	0.005	0.002	0	0	0
IFX_MTX	0.074	0.111	0.128	0.134	0.114	0.088	0.088	0.069	0.059	0.04	0.035	0.021	0.018	0.012	0.009
MTX	0	0	0	0	0.001	0.003	0.005	0.01	0.018	0.031	0.052	0.072	0.106	0.212	0.49
NTZ	0	0	0	0.002	0.006	0.013	0.033	0.081	0.162	0.27	0.237	0.126	0.052	0.018	0
NTZ_IFX	0.336	0.187	0.102	0.092	0.069	0.061	0.045	0.032	0.023	0.017	0.013	0.009	0.006	0.006	0.002
P	0	0	0	0	0	0	0	0	0.002	0.004	0.019	0.098	0.348	0.295	0.235
PRED	0.165	0.161	0.181	0.151	0.159	0.103	0.041	0.019	0.011	0.005	0.002	0.001	0	0	0
UST	0.005	0.011	0.023	0.034	0.061	0.074	0.114	0.143	0.151	0.142	0.106	0.07	0.037	0.018	0.01
VDZ	0	0.004	0.01	0.016	0.05	0.09	0.141	0.213	0.215	0.146	0.066	0.034	0.012	0.001	0

The overall sum of each column or row should total 1 (100%)

FIGURE 3: PROBABILITIES FOR EACH TREATMENT OF BEING THE BEST, SECOND, THIRD…

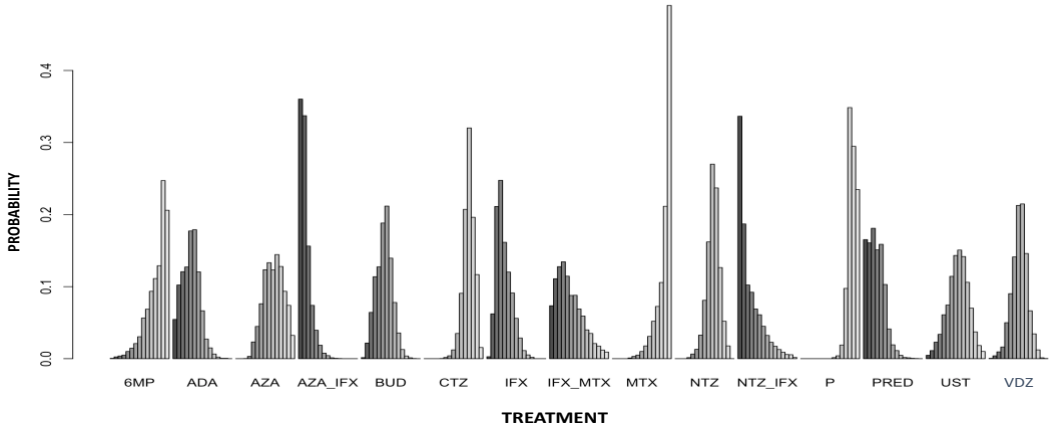
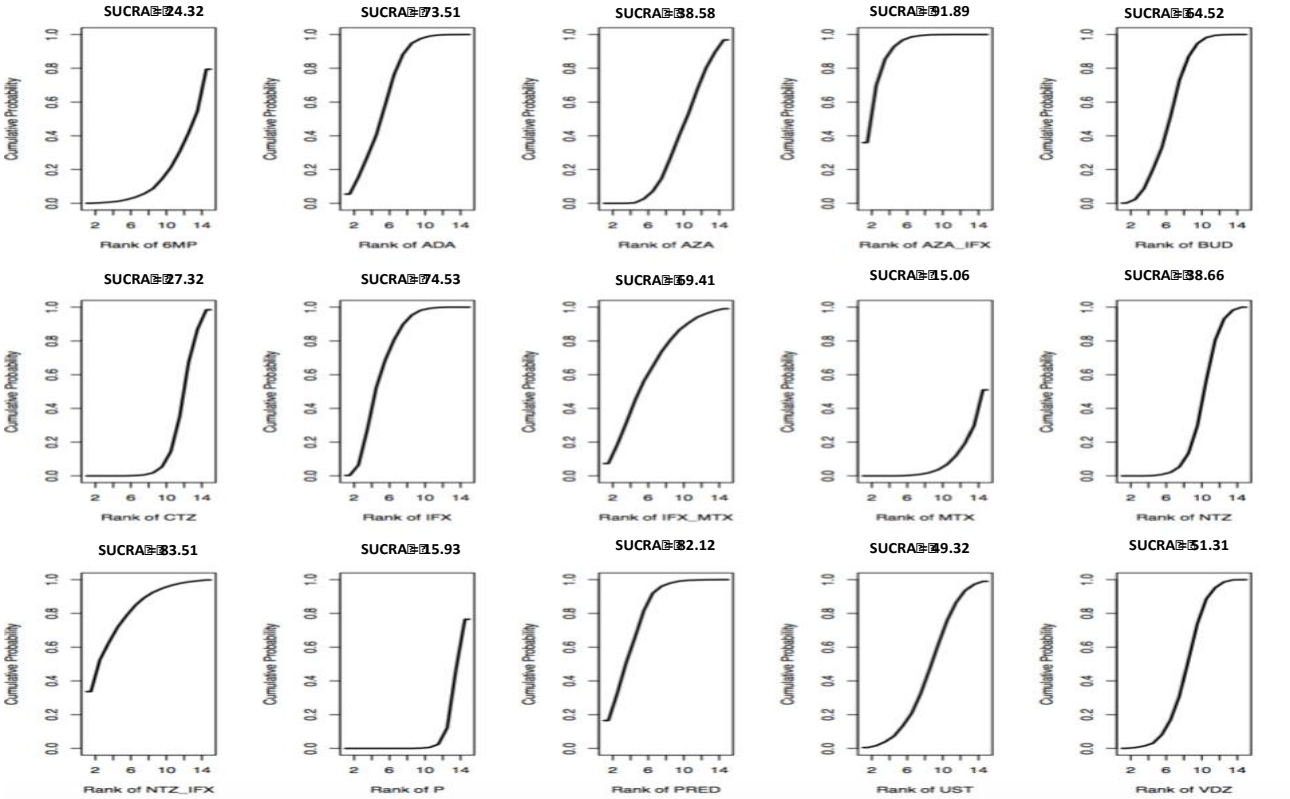


FIGURE 4: SURFACE UNDER THE CUMULATIVE RANKING CURVE (SUCRA) PLOTS FOR EACH TREATMENT



2.4 DISCUSSION

2.4.1 Key findings and comparisons with existing evidence

This research encompassed a systematic review and network meta-analysis of randomized controlled trials of pharmacological treatments, approved by regulatory bodies, for the induction of remission in adult patients with moderate to severe Crohn's disease. The search identified 28 trials, most of which (19 trials, 68%) had placebo as the comparator agent. Based on this network meta-analysis the combination of infliximab and azathioprine was the most effective therapy for inducing remission in patients with moderate to severe Crohn's disease.

Most drugs included in this analysis showed greater efficacy in inducing remission compared to placebo, however this difference was not statistically significant when the IS (methotrexate, azathioprine, 6-mercaptopurine), the combination of infliximab with methotrexate and two biologic mono-therapies CTZ and UST were compared to placebo.

The finding of AZA and 6MP not being different from placebo for the induction of remission is consistent with findings from a Cochrane meta-analysis[212] and from a published network meta-analysis of IS and biologic agents in patients with Crohn's disease[7]. The efficacy of thiopurines for the treatment of CD has been a topic of debate for years with some studies showing positive[213-216] and some others negative results[217-219]. The conflicting results between trials were attributed to the drugs not having been used at the right dose and for the right follow-up period[220,221]. However, the pairwise meta-analysis of RCT by Chande et al.[212], while accounting for the duration of therapy, drug dosages and concomitant therapies, has confirmed the lack of efficacy of these drugs for the induction of remission but has shown their beneficial effects in reducing patients' steroid consumption. This finding also supports current clinical practice whereby monotherapy with thiopurines is not used for the induction of remission but is rather considered an alternative option for the maintenance of remission and as a steroid-sparing agent in patients with moderate to severe CD. As for MTX, the finding in this analysis of this agent not being different from placebo in inducing remission was corroborated in the recent technical review of the American Gastroenterology Association on the use of MTX (and thiopurines) in CD[122]. This report concluded that this IS was no more effective than placebo in inducing remission in CD. Also, a meta-analysis by the Cochrane Collaborative group[222] has shown low doses of MTX not to be statistically

different in failure to induce remission when compared to placebo or to 6MP. This meta-analysis has however shown, based on one trial, that the high dose of this agent (25 mg/kg/week) to be more effective than placebo in inducing remission and complete withdrawal of steroid in patients with refractory CD[222]. More dose-ranging trials of this IS are needed to determine the appropriate dose for induction and maintenance of remission in patients with CD.

The finding from this research showing the combination of IFX_MTX not to be more effective than placebo was demonstrated in the NMA by Hazlewood et al.[7] and the result of it being less effective than IFX monotherapy was similarly shown in a RCT trial including 126 patients with moderate to severe CD[188,223]. This finding negates the positive result seen in a small pilot, open-label trial of this combination vs IFX alone[223]. The results regarding this combination need to be considered with caution while accounting for the fact they are based on a single trial.

With regards to CTZ not being different from placebo and being less effective than other anti-TNF agents included in the analysis, this was also demonstrated in two other NMA[5,7] looking at the comparative efficacy of biologic agents in patients with moderate to severe CD. As for the results of UST not being different from placebo in this analysis, they were based on a single RCT. A recent pairwise meta-analysis[224] that included the latest (2016) phase III trials' results with UST[225] suggested greater efficacy of this drug over placebo for inducing remission in active Crohn's disease.

The other agents included in the analysis have shown significant positive results when compared to placebo. The results of BUD and PRED having greater efficacy in inducing remission when compared to placebo were also shown in other research, pairwise[226,227] and network meta-analyses[1,3] assessing the efficacy of either one or both against placebo or against active comparators. The meta-analysis by the Cochrane Collaboration group, evaluating systemic corticosteroids[226], showed greater efficacy when these drugs were used for more than 15 weeks. The meta-analysis looking at the efficacy of BUD[227] showed its short-term efficacy to be less than with conventional steroids, particularly in patients with severe CD or extensive colonic involvement.

As for the combination of biologic agents with IS, the combination AZA_IFX had the highest efficacy rates among all other treatments with differences reaching statistical

significance when compared to IS (AZA, 6-MP, MTX), CTZ, NTZ and to placebo. The higher efficacy rates of this combination was also shown in the NMA conducted by Hazlewood et al[7] and supports the results of the SONIC[185] trial which showed superiority of the combination therapy vs IFX and AZA monotherapies. Whether combining other anti-TNF agents with immunosuppressive therapy would result in similar increased efficacy rates still needs to be researched. One MA[228] of RCTs with infliximab, adalimumab and certolizumab showed that only the association of infliximab with IS offered improved clinical remission rates. With regards to the combination of NTZ_IFX, although the efficacy rates were numerically higher than most agents, with difference reaching statistical significance vs MTX and placebo, those results were based on one trial with relatively small sample size and should be considered with caution given the weak precision of the trial as indicated by the wide CrI obtained around the relative effects.

When looking at biologic monotherapies, the results of this research have shown that IFX was more effective than CTZ, MTX, AZA and placebo and ADA was superior to CTZ, NTZ, MTX and placebo. The NMA by Hazelwood et al.[7] also showed higher efficacy rates with ADA in comparison with CTZ but the study did not include the trials of NTZ. A NMA by Stidham et al.[6] with a literature search up to August 2013 and focusing on anti-TNF∝ monotherapies, showed no statistically significant difference among IFX, ADA and CTZ, but numerically IFX had greater efficacy than ADA and CTZ and ADA was superior to CTZ in inducing remission in CD. The study, however, included fewer trials particularly of infliximab. A more recent NMA by Miligkos, et al.[9], covering the period from 1997 to 2014, showed no statistically significant difference between anti-TNF∝ and anti-integrin agents with respect to induction and maintenance of response and remission. The analysis included a different set of studies given the time-period covered and looked at monotherapies, considering any combination drug as a placebo, which may have contributed to the differences seen between the results.

Finally, the analysis of the ranking probabilities of each treatment being the best, second best, third best and so on, as well as of the surface under the cumulative ranking curves suggested that the combination of IFX_AZA had the highest probability of being ranked number one followed by the combination of NTZ_IFX and by PRED. The ranking results of IFX_AZA were also shown in the NMA by Hazlewood et al[7]. The results of NTZ_IFX

should be considered with caution given they were based on one small trial. Also, the probabilities of being in each rank and the SUCRA results should always be considered along with the relative treatment effect and CI of an intervention given that the probabilities are based on the size of effect of a given treatment without consideration to the uncertainty around the measurement.

As is usually the case in clinical practice, these efficacy results need to be weighed against the potential risk for adverse events. The immunosuppression induced by CD treatments has been suspected to lead to increased risk of infections and cancer. Observational studies, RCT and MA have been conducted to identify any treatment-exposure relationship. The results of key studies are summarized in table 10 for infections and table 11 for malignancies. First regarding the risk of infections, the data from the TREAT registry[229] have shown that prednisone and infliximab were associated with an increased risk of serious infections, while the combination of IFX with an immunosuppressant did not increase the risk beyond what was seen with infliximab monotherapy. The data also showed that moderate to severe CD was an independent risk factor for serious infections which put to question whether the observed serious infections were due to the treatment or to IBD itself. The SONIC trial[132] reported the rates of serious infections observed in patients on AZA and IFX monotherapies as well as in those on combination therapy. The results showed there was no increased risk of serious infections in patients on the combination therapy compared to those on monotherapy. This result was confirmed in a MA by Lin et al.[230]. Other MA[10,231] have assessed the risk of infections with biologics and have shown an increased risk of opportunistic infections with these agents but not of serious infections. This result contradicts the results from a NMA by Singh et al.[232] which showed an increased risk of serious infections with biologics. However, this NMA did not include any head-to-head treatment comparisons and was based only on indirect evidence, which may have caused less precise estimates. Tuberculosis (TB) is on the other hand a relatively rare event, and hence although the NMA by Bonovas et al.[10] has shown an increased risk of this event with biologics, the result was not statistically significant compared to the control group. This increased risk of TB was not shown in the MA by Ford et al.[231]

TABLE 10: RISK OF SERIOUS INFECTIONS	
	OR (CI)

OBSERVATIONAL DATA
• TREAT
  ○ Prednisone
  ○ Infliximab
  ○ CS + IS or anti-TNF
  ○ IS + anti-TNF
	
	1.57 (1.17-2.10)
	1.43 (1.11-1.84)
	↑ risk when CS added
	No additional risk with combo vs alone

	% (p-value)

RCT
• SONIC
  ○ AZA
  ○ IFX
  ○ AZA + IFX
	
	5.6
	4.9 (NS)
	3.9 (NS)

	OR (CI)

MA
• Pairwise (Lin)
  ○ IFX vs IFX + IS
• Pairwise (Ford)
  ○ Anti-TNF vs control
  ▪ Opportunistic infections (OI)
  ▪ Serious Inf.
  ▪ Tuberculosis
• NMA (Singh)
  ○ Biologics vs Control
• NMA (Bonovas)
  ○ Biologics vs Control
  ▪ OI
  ▪ Serious Inf.
  ▪ Tuberculosis
	
	0.68 (0.37-1.24)
	
	2.05 (1.10-3.85)
	
	1.95 (0.97-3.90)
	2.52 (0.62-10.21)
	
	1.37 (1.04-1.82)
	
	1.90 (1.21-3.01)
	0.89 (0.71-1.12)
	2.04 (0.71-5.89)

As for the risk of cancer, three observational studies have assessed the risk of non-melanoma skin cancer (NMSC). The first, a prospective study[233] using the CESAME registry, included 20,000 patients with a median follow-up time of 35 months and 49,719 patient-years. The study showed an increased risk of NMSC in patients continuing or previously exposed to thiopurine compared to thiopurine-naïve patients with IBD in whom the risk of NMSC was similar to that observed in the general population. The study did not show an increased risk of NMSC with ongoing or previous exposure to other immunosuppressant such as anti-TNF, methotrexate, cyclosporine, mycophenolate mofetil

and cyclophosphamide. The second study[234] assessed the risk of cancer in patients on infliximab compared to patients on other treatments-only using data from the TREAT registry. Like the data from the CESAME registry, this analysis did not show any additional risk of NMSC in the group of patients receiving infliximab. The third, a retrospective study[235], included 53,377 patients (26,403 with CD) with a median follow-up of 730 days. This study showed an increased risk of NMSC with ongoing and previous exposure to thiopurine and to any other immunosuppressive therapy, including the combination of immunomodulator and biologic. The differences in results between the observational studies regarding the risk associated with the other immunosuppressive therapies, or with combination therapies, may have been due to the differences in design, patient population and exposure-time to medication.

The risk of non-Hodgkin's lymphoma (NHL) was also evaluated using the CESAME registry data[236]. The results from this analysis showed an increased risk of NHL with thiopurines, anti-TNF, combination therapy of thiopurine and anti-TNF, as well as in patients continuing the thiopurine treatment but who discontinued the anti-TNF agent, as compared to the control group. The analyses of the patient-population receiving anti-TNF were however underpowered to detect any meaningful differences given that the sample was small (approximately 5% of the cohort). The analysis of the TREAT data[234] on the other hand, showed no additional risk in patients receiving infliximab compared to the control group. Consistent with the analysis of the TREAT data, a NMA by Singh et al.[232] looking at the adverse effects associated with biologics found no increased risk of lymphoma in patients receiving biologics compared to the control group. Also, an analysis of the Cochrane data on biologics from 2014[237], has concluded that there was no clear evidence of an increased risk of NHL with biologics beyond the risk seen with thiopurine alone.

Finally, the overall risk of cancer was assessed in two observational studies using the CESAME[236] and TREAT[234] registries as well as in a NMA[10] of thirty-three RCT of biologic agents. All the analyses showed no increased risk of overall malignancies with biologics as compared to the control treatment.

TABLE 11: RISK OF CANCER	
	OR (CI)
NON-MELANOMA SKIN CANCER	
□ Observational (CESAME) (20,000 pts – 35 months)	
○ Thiopurine ongoing	5.9 (2.1-16.4)
○ Thiopurine past	3.9 (1.3-12.1)
○ Other IS including anti-TNF ongoing	0.8 (0.3-2.6)
○ Other IS including anti-TNF – past	1.0 (0.4-2.7)
□ Observational (TREAT)	
○ Infliximab vs control	0.89 (0.45-1.74)
□ Retrospective cohort (53,377 pts – 730 days) (results: for use > 365d)	
○ Immunomodulators	4.45 (2.94-6.75)
○ Anti-TNF (IFX or ADA)	3.23 (1.24-8.45)
○ Combination	6.75 (2.74-16.65)
Non-Hodgkin's Lymphoma	
□ Observational (CESAME)	
○ Thiopurine (TH)	6.86 (3.85-11.31)
○ Anti-TNF (small sample ~5%)	4.53 (0.55-16.4)
○ TH + anti-TNF	10.2 (1.24-36.9)
○ TH + discontinued anti-TNF	6.53 (3.48-11.2)
○ Never received TH or anti-TNF	1.45 (0.53-3.16)
□ Observational (TREAT)	
○ Infliximab vs control	RR: 0.98 (0.34-2.82)
□ NMA	
○ Biologics vs control	0.53 (0.17-1.66)
Overall Cancer	
□ Observational (TREAT)	
○ Anti-TNF vs Control	RR: 0.74 (0.49-1.12)
□ Observational (CESAME)	
○ Anti-TNF vs Control	0.62 (-0.45-0.18)
□ NMA (Bonovas)	
○ Biologics vs Control	0.90 (0.54-1.50)

2.4.2 Limitations and Future Needs

The validity of NMA is built upon the assumption that patients in the network are similar with respect to key effect modifiers and could, in principle, be randomized to any of the treatments. In this analysis, the selection of trials was based on strict inclusion criteria, such as study design (RCT only), age (adults ≥ 18) and baseline CDAI (220 – 450) to minimize bias. However, randomization, although a guarantee of reduced bias within a given trial, is not a guarantee of reduced bias between trials. The trials in this network differed in several aspects including dosing of medication, duration of treatment, definition of remission, concomitant medications and exclusion criteria related to CD which may have introduced heterogeneity in the network and influenced the assessment of the relative efficacy of treatments. Nevertheless, as reported in the results section, the regression analysis (GEE) did

not show any statistically significant impact on the treatment effect that may have resulted from differences in these covariates. Also, a random effect model was used for the analysis which accounts for heterogeneity between the trials.

CDAI is the standard scoring index used in clinical trials to assess the disease severity. However, as discussed earlier, CDAI does not correlate well with endoscopic measurement of inflammation and is not a good predictor of remission or of disease burden[238,239], hence, it is a limitation of any effectiveness analysis that is based on this scoring system. The limited number of trials assessing mucosal healing as a primary endpoint makes it difficult today to use it as criteria for remission when conducting comparative effectiveness research. There is currently a strong need for a rapid change in research and regulatory requirements whereby therapeutic remission in CD, and more generally in IBD, will incorporate objective endpoints (endoscopic, histological, biomarkers) and patient reported outcomes (PRO).

This NMA has found the combination of IFX and AZA to be the most effective treatment for the induction of remission in CD. Previous research has found the combination of IFX_AZA to be effective in reducing anti-drug-antibody levels and to reduce immunogenicity[240,241]. Immunogenicity is a major concern with biologic drugs. Although studies have shown the combination of other anti-TNF (ADA and CTZ) with IS to have anti-drug antibody effect, there are currently no direct comparative studies demonstrating that this anti-immunogenic effect would result in better efficacy of these combined agents and data from subgroups analyses and observational studies are conflicting[242-246]. More research is needed in this area which may offer clinicians new evidence in support of alternative treatment options for managing their patients' disease.

While there are no clear guidelines today on the number of closed loops that constitutes a strong network, this research included four closed loops and showed consistency between direct and indirect treatment effects within the loops. However, the small number of head-to-head trials and reliance on indirect evidence for certain comparisons may have resulted in less precise estimates (wide CI) of the drugs' efficacy.

Finally, the conservative approach used for the analysis, i.e. non-informative priors and allowing the data to dominate, favors type II error (false negative) and reduces chances of type I error (false positive)[247-249].

2.4.3 Conclusion

This network meta-analysis is the first to integrate in one analysis an evaluation of the efficacy of all agents that are recommended today for the management of patients with moderate to severe Crohn's disease and hence, to allow a comparison between classes including corticosteroid agents.

The analysis has shown all agents to be more efficacious than placebo, but differences between the immuno-suppressants (AZA, 6-MP, MTX), the combination IFX_MTX, CTZ, UST and placebo were not statistically significant. Any conclusion regarding the relative efficacy of UST, IFX_MTX and NTZ_IFX should, however, be made with caution, given that only one trial of each of these agents was included in the analysis. Looking at the relative efficacy of monotherapies, the analysis showed PRED to have higher relative effects than all other agents, followed by IFX and ADA although statistical significance was reached only when these agents were compared to: 1) 6MP, CTZ, MTX, NTZ for PRED, 2) AZA, CTZ, MTX for IFX, 3) CTZ, MTX, NTZ for ADA.

Overall, this analysis indicates that the combination of IFX_AZA is the most efficacious treatment for the induction of remission in patients with moderate to severe Crohn's disease. More research encompassing objective measures of disease activity and patient-reported outcomes, as well as complete reporting of key prognostic factors (disease duration, location and behavior, previous surgery, presence of fistulas, previous and concomitant medications) in clinical research trials, would add to the strength of inferences and the quality of evidence from comparative effectiveness analyses.

APPENDIX I

SEARCH STRATEGY
1990 – 0CTOBER 2015

EMBASE – BIOLOGIC DRUGS

#	Search Statement
1	(Inflammatory Bowel Diseases or Inflammatory Bowel Disease).mp. or inflammatory bowel disease/
2	(ileitis or enteritis or ileocolitis or colitis).ti,ab.
3	1 or 2
4	Crohn*.ti,ab.
5	3 and 4
6	Crohn disease/
7	(Crohn's Disease or Crohn Disease or Crohns Disease).mp.
8	5 or 6 or 7
9	clinical trial/
10	69rench6969du controlled trial/
11	randomization/
12	single blind procedure/
13	double blind procedure/
14	crossover procedure/
15	placebo/
16	randomi?ed controlled trial$.tw.
17	rct.tw.
18	random allocation.tw.
19	randomly allocated.tw.
20	allocated randomly.tw.
21	(allocated adj2 random).tw.
22	single blind$.tw.
23	double blind$.tw.

24	((treble or triple) adj blind$).tw.
25	placebo$.tw.
26	prospective study/
27	or/9-26
28	case study/
29	case report.tw.
30	abstract report/ or letter/
31	or/28-30
32	27 not 31
33	animal/ not human/
34	32 not 33
35	8 and 34
36	adult/ or adult.mp. or adults.mp.
37	35 and 36
38	adalimumab/
39	infliximab/
40	certolizumab pegol/
41	natalizumab/
42	ustekinumab/
43	(adalimumab or infliximab or certolizumab o rnatalizumab or ustekinumab).mp.
44	[monoclonal antibody/ae, ct, ad, do, dt, pe [Adverse Drug Reaction, Clinical Trial, Drug Administration, Drug Dose, Drug Therapy, Pharmacoeconomics]]
45	[antibody/ae, ct, ad, do, dt, pe [Adverse Drug Reaction, Clinical Trial, Drug Administration, Drug Dose, Drug Therapy, Pharmacoeconomics]]
46	Anti-Inflammatory Agents/
47	“anti-inflammatory agent*”.ti,ab.
48	(anti-tumour necrosis or anti-tumor necrosis or anti-TNF or biologic or biologics).ti,ab.
49	tumor necrosis factor/
50	tumor necrosis factor alpha/
51	(tumor necrosis factor or tnf).ti,ab.
52	49 or 50 or 51

53	(antibod* or antagonist or antagonists or inhibitor*).ti,ab.
54	(agent* or treatment* or treated or therap* or drug or drugs or medication*).ti,ab.
55	52 and 53 and 54
56	or/38-48
57	56 or 55
58	37 and 57
59	limit 58 to ((71rench71 or 71rench) and yr=”1990 –Current”)

EMBASE – CORTICOSTEROID DRUGS

#	Search Statement
1	(Inflammatory Bowel Diseases or Inflammatory Bowel Disease).mp. or inflammatory bowel disease/
2	(ileitis or enteritis or ileocolitis or colitis).ti,ab.
3	1 or 2
4	Crohn*.ti,ab.
5	3 and 4
6	Crohn disease/
7	(Crohn’s Disease or Crohn Disease or Crohns Disease).mp.
8	5 or 6 or 7
9	clinical trial/
10	71rench7171du controlled trial/
11	randomization/
12	single blind procedure/
13	double blind procedure/
14	crossover procedure/
15	placebo/
16	randomi?ed controlled trial$.tw.
17	rct.tw.
18	random allocation.tw.

19	randomly allocated.tw.
20	allocated randomly.tw.
21	(allocated adj2 random).tw.
22	single blind$.tw.
23	double blind$.tw.
24	((treble or triple) adj blind$).tw.
25	placebo$.tw.
26	prospective study/
27	or/9-26
28	case study/
29	case report.tw.
30	abstract report/ or letter/
31	or/28-30
32	27 not 31
33	animal/ not human/
34	32 not 33
35	8 and 34
36	adult/ or adult.mp. or adults.mp.
37	35 and 36
38	glucocorticoid/ or budesonide/
39	“glucocorticoid*”.ti,ab.
40	budesonide.mp.
41	hydrocortisone/
42	hydrocortisone.ti,ab.
43	methylprednisolone/
44	methylprednisolone.ti,ab.
45	prednisolone/
46	prednisolone.ti,ab.
47	prednisone/
48	prednisone.ti,ab.

49	6-methylprednisolone.ti,ab.
50	corticosteroid/ or corticosteroid*.mp.
51	38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50
52	37 and 51
53	limit 52 to ((73rench73 or 73rench) and yr=”1990 –Current”)

EMBASE – IMMUNOSUPPRESSANT DRUGS

#	Search Statement
1	(Inflammatory Bowel Diseases or Inflammatory Bowel Disease).mp. or inflammatory bowel disease/
2	(ileitis or enteritis or ileocolitis or colitis).ti,ab.
3	1 or 2
4	Crohn*.ti,ab.
5	3 and 4
6	Crohn disease/
7	(Crohn’s Disease or Crohn Disease or Crohns Disease).mp.
8	5 or 6 or 7
9	clinical trial/
10	73rench7373du controlled trial/
11	randomization/
12	single blind procedure/
13	double blind procedure/
14	crossover procedure/
15	placebo/
16	randomi?ed controlled trial$.tw.
17	rct.tw.
18	random allocation.tw.
19	randomly allocated.tw.
20	allocated randomly.tw.
21	(allocated adj2 random).tw.

22	single blind$.tw.
23	double blind$.tw.
24	((treble or triple) adj blind$).tw.
25	placebo$.tw.
26	prospective study/
27	or/9-26
28	case study/
29	case report.tw.
30	abstract report/ or letter/
31	or/28-30
32	27 not 31
33	animal/ not human/
34	32 not 33
35	8 and 34
36	adult/ or adult.mp. or adults.mp.
37	35 and 36
38	immunosuppressive agent/
39	immunosuppressive agent*.mp.
40	immunosuppressive treatment/
41	Immunosuppression.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
42	immunosuppressive.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
43	immunosuppressives.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
44	immunomodulating agent/
45	(74rench7474dulatory or immunomodulating).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
46	antineoplastic antimetabolite/
47	anti-metabolite.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword

	heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
48	azathioprine/
49	methotrexate/
50	mercaptopurine/
51	(6-Mercaptopurine or Methotrexate or azathioprine).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
52	38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51
53	37 and 52
54	limit 53 to ((75rench75 or 75rench) and yr="1990 –Current")

MEDLINE – BIOLOGIC DRUGS

#	Search Statement
1	Inflammatory Bowel Diseases.mp. or Inflammatory Bowel Diseases/
2	Inflammatory Bowel Disease.mp.
3	(ileitis or enteritis or ileocolitis or colitis).ti,ab.
4	1 or 2 or 3
5	Crohn*.ti,ab.
6	4 and 5
7	Crohn Disease/
8	(Crohn's Disease or Crohn Disease or Crohns Disease).mp.
9	6 or 7 or 8
10	randomized controlled trial/ or pragmatic clinical trial/
11	controlled clinical trials as topic/ or randomized controlled trials as topic/ or pragmatic clinical trials as topic/
12	random allocation/
13	double-blind method/
14	single-blind method/
15	controlled clinical trial.pt.
16	randomized controlled trial.pt.

17	clinical trial/ or clinical trial, phase iii/ or clinical trial, phase iv/ or controlled clinical trial/
18	clinical trial.ab,ti.
19	or/10-18
20	animals/ not humans/
21	19 not 20
22	9 and 21
23	adult/ or adult.mp. or adults.mp.
24	22 and 23
25	adalimumab.mp.
26	infliximab.mp.
27	certolizumab.mp.
28	natalizumab.mp.
29	ustekinumab.mp.
30	Antibodies, Monoclonal/ad, ae, ai, tu [Administration & Dosage, Adverse Effects, Antagonists & Inhibitors, Therapeutic Use]
31	Antibodies/ad, ae, ai, tu [Administration & Dosage, Adverse Effects, Antagonists & Inhibitors, Therapeutic Use]
32	Anti-Inflammatory Agents/
33	“anti-inflammatory agent*”.ti,ab.
34	(anti-tumour necrosis or anti-tumor necrosis or anti-TNF or biologic or biologics).ab,ti.
35	tumor necrosis factor-alpha/ or tumor necrosis factors/
36	(tumour necrosis factor or tumor necrosis factor or TNF).ab,ti.
37	(tumour necrosis factor-alpha or tumor necrosis factor-alpha or TNF-alpha).ab,ti.
38	35 or 36 or 37
39	(antibod* or antagonist or antagonists or inhibitor*).ab,ti.
40	(agent* or treatment* or treated or therap* or drug or drugs or medication*).ab,ti.
41	38 and 39 and 40
42	or/25-34
43	42 or 41
44	24 and 43
45	limit 44 to (76rench76 or 76rench)

46	limit 45 to yr=”1990 –Current”

MEDLINE – CORTICOSTEROID DRUGS

#	Search Statement
1	Inflammatory Bowel Diseases.mp. or Inflammatory Bowel Diseases/
2	Inflammatory Bowel Disease.mp.
3	(ileitis or enteritis or ileocolitis or colitis).ti,ab.
4	1 or 2 or 3
5	Crohn*.ti,ab.
6	4 and 5
7	Crohn Disease/
8	(Crohn’s Disease or Crohn Disease or Crohns Disease).mp.
9	6 or 7 or 8
10	randomized controlled trial/ or pragmatic clinical trial/
11	controlled clinical trials as topic/ or randomized controlled trials as topic/ or pragmatic clinical trials as topic/
12	random allocation/
13	double-blind method/
14	single-blind method/
15	controlled clinical trial.pt.
16	randomized controlled trial.pt.
17	clinical trial/ or clinical trial, phase iii/ or clinical trial, phase iv/ or controlled clinical trial/
18	clinical trial.ab,ti.
19	or/10-18
20	animals/ not humans/
21	19 not 20
22	9 and 21
23	adult/ or adult.mp. or adults.mp.
24	22 and 23
25	glucocorticoid.mp. or Glucocorticoids/
26	budesonide.mp. or Budesonide/

27	hydrocortisone.mp. or hydrocortisone/
28	methylprednisolone.mp. or methylprednisolone/
29	prednisolone.mp. or prednisolone/
30	prednisone.mp. or prednisone/
31	6-methylprednisolone.mp. or 6-methylprednisolone/
32	corticosteroid*.mp.
33	25 or 26 or 27 or 28 or 29 or 30 or 31 or 32
34	24 and 33
35	limit 34 to (yr=”1990 –Current” and (78rench78 or 78rench))

MEDLINE – IMMUNOSUPPRESSANT DRUGS

#	Search Statement
1	Inflammatory Bowel Diseases.mp. or Inflammatory Bowel Diseases/
2	Inflammatory Bowel Disease.mp.
3	(ileitis or enteritis or ileocolitis or colitis).ti,ab.
4	1 or 2 or 3
5	Crohn*.ti,ab.
6	4 and 5
7	Crohn Disease/
8	(Crohn’s Disease or Crohn Disease or Crohns Disease).mp.
9	6 or 7 or 8
10	randomized controlled trial/ or pragmatic clinical trial/
11	controlled clinical trials as topic/ or randomized controlled trials as topic/ or pragmatic clinical trials as topic/
12	random allocation/
13	double-blind method/
14	single-blind method/
15	controlled clinical trial.pt.
16	randomized controlled trial.pt.
17	clinical trial/ or clinical trial, phase iii/ or clinical trial, phase iv/ or controlled clinical trial/
18	clinical trial.ab,ti.

19	or/10-18
20	animals/ not humans/
21	19 not 20
22	9 and 21
23	adult/ or adult.mp. or adults.mp.
24	22 and 23
25	immunosuppressive agents.mp. or Immunosuppressive Agents/
26	immunosuppression.mp. or Immunosuppression/
27	immunosuppressive.mp.
28	immunosuppressives.mp.
29	immunomodulator.mp.
30	immunomodulating.mp.
31	Antimetabolites, Antineoplastic/ or anti-metabolite.mp.
32	Antimetabolites, Antineoplastic/ or anti-metabolites.mp.
33	azathioprine.mp. or Azathioprine/
34	methotrexate.mp. or Methotrexate/
35	6-mercaptopurine.mp. or 6-Mercaptopurine/
36	25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35
37	24 and 36
38	limit 37 to (yr=”1990 –Current” and (79rench79 or 79rench))

COCHRANE CENTRAL REGISTRY

BIOLOGIC DRUGS

ID	Search
#1	MeSH descriptor: [Inflammatory Bowel Diseases] this term only
#2	(Inflammatory Bowel Diseases or Inflammatory Bowel Disease)
#3	(ileitis or enteritis or ileocolitis or colitis):ti,ab
#4	#1 or #2 or #3
#5	Crohn*:ti,ab
#6	#4 and #5
#7	MeSH descriptor: [Crohn Disease] explode all trees
#8	(Crohn’s Disease or Crohn Disease or Crohns Disease)
#9	#6 or #7 or #8
#10	adalimumab

#11	infliximab
#12	certolizumab
#13	natalizumab
#14	ustekinumab
#15	MeSH descriptor: [Antibodies, Monoclonal] explode all trees
#16	MeSH descriptor: [Antibodies] this term only
#17	MeSH descriptor: [Anti-Inflammatory Agents] this term only
#18	anti-inflammatory agent:ti,ab
#19	anti-tumour necrosis or anti-tumor necrosis or anti-TNF or biologic or biologics:ti,ab
#20	MeSH descriptor: [Tumor Necrosis Factor-alpha] this term only
#21	MeSH descriptor: [Receptors, Tumor Necrosis Factor, Type I] this term only
#22	tumour necrosis factor or tumor necrosis factor or TNF:ti,ab
#23	tumour necrosis factor-alpha or tumor necrosis factor-alpha or TNF-alpha:ti,ab
#24	#20 or #21 or #22 or #23
#25	antibod* or antagonist or antagonists or inhibitor*:ti,ab
#26	agent* or treatment* or treated or therap* or drug or drugs or medication*:ti,ab
#27	#24 and #25 and #26
#28	#10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19
#29	#28 or #27
#30	#9 and #29
#31	adult or adults
#32	MeSH descriptor: [Adult] explode all trees
#33	#31 or #32
#34	#30 and #33

CORTICOSTEROID DRUGS

ID	Search
#1	MeSH descriptor: [Inflammatory Bowel Diseases] this term only
#2	(Inflammatory Bowel Diseases or Inflammatory Bowel Disease)
#3	(ileitis or enteritis or ileocolitis or colitis):ti,ab
#4	#1 or #2 or #3
#5	Crohn*:ti,ab
#6	#4 and #5
#7	MeSH descriptor: [Crohn Disease] explode all trees
#8	(Crohn's Disease or Crohn Disease or Crohns Disease)
#9	#6 or #7 or #8
#10	MeSH descriptor: [Adult] explode all trees
#11	adults or adult
#12	#10 or #11
#13	#9 and #12
#14	glucocorticoid
#15	MeSH descriptor: [Glucocorticoids] explode all trees
#16	budesonide
#17	MeSH descriptor: [Budesonide] explode all trees
#18	hydrocortisone
#19	MeSH descriptor: [Hydrocortisone] explode all trees
#20	methylprednisolone
#21	MeSH descriptor: [Methylprednisolone] explode all trees
#22	prednisolone
#23	MeSH descriptor: [Prednisolone] this term only

#24 prednisone
#25 MeSH descriptor: [Prednisone] explode all trees
#26 6-methylprednisolone
#27 corticosteroid*
#28 #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27
#29 #13 and #28

IMMUNOSUPPRESSANT DRUGS

ID Search
#1 MeSH descriptor: [Inflammatory Bowel Diseases] this term only
#2 (Inflammatory Bowel Diseases or Inflammatory Bowel Disease)
#3 (ileitis or enteritis or ileocolitis or colitis):ti,ab
#4 #1 or #2 or #3
#5 Crohn*:ti,ab
#6 #4 and #5
#7 MeSH descriptor: [Crohn Disease] explode all trees
#8 (Crohn's Disease or Crohn Disease or Crohns Disease)
#9 #6 or #7 or #8
#10 MeSH descriptor: [Adult] explode all trees
#11 adults or adult
#12 #10 or #11
#13 #9 and #12
#14 immunosuppressive agents
#15 immunosuppression
#16 MeSH descriptor: [Immunosuppression] explode all trees
#17 MeSH descriptor: [Immunosuppressive Agents] this term only
#18 immunosuppressive
#19 immunosuppressives
#20 immunomodulator
#21 immunomodulating
#22 MeSH descriptor: [Antimetabolites, Antineoplastic] this term only
#23 anti-metabolite
#24 anti-metabolites
#25 azathioprine
#26 MeSH descriptor: [Azathioprine] this term only
#27 methotrexate
#28 MeSH descriptor: [Methotrexate] explode all trees
#29 6-mercaptopurine
#30 MeSH descriptor: [6-Mercaptopurine] this term only
#31 #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30
#32 #13 and #31

CLINICALTRIALS.GOV

Closed Studies | Studies With Results | Crohn | Adult, Senior

APPENDIX II

LIST OF VARIABLES FOR DATA COLLECTION

Study Information	
	Study number
	Author Name
	Study Name
	Journal name
	Year of publication
	Location
	Number of sites
	Study period
	Design type
	Induction or Maintenance
Inclusion/Exclusion Criteria	
	Patients' age
	CDAI score
	Other
Intervention & Population	
	Number of patients screened
	Number of patients randomized
	Intervention/dosing/frequency/timing/route
	Duration of treatment
	Patients' sex
	Smoking status
	Mean/median age
	Disease duration
	Disease location
	Disease complications
	Disease behavior
	Previous surgery
	Disease symptoms indices score
	Disease laboratory assessment (ESR, CRP)
	Previous medications
	Concomitant medications
Efficacy Outcome	
	Definition
	Number of patients in remission
	Number of patients with response (70 or 100 points)
	Total number of patients (ITT)
	Mean change in CDAI
	Mean change in ESR, CRP

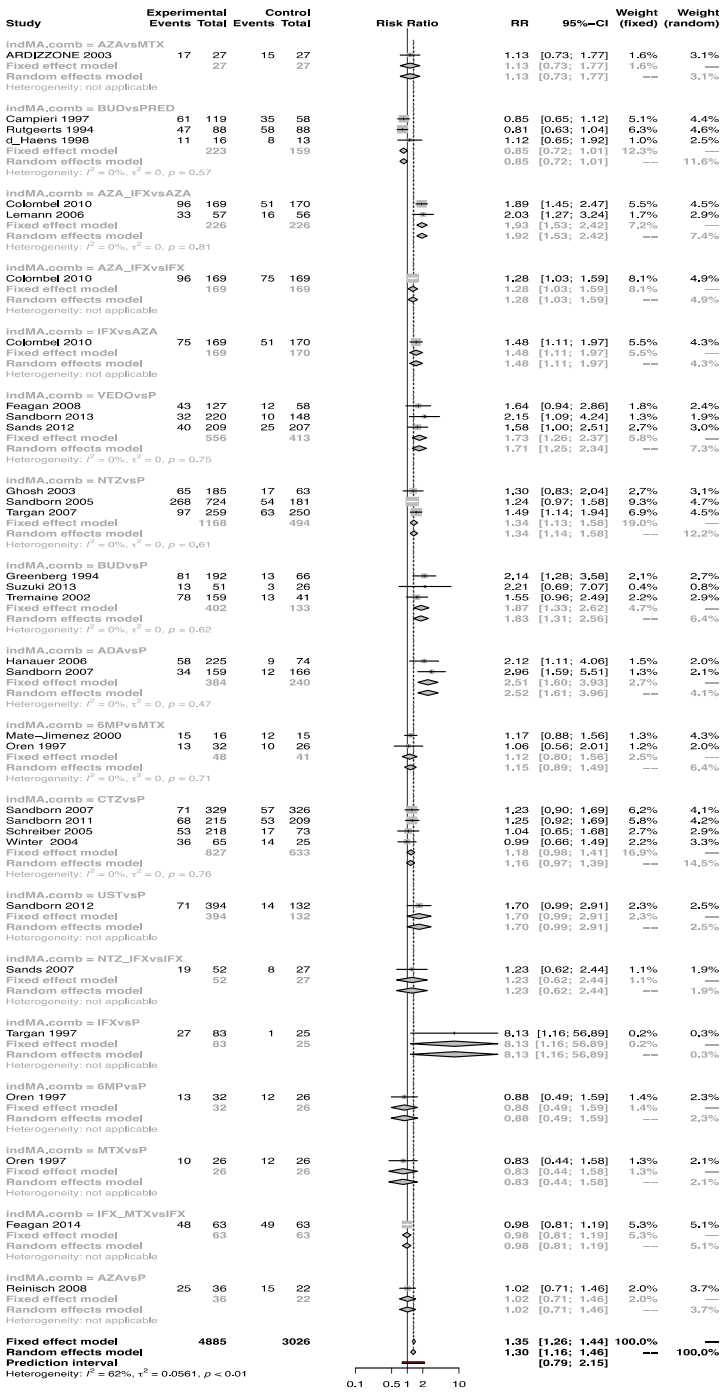
	Time of measurement

APPENDIX III

TRIALS' KEY CHARACTERISTICS

CHARACTERISTICS OF TRIALS INCLUDED IN THE INDUCTION ANALYSIS									
STUDY	YEAR	LOCATION, # OF CENTERS	DRUG	DOSAGE	# OF RANDOMIZED PATIENTS	DEFINITION OF REMISSION	TIME OF PRIMARY OUTCOME MEASUREMENT (W)	CONCOMITANT MEDICATIONS	PREVIOUS ANTI-TNF EXPOSURE
ARDIZZONE [189]	2003	Italy, 1	AZA, MTX	2mg/kg/day, 25mg/wk IV for 3 mths followed by oral	54	Steroid-free and CDAI <150	24	apering of steroids	0%
Campieri [190]	1997	Multicenter, 26	BUD, PRED	9mg and 4.5mg 40mg tapered	177	CDAI <=150	8	No	0%
Colombel [191]	2010	Multicenter, 92	IFX, AZA, IFX+AZA,	5mg/kg IV at 0, 2, 6, 14, 22W 2.5mg/kg/day 5mg/kg IV	508	CDAI <150	26	roids, Mesalamine	0%
d_Haens [192]	1998	Belgium, 1	BUD, METHYLPRED	9mg 32mg tapered	41	Response	10	No	0%
Feagan [193]	2008	Multicenter, 21	VDZ, P	0.5mg/kg, 2mg/kg IV at 0 and 4W	185	CDAI <150 1ry endpoint = Response >=70	8	Mesalamine	0%
Feagan [194]	2014	Multicenter, 15	IFX, IFX+MTX	5mg/kg IV every 8W + P 5mg/kgiv every 8W+MTX 25mg sc W	126	CDAI <150 and steroids free	14	Steoids tapered	0%
Ghosh [195]	2003	Multicenter, 35	NTZ, P	3mg/kg, 6mg/kg, 12mg/kg IV every 4W		CDAI <150	6	5_ASA, Steroids, IS	0%
Greenberg [196]	1994	Multicenter, 27	BUD, P	3mg, 9mg, 15mg	258	CDAI <=150	8	No	0%
Hanauer [197]	2006	Multicenter, 55	ADA, P	40mg/20mg, 40mg/80mg,	299	CDAI <150	4	Steroids, IS	0%
Lemann [198]	2006	Multicenter, 20	IFX+AZA or 6_MP, AZA or 6_MP	5mg/kg IV at 0, 2, 6 W + IS 2_3mg/kg or 1_1.5	115	CDAI <150 and steroids free	24	Steoids tapered	0%
Mate-Jimenez [199]	2000	Spain, 1	6_MP, MTX, Mesalamine	1.5mg/kg, /D 15mg/W 3g/D	38	Failure of remission CDAI >150	36	Steoids tapered	0%
Oren [200]	1997	Multicenter, 12	MTX, 6_MP, P	12.5mg/W, 50mg/D	84	HBI <=3 and steroids free	36	Steroids	0%
Reinisch [201]	2008	Multicenter, 38	AZA, P	2.5mg/kg/D	138	CDAI <150 and steroids free	28	Steoids tapered	0%
Rutgeerts [202]	1994	Multicenter, 11	BUD, PRED	9mg 40mg tapered	176	CDAI <=150	10	No	0%
Sandborn [203]	2005	Multicenter, 142	NTZ, P	300mg IV every 4 W	905	CDAI <150	10	_ASA, Steroids, IS	39.80%
Sandborn [204]	2013	Multicenter, 285	VDZ, P	300mg IV at 0 and 2 W	368	CDAI <150	6	Steroids, IS	62%
Sandborn [205]	2007	Multicenter, 171	CTZ, P	400mg sc at 0, 2, 4 and every 4 W	662	CDAI <150	26	Steroids, IS	28%
Sandborn [206]	2012	Multicenter, 153	UST, P	1, 3, 6mg/kg every 8 W	526	CDAI <150	6	_ASA, Steroids, IS	99.60%
Sandborn [207]	2007	Multicenter, 52	ADA, P	160/80mg sc at 0, 2 W	325	CDAI <150	4	Steroids, IS	100%
Sandborn [208]	2011	Multicenter, 120	CTZ, P	400mg sc at 0, 2, 4 W	439	CDAI <150	6	Steroids, IS	0%
Sands [209]	2014	Multicenter, 107	VDZ, P	300mg IV at 0, 2, 6 W	416	CDAI <150	6	Steroids, IS	76%%
Sands [210]	2007	Multicenter, 171	IFX + P, NTZ + IFX	5mg/kg 300mg/kg+5mg/kg	79	CDAI <150	10	_ASA, Steroids, IS	100%
Schreiber [211]	2005	Multicenter, 56	CTZ, P	100, 200, 400mg sc at 0, 4, 8 W	292	CDAI <150	12	Steroids, IS	22%
Suzuki [212]	2013	Japan, 21	BUD, P	9, 15mg	77	CDAI <=150	8	5_ASA	0%
Targan [213]	2007	Multicenter, 114	NTZ, P	300mg at 0, 4, 8 W	509	CDAI <150	12	_ASA, Steroids, IS	0%
Targan [214]	1997	Multicenter, 18	IFX, P	5, 10, 20mg/kg IV at W 0	108	CDAI <150	4 & 12	Steroids, IS	0%
Tremaine [215]	2002	Multicenter, 24	BUD, P	9 bd, 4.5 bid	200	CDAI <=150	8	No	0%
Winter [216]	2004	Multicenter, 24	CTZ, P	5, 10, 20mg/kg IV at W 0	92	CDAI <150	4	Steroids, IS	24%

APPENDIX IV
PAIRWISE META-ANALYSIS

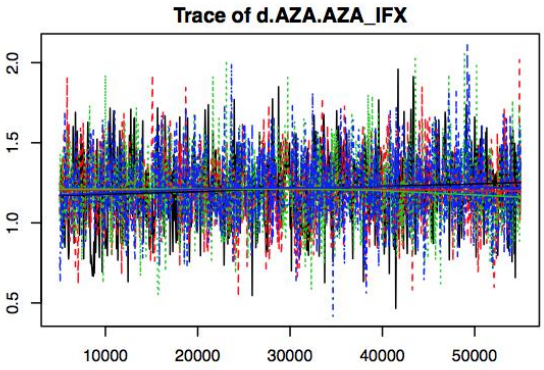


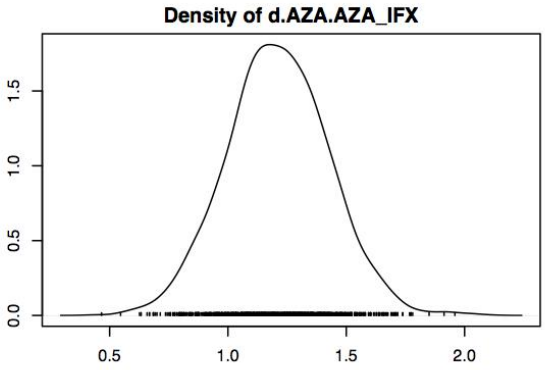
APPENDIX V

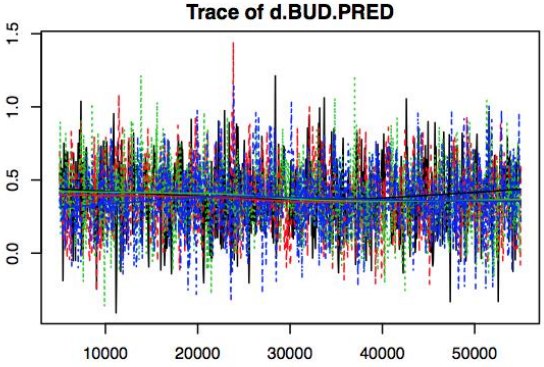
GENERALIZED ESTIMATING EQUATIONS MODEL WITH REPEATED MEASURES

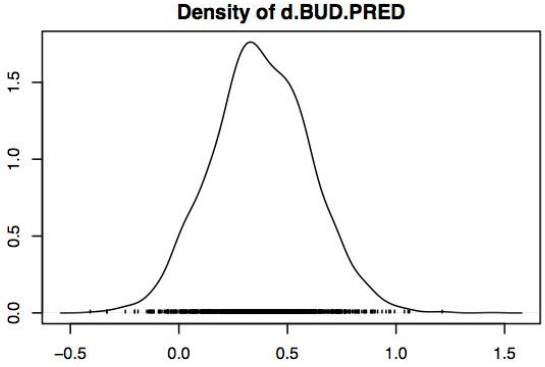
Model	Covariate	P-value (Type 3 Test)
1	RxdurationW	0.1049
	treatment	0.0540
2	age	0.8021
	treatment	0.1153
3	sexM	0.0686
	treatment	0.0702
4	disdurmeanM	0.3378
	treatment	0.1011
5	colonic	0.0563
	treatment	0.0827
6	ileal	0.5723
	treatment	0.1180
7	ileocol	0.1750
	treatment	0.1687
8	fistulas	0.0861
	treatment	0.4232
9	previoussur	0.0065
	treatment	0.1840
10	cdaibasemean	0.0067
	treatment	0.1257
11	crpbasemean	0.4202
	treatment	0.1811
12	prioranti_T	0.6662
	treatment	0.2237

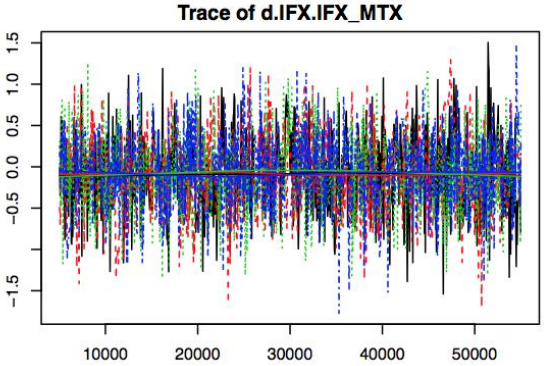
APPENDIX VI
ALGORITHMS FROM MCMC SIMULATIONS

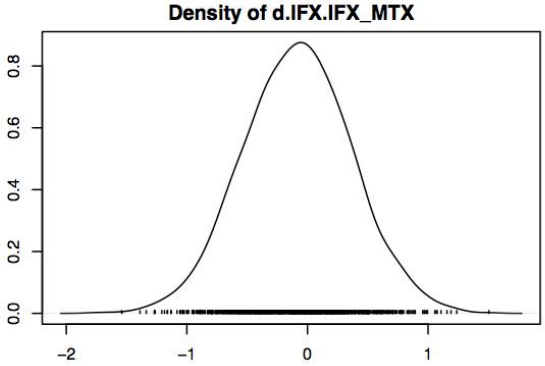


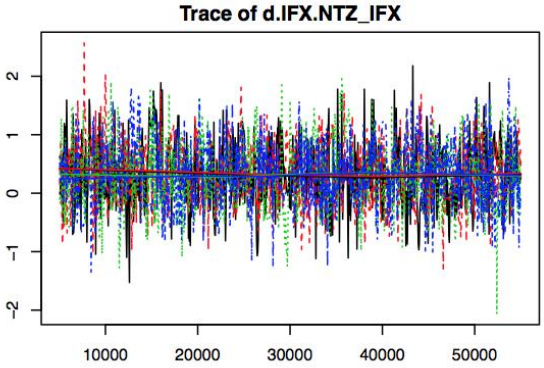


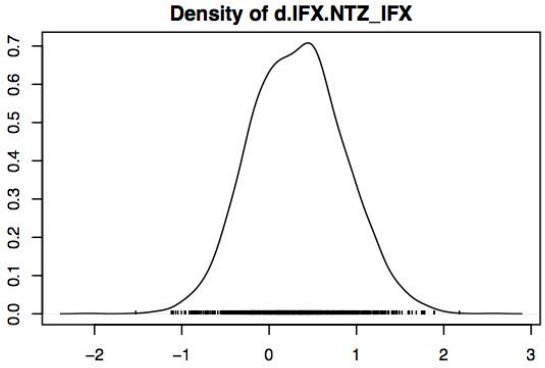


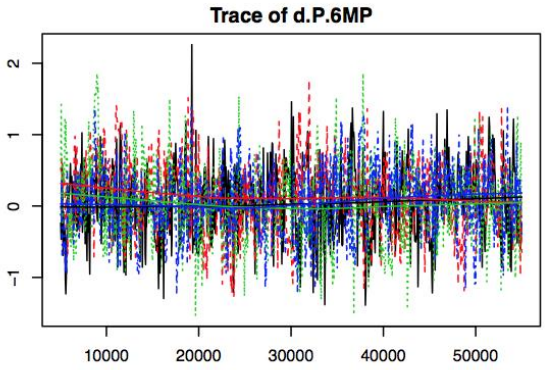











Trace of d.P.6MP
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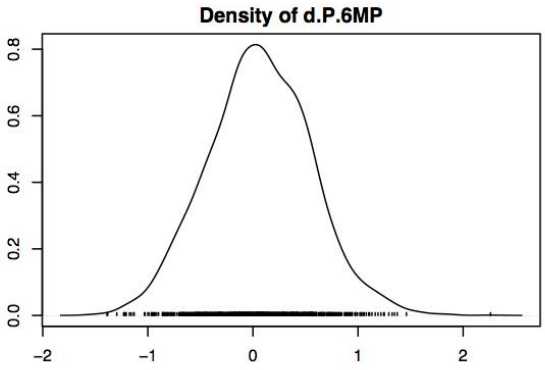
0
−1
10000
20000
30000
40000
50000


Density of d.P.6MP
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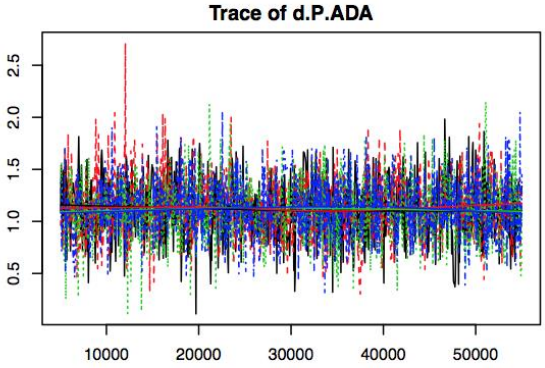
0.6
0.4
0.2
0.0
−2
−1
0
1
2


Trace of d.P.ADA
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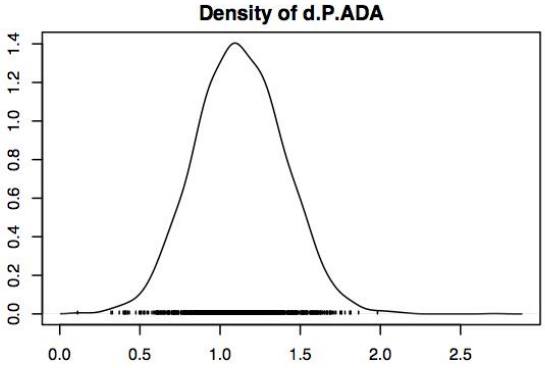
30000
40000
50000


Density of d.P.ADA
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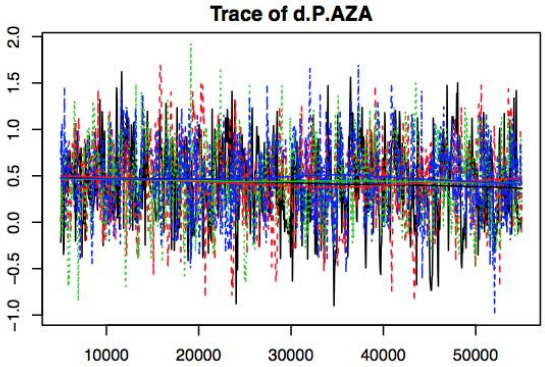
0.6
0.4
0.2
0.0
0.0
0.5
1.0
1.5
2.0
2.5


Trace of d.P.AZA
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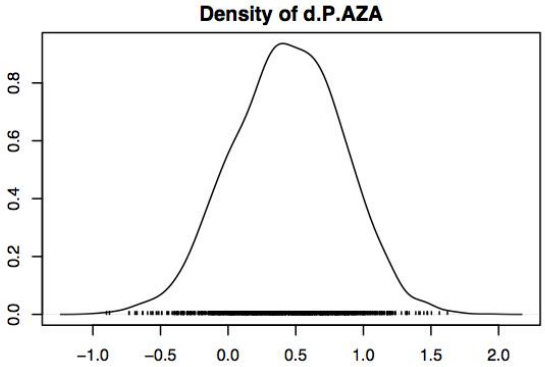
40000
50000


Density of d.P.AZA
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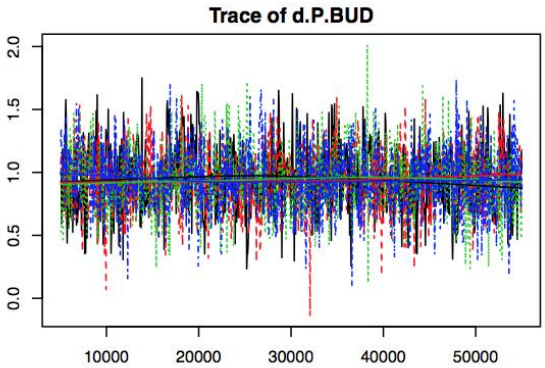
−1.0
−0.5
0.0
0.5
1.0
1.5
2.0


Trace of d.P.BUD
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0.0
10000
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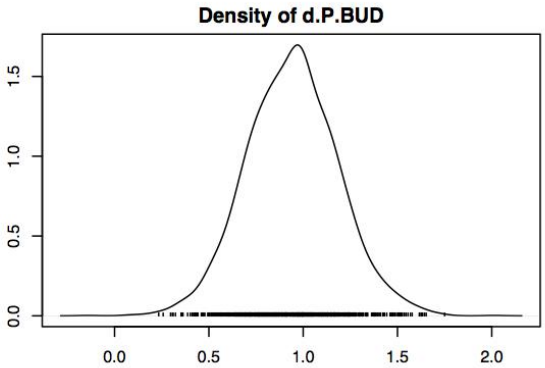
30000
40000
50000


Density of d.P.BUD
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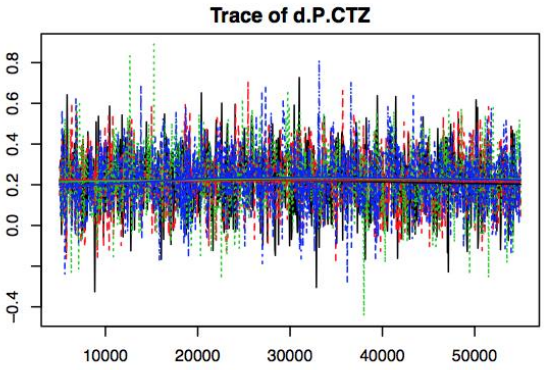
0.0
0.5
1.0
1.5
2.0


Trace of d.P.CTZ
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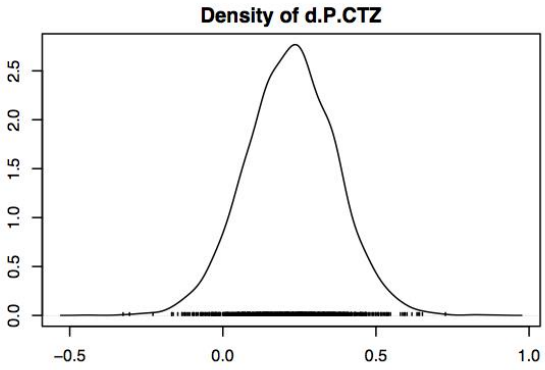
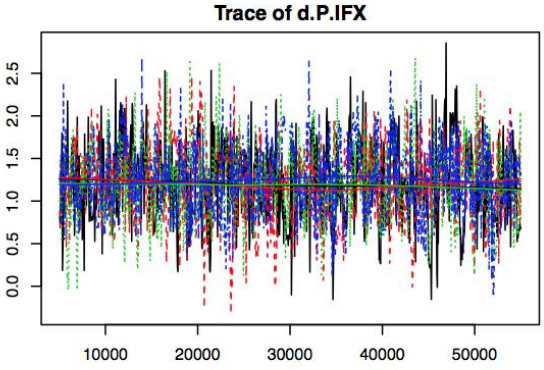
40000
50000


Density of d.P.CTZ


Trace of d.P.IFX
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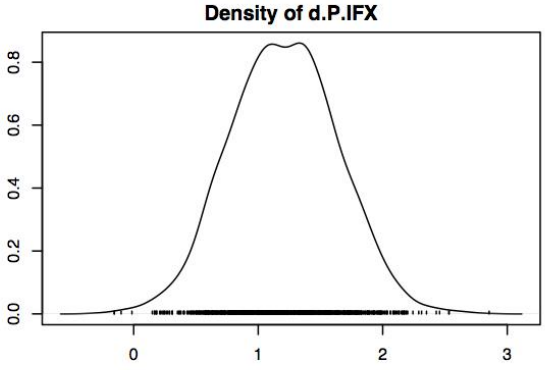
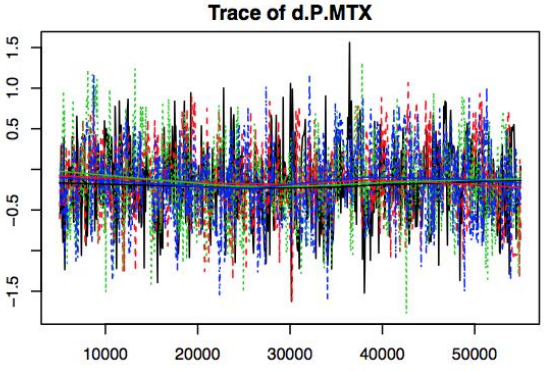
30000
40000
50000


Density of d.P.IFX


Trace of d.P.MTX
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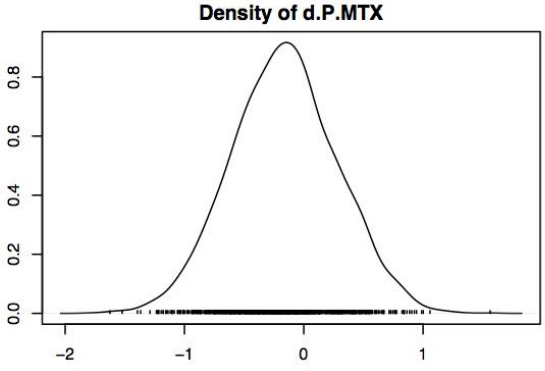
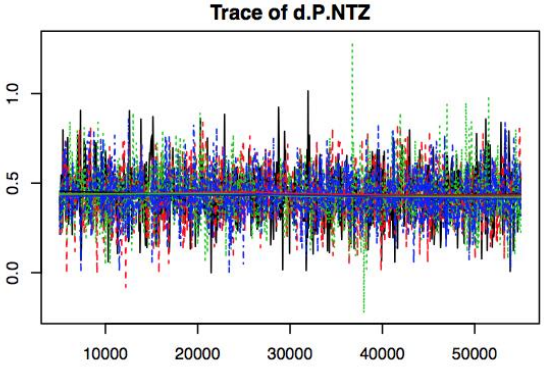
50000


Density of d.P.MTX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40000
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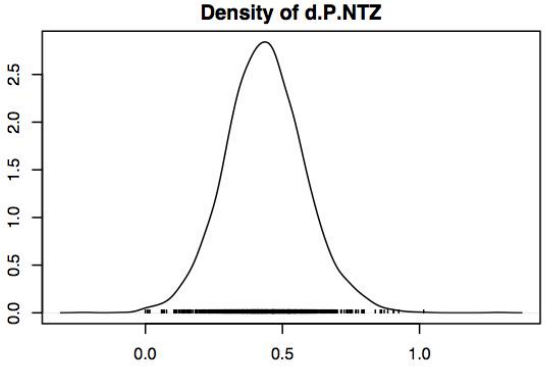
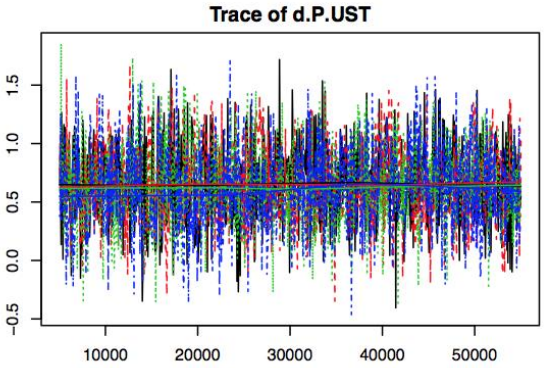

Density of d.P.NTZ


Trace of d.P.UST
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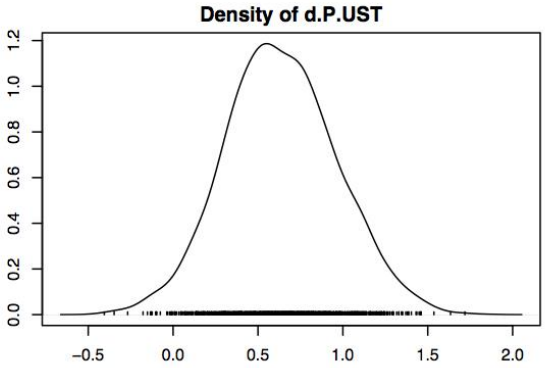
0.5
1.0
1.5
10000
20000
30000
40000
50000


Density of d.P.UST
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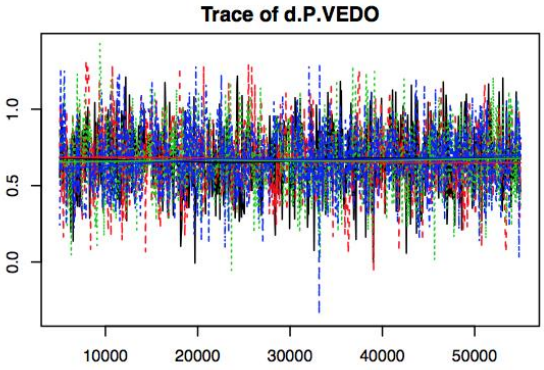
0.4
0.6
0.8
1.0
1.2
−0.5
0.0
0.5
1.0
1.5
2.0


Trace of d.P.VEDO
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10000
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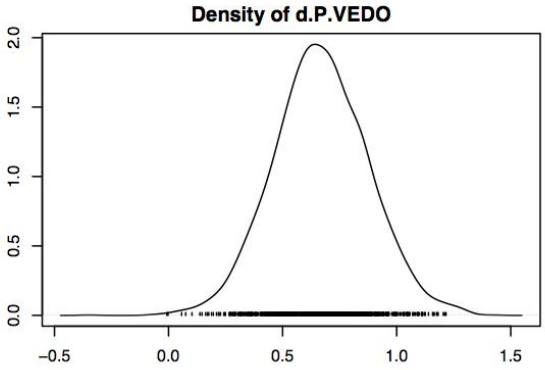
Density of d.P.VEDO
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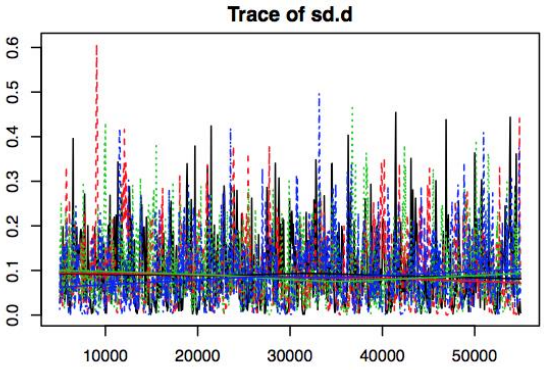
1.5
2.0
−0.5
0.0
0.5
1.0
1.5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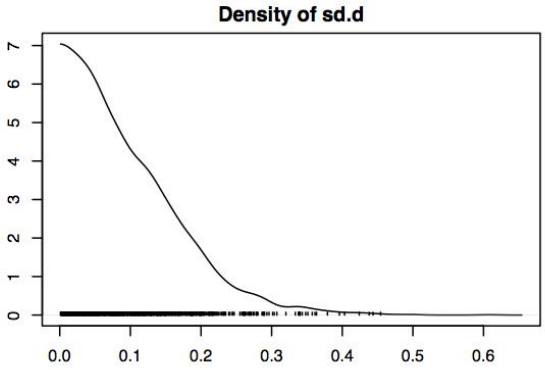
Density of sd.d
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1
2
3
4
5
6
7
0.0
0.1
0.2
0.3
0.4
0.5
0.6

APPENDIX VII

BAYESIAN LINEAR RANDOM EFFECTS MODEL WITH UNIFORM (0,2)

Results on the Log Odds Ratio scale

Iterations = 5050:55000
Thinning interval = 50
Number of chains = 4
Sample size per chain = 1000

1. Empirical mean and standard deviation for each variable,
   plus standard error of the mean:

	Mean	SD	Naive SE	Time-series SE
d.AZA.AZA_IFX	1.21109	0.21702	0.003431	0.005144
d.BUD.PRED	0.37775	0.22663	0.003583	0.005405
d.IFX.IFX_MTX	-0.08326	0.45025	0.007119	0.012311
d.IFX.NTZ_IFX	0.32360	0.53534	0.008464	0.016744
d.P.6MP	0.06120	0.49278	0.007791	0.018268
d.P.ADA	1.12217	0.27875	0.004407	0.006930
d.P.AZA	0.43898	0.40582	0.006417	0.015105
d.P.BUD	0.94187	0.24298	0.003842	0.006573
d.P.CTZ	0.22264	0.14608	0.002310	0.002742
d.P.IFX	1.20618	0.43239	0.006837	0.015718
d.P.MTX	-0.16429	0.44249	0.006996	0.015552
d.P.NTZ	0.43585	0.14524	0.002296	0.002854
d.P.UST	0.63516	0.32892	0.005201	0.007937
d.P.VEDO	0.66797	0.20829	0.003293	0.004904
sd.d	0.09683	0.07807	0.001234	0.002331

APPENDIX VII (Cont'd)

BAYESIAN LINEAR RANDOM EFFECTS MODEL WITH UNIFORM (0,2)

2. Quantiles for each variable:

	2.5%	25%	50%	75%	97.5%
d.AZA.AZA_IFX	0.794661	1.06847	1.20801	1.3539	1.6400
d.BUD.PRED	-0.052243	0.23001	0.37330	0.5311	0.8280
d.IFX.IFX_MTX	-0.967948	-0.38682	-0.08383	0.2189	0.8013
d.IFX.NTZ_IFX	-0.686983	-0.05241	0.32347	0.6783	1.4055
d.P.6MP	-0.886482	-0.26439	0.06217	0.3925	1.0569
d.P.ADA	0.594523	0.93182	1.11648	1.3073	1.6678
d.P.AZA	-0.351867	0.15979	0.44476	0.7217	1.1962
d.P.BUD	0.475848	0.77784	0.94632	1.1025	1.4318
d.P.CTZ	-0.065525	0.12844	0.22503	0.3221	0.5089
d.P.IFX	0.374178	0.90541	1.20468	1.5045	2.0375
d.P.MTX	-1.029203	-0.46014	-0.16355	0.1274	0.7180
d.P.NTZ	0.151901	0.34096	0.43265	0.5288	0.7369
d.P.UST	0.005502	0.40818	0.62396	0.8514	1.2942
d.P.VEDO	0.269888	0.53212	0.66504	0.8061	1.0798
sd.d	0.003459	0.03618	0.07893	0.1390	0.2886

-- Model fit (residual deviance):

Dbar	pD	DIC
50.90269	43.56493	94.46762

58 data points, ratio 0.8776, I^2 = 0%

APPENDIX VIII
Analysis of convergence using Brooks-Gelman-Rubin diagnostic test

```
> gelman.diag(results)
Potential scale reduction factors:

                Point est. Upper C.I.
d.AZA.AZA_IFX         1.00       1.01
d.BUD.PRED            1.00       1.01
d.IFX.IFX_MTX         1.00       1.00
d.IFX.NTZ_IFX         1.00       1.00
d.P.6MP               1.01       1.03
d.P.ADA               1.00       1.00
d.P.AZA               1.01       1.03
d.P.BUD               1.00       1.01
d.P.CTZ               1.00       1.01
d.P.IFX               1.01       1.03
d.P.MTX               1.00       1.00
d.P.NTZ               1.00       1.00
d.P.UST               1.00       1.01
d.P.VEDO              1.00       1.01
sd.d                  1.00       1.01

Multivariate psrf

1.02
```

APPENDIX IX
Analyses of consistency

Consistency effect summaries:

```
> a$consEffects
        t1      t2          pe         ci.l        ci.u
1      6MP     MTX -0.20311119 -1.163014999  0.69441848
2      6MP       P -0.05045166 -1.014364560  0.92450327
3      ADA       P -1.11513553 -1.704889414 -0.57709361
4  AZA_IFX     IFX -0.44893533 -0.910300149  0.04144247
5      AZA AZA_IFX  1.21235338  0.777320966  1.65645744
6      AZA     IFX  0.76348736  0.306417436  1.26000027
7      AZA     MTX -0.60451852 -1.502303438  0.27635862
8      AZA       P -0.43594827 -1.258196485  0.32608998
9      BUD       P -0.94844693 -1.447706831 -0.47511149
10     BUD    PRED  0.39107116 -0.056951949  0.83790799
11     CTZ       P -0.21637238 -0.506156678  0.07338460
12     IFX IFX_MTX -0.09447165 -0.993485726  0.79380089
13     IFX NTZ_IFX  0.33045380 -0.702053660  1.39695266
14     IFX       P -1.19542270 -2.071359239 -0.38776453
15     MTX       P  0.15808567 -0.688562063  1.08992288
16     NTZ       P -0.43603650 -0.719339849 -0.14858439
17       P     UST  0.63915309 -0.001687622  1.33151469
18       P    VEDO  0.66839924  0.266872474  1.07713339
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APPENDIX IX (Cont'd)

Unrelated Mean Effects summaries or pair-wise pooled effect summaries:

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> a$pairEffects
        t1      t2          pe         ci.l        ci.u
1      6MP     MTX -0.46137407 -1.525753961  0.69210411
2      6MP       P  0.24017692 -1.050378382  1.58805676
3      ADA       P -1.11368880 -1.686040961 -0.58192287
4  AZA_IFX     IFX -0.50661779 -1.069587899  0.06362913
5      AZA AZA_IFX  1.17118780  0.687724328  1.66150923
6      AZA     IFX  0.62718926  0.022788568  1.22109275
7      AZA     MTX -0.31965490 -1.475917192  0.80845516
8      AZA       P -0.05083855 -1.226204428  1.17092785
9      BUD       P -0.95088807 -1.463433091 -0.48464470
10     BUD    PRED  0.38929994 -0.068384411  0.85086391
11     CTZ       P -0.21775600 -0.507596712  0.07001099
12     IFX IFX_MTX -0.06918030 -0.964075269  0.80368082
13     IFX NTZ_IFX  0.32828644 -0.675663067  1.39603718
14     IFX       P -2.79810376 -6.383542631 -1.00751967
15     MTX       P  0.39515346 -1.130268172  1.78401412
16     NTZ       P -0.43534379 -0.718390233 -0.15818952
17       P     UST  0.62614033 -0.003228227  1.31908384
18       P    VEDO  0.66390153  0.279458942  1.07335521
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