Utilization and Risk of Serious Infection Associated with TNF-α Inhibitors in Children and Young Adults

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THESIS

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Chapter 1 is a literature review of the disease and medication use, in which gaps in the literature were identified, and study aims and the significance of the research were elaborated. Chapter 2 to 5 represent four manuscripts for which I was the primary author and major driver of the research. The manuscript presented in Chapter 2 is now in press in the journal *Pharmacotherapy*. Chapter 3 has been published in the journal Inflammatory Bowel Disease (Lee WJ, Briars L, Lee TA, Calip GS, Suda KJ, Schumock GT. Top-down Versus Step-up Prescribing Strategies for Tumor Necrosis Factor Alpha Inhibitors in Children and Young Adults with Inflammatory Bowel Disease. *Inflamm Bowel Dis.* 2016;22:2410-2417). Chapter 4 is being considered for publication as an article in the journal *Rheumatology* and has been reviewed by the journal personnel; it is currently being revised for resubmission. Chapter 5 has been submitted for consideration for publication as an article in the journal *American Journal of Gastroenterology*.

In each study from Chapter 2 to 5, I conceptualized the study questions, carried out the analyses, presented the results, interpreted the findings, and drafted, finalized, and submitted the manuscript to the journal. Each of my committee members contributed to these four studies and is a co-author of each manuscript. Dr. Todd Lee and Dr. Gregory Calip provided guidance primarily in methodology, including study designs, analysis approach, and presentation of the results. Dr. Lee and Dr. Gregory also gave technical support when analyzing claims data in complex modeling. Dr. Leslie Briars provided inputs from a clinical perspective in interpreting the findings and help me add the clinical importance in the discussion section, including comments of current practice, insurance restrictions, and application of the study findings for healthcare professionals. Dr. Katie Suda helped to identify the infection diagnoses, suggested the approach to analyze infection, and assisted in determining the site of infection in claims data. My research advisor, Dr. Glen Schumock, assisted and supervised the completion of these four manuscripts and guided me throughout the whole process conducting my dissertation, from suggestions in study design, interpretation of study results, to review and revision of the manuscripts. He is also the corresponding author for the four manuscripts.

In the last Chapter, Chapter 6, an overall conclusion of this dissertation work was presented. The main results of each study and the application of the study findings were summarized. Suggestions for future studies were also described.

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LIST OF ABBREVIATIONS

5-ASA	5-Aminosalicylic Acid
ACR	American College Of Rheumatology
ACT 1	Active Ulcerative Colitis 1
ACT 2	Active Ulcerative Colitis 2
ADHD	Attention Deficit Hyperactivity Disorder
ANA	Antinuclear Antibodies
anti-dsDNA	Anti-double stranded DNA
CARRA	Childhood Arthritis And Rheumatology Research Alliance
CD	Crohn’s Disease
CI	Confidence Interval
CORRONA	Consortium Of Rheumatology Researchers Of North America
DAG	Directed Acyclic Graph
DMARD	Disease-Modifying Antirheumatic Drug
ECCO	European Crohn's And Colitis Organisation
ED	Emergency Department
ESPGHAN	European Society For Paediatric Gastroenterology Hepatology And Nutrition
FAERS	FDA Adverse Event Report System
FDA	Food and Drug Administration
GAIN trial	Gauging Adalimumab Efficacy In Infliximab Non-Responders Trial
GI	Gastrointestinal
hdPS	High-Dimensional Propensity Score
HR	Hazard Ratio
IBD	Inflammatory Bowel Disease

LIST OF ABBREVIATIONS (continued)

ICD-9-CM	International Classification Of Diseases, Ninth Revision, Clinical Modification
Ig	Immunoglobin
IL	Interleukin
IQR	Interquartile Range
IRB	Institutional Review Board
IRR	Incidence Rate Ratio
IV	Intravenous
JIA	Juvenile Idiopathic Arthritis
NA	Not Applicable
NASPGHAN	Pediatric Gastroenterology Hepatology And Nutrition
NSAID	Non-Steroidal Anti-Inflammatory Drug
OR	Odds Ratio
PCDAI	Pediatric Crohn Disease Activity Index
PDC	Proportion Of Days Covered
PUCAI	Pediatric Ulcerative Colitis Activity Index
ROR	Reporting Odds Ratio
RR	Relative Risk
SC	Subcutaneous
SD	Standard Deviations
SONIC	Study Of Biologic And Immunomodulator Naive Patients In Crohn’s Disease
TNF-alpha	Tumor Necrosis Factor-Alpha
TNFI	Tumor Necrosis Factor-Alpha Inhibitor
UC	Ulcerative Colitis

SUMMARY

This dissertation examines the utilization patterns of tumor necrosis factor-alpha inhibitors (TNFI) and evaluates the risk of serious infection associated with TNFIs in children and young adults with juvenile idiopathic arthritis (JIA)/rheumatoid arthritis (RA) or inflammatory bowel disease (IBD). The United States Food and Drug Administration (FDA) issued a black box warning for TNFI-related serious infection that may lead to hospitalization or death in 2008. Physicians may be more cautious when prescribing TNFIs because of the warning, and may even reduce the use of the drugs. On the other hand, recent studies have promoted early use of TNFIs in the disease course to achieve better clinical outcomes and reduced use of corticosteroids. This may be particularly beneficial for children because corticosteroid use could affect pubertal growth and final height. However, the TNFI utilization after the warning, especially early use of TNFIs, was not well studied in children and young adults. In addition, although this warning applied to both adults and children exposed to TNFIs, studies evaluating the TNFI-infection association were primarily conducted in adults, and the findings were conflicting. Studies conducted in children and young adults were usually small and lacked statistical power needed to make a valid evaluation of the association. Therefore, more objective evidence on the TNFI utilization and evaluation of the TNFI-infection association in children and young adults was needed. The goal of this dissertation was to provide such evidence, and in doing so inform prescribers and patients about current TNFI utilization and the risk-benefit profile when considering TNFI treatment.

The dissertation is comprised of six chapters. In the first chapter, background literature on the disease course and study medications was reviewed. We also summarized the current evidence of utilization of TNFIs and of the association between TNFIs and infection, including clinical trials, meta-analyses, post-marketing observational studies, and registry studies. However, we found conflicting results, and studies conducted in children were scarce. We thus generated our study hypotheses and objectives based on the gap identified in the literature. These gaps helped establish four aims to be investigated in this dissertation. These were (1) to characterize the utilization of TNFIs among children and young adults with JIA/RA; (2) to characterize the utilization of TNFIs among children and young adults with IBD; (3) to determine the association between TNFIs and serious infection in children with JIA; (4) to determine the association between TNFIs and serious infection and to examine the comparative risk of infection among TNFI agents in children and young adults with IBD. Based on these aims we conducted four retrospective cohort studies using the Truven Health MarketScan® Commercial Claims and Encounters databases between 2009 and 2013, and each study was summarized in a separate chapter (chapter two to five) in this dissertation.

The second chapter of the dissertation describes the study conducted to address aim (1) and has been published as an article in the journal *Pharmacotherapy*. The paper is titled "Utilization of tumor necrosis factor-alpha inhibitors in children and young adults with juvenile idiopathic arthritis or rheumatoid arthritis." We identified the treatment patterns of TNFIs, including monotherapy, combination, adherence, persistence, time from diagnosis to first TNFI prescription, and early use of TNFIs prior to traditional disease-modifying antirheumatic drugs (DMARD). We found a more aggressive pattern of TNFI use in this sample of children and young adults with JIA/RA.

The third chapter of this dissertation describes the study conducted to address aim (2) and has been published as an article in the journal *Inflammatory Bowel Disease.* The paper is titled "Top-down versus step-up prescribing strategies for tumor necrosis factor-alpha inhibitors in children and young adults with inflammatory bowel disease." The objective of this study was to examine the use of the top-down approach for children and young adults with IBD and more specifically to compare medication utilization between the step-up and top-down strategies. We found that the rate of the top-down approach increased over time and that patients treated in this fashion had lower rates of corticosteroid use compared to the step-up patients.

The fourth chapter of this dissertation describes the study conducted to address aim (3) and was submitted to the journal *Rheumatology.* The article is titled "Risk of serious bacterial infection associated with tumor necrosis factor-alpha inhibitors in children with juvenile idiopathic arthritis." A retrospective cohort study was conducted to determine the risk of serious infection posed by TNFIs compared to DMARDs in children with JIA. Children <16 years old with JIA who initiated TNFIs or DMARDs were identified and followed for occurrence of a bacterial infection requiring hospitalization. Cox proportional hazard models were used to estimate hazard ratios (HR) for infection associated with TNFIs compared to DMARDs, adjusting for potential confounders with high-dimensional propensity scores (hdPS) and time-varying corticosteroid use. We found that use of the TNFIs poses a higher risk of serious infection compared to DMARDs in children with JIA, and our analysis confirms the FDA warning about TNFI-associated infection in children with JIA.

The fifth chapter of this dissertation describes the study conducted to address aim (4) and was submitted to the journal *American Journal of Gastroenterology.* This article is titled "Risk of serious bacterial infection associated with tumor necrosis factor-alpha inhibitors in children and young adults with inflammatory bowel disease." In this study we sought to evaluate

the risk of serious infection associated with TNFIs compared to non-biologic immunomodulators in children and young adults with IBD and to compare the risk among individual TNFIs. The study cohort comprised of patients aged <30 years with a diagnosis of IBD who initiated treatment with a TNFI or immunomodulator (thiopurines or methotrexate). The outcome of interest was serious infection, defined as a non-gastrointestinal bacterial infection requiring hospitalization. Cox proportional hazard models were used to estimate HR and 95% confidence intervals (CI) for serious infection associated with TNFIs compared to immunomodulators. Among TNFI users, analyses examining the risk of infection by specific TNFI agents and by route of administration were conducted. We found that TNFIs were associated with a higher risk of serious infection compared to immunomodulators in children and young adults with IBD, and this risk differed among individual TNFIs and routes of administration.

The final chapter provides an overall conclusion for the entire dissertation. We summarized the main study findings from each study and described the interpretation and potential application of our research. From our first two studies aiming to evaluate the utilization of TNFIs, we concluded that TNFIs are used earlier and a more aggressive treatment approach has emerged for children and young adults with JIA/RA and IBD despite the FDA warning. From our findings from the latter two studies, we concluded that TNFIs are associated with an increased risk of serious infection compare to non-biologic immunomodulators among children and young adults with JIA and IBD, which confirms the FDA warning about TNFI-associated serious infection in children with JIA and IBD. This dissertation and papers associated with it provides insight on how TNFIs are being used and helps inform decision-making by physicians and patients about these drugs, particularly around the balance between benefit and risk of TNFIs. Nevertheless, future studies should be done to confirm our findings in this vulnerable, under-representative population. In particular more studies are needed that compare TNFIs in

terms of risk of serious infection, in order to provide a more definite comparative safety profile for clinicians and patients when selecting a TNFI agent.

1. BACKGROUND AND STUDY OBJECTIVES

1.1 Autoimmune Diseases in Children

The immune system is one of the human body's main defenses against foreign substances. When a pathogen invades, the immune cells are activated to defend against it. However, autoimmune diseases may develop when the immune system becomes overactive and/or misidentifies healthy cells as foreign. What causes autoimmune diseases is largely unknown. While there is no single cure, drugs are available that modulate the immune system and can help relieve disease symptoms.

Autoimmune disease collectively is reported to be one of the top ten leading causes of death in women and female children.[1,2] Autoimmune diseases can affect different organ systems and may negatively influence the growth and function of organs. Because of the rapid growth and development that occurs in childhood, children are particularly susceptible to the damage caused by autoimmune diseases. The progression of disease and the long-term use of immunosuppressant treatment may have life-long health consequences.

This proposed dissertation focused on two autoimmune diseases in children: JIA and pediatric IBD. JIA is one of the most common autoimmune diseases in children and pediatric IBD is increasingly prevalent globally.[3] One common and important class of biologic drugs used to treat these two diseases is the tumor necrosis factor-alpha inhibitors. Below we provide more information on JIA and pediatric IBD, including the disease definitions, epidemiology, disease activity measurements and pharmacological therapy.

1.1.1 Juvenile Idiopathic Arthritis

JIA is defined as arthritis (inflammation of joints with swelling, heat and pain) persistent for at least 6 months in patients less than 16 years of age.[4] JIA is considered an autoimmune disease with unknown etiology and is one of the most common chronic diseases in children. The prevalence of JIA is around 1 per 1,000[5,6] and the incidence is 11 per 100,000 children.[7,8]

The disease can have a serious impact on quality of life. Children with JIA are more likely to miss classes and have more days of missed school per year.[9] In many cases, JIA persists into adulthood and causes serious physical disability.[10-12] The economic burden of JIA is also substantial. The annual average direct medical costs for JIA is about $3000 per year per person, and the cost of medications ($1300) is a major component of the total costs of the disease.[9,13] Compared to children without chronic diseases, children with JIA had additional $1600 per year per person.[9]

There are several disease activity indexes that are used to measure the disease activity and prognostic factors for patients with JIA. A core set of six indicators defined by American College of Rheumatology (ACR) for children with JIA is often used in the clinical trials to measure disease response to therapy. These include 1) the number of active joints (joints with swelling, or joints with limitation of motion and with pain, tenderness), 2) the number of joints with limited range of motion, 3) physician global assessment of disease severity (10-cm visual analogue scale), 4) parent global assessment of patient's overall well-being (10-cm visual analogue scale), 5) functional ability assessed by The Juvenile Arthritis Functional Assessment Report and 6) erythrocyte sedimentation rate.[14] Certain thresholds are commonly used to identify improvement in this set of indicators following therapy. For example, a 30% improvement in three or more of the six indicators, and with no more than one variable worsening > 30% from baseline, is called "ACR 30".[15] Similarly, ACR 50 and ACR 70 are

defined as at least 50% and 70% improvement in three or more variables, without two or more variable worsening > 30% from baseline, respectively.

Treatment for JIA depends on the disease activity and presence of poor prognostic features.[16] In patients with low disease activity and without active systemic features, monotherapy with non-steroidal anti-inflammatory drugs (NSAIDs) is used. Intraarticular glucocorticoids injections are added following one- to two-months of treatment with NSAIDs if symptoms continue. Patients with persistent high disease activity may be treated with traditional DMARDs, including methotrexate or sulfasalazine, for three to six months. If there is minimal response to traditional DMARDs then TNFIs (e.g., infliximab, etanercept, and adalimumab) are recommended. Patients may switch to a second TNFI agent or abatacept after 4 months of initial TNFI treatment. When receiving traditional DMARDs or TNFIs, adjunctive NSAIDs or joint injections of glucocorticoids is used as needed.

For patients with systemic JIA and active systemic features, defined by fever, elevated inflammatory markers, or requirement of systemic glucocorticoid treatment, the treatment approach may be slightly different.[17] In order to control active inflammation, systemic glucocorticoids are recommended following one month of NSAIDs. After two-weeks of monotherapy with systemic glucocorticoids without resolution of disease activity, an interleukin receptor inhibitor (such as anakinra, canakinumab, rilonacept, or tocilizumab) is recommended. In some cases, patients can use methotrexate, leflunomide or TNFIs if disease activity continues following one month of anakinra.[16,17] The recommended dose for TNFIs used in the treatment of JIA and RA is shown in **TABLE I**.

TABLE I
DOSING OF TNFIS FOR JIA CHILDREN AND RA ADULTS

Drug	Children with JIA	Adults with RA
Infliximab	NA[a]	3mg/kg at 0, 2, 6 weeks followed by 3mg/kg every 8 weeks
Etanercept	• < 65 kg (138 lbs.): 0.8 mg/kg weekly • ≥ 65 kg (138 lbs.): 50 mg weekly	50 mg weekly
Adalimumab	• 10 kg(22 lbs.) to <15 kg (33 lbs.): 10 mg every other week • 15 kg (33 lbs.) to <30 kg (66 lbs.): 20 mg every other week • ≥ 30kg (66 lbs.): 40 mg every other week	40 mg every other week
Certolizumab	NA[a]	• 400 mg at 2, 4 week, followed by 200 mg every other week • In maintenance phase, 400 mg every 4 weeks
Golimumab	NA[a]	50 mg once a month

[a]Infliximab, certolizumab and golimumab do not have official pediatric indication for JIA. However, the ACR guideline recommended a maximum typical dose of infliximab (10 mg/kg every 4 weeks) for JIA[16]

1.1.2 Pediatric Inflammatory Bowel Disease

IBD is an immune-mediated disorder that is characterized by chronic inflammation in the gastrointestinal (GI) tract.[18] There are two main types of IBD: Crohn's disease (CD) and ulcerative colitis (UC). In UC the inflammation affects the top layer (mucosal) of the intestinal wall, and the ulcer occurs only in the large intestine (colon). In contrast, in CD the inflammation could be transmural (i.e., any layer of the bowel wall), and can involve any part of GI tract (i.e., from month to anus).[19]

Pediatric IBD accounts for around 30% of all IBD cases.[20] The incidence of IBD in children age 1 to 17 is 2.14 per 100,000 for UC and 4.56 per 100,000 in CD,[20,21] and had been increasing globally.[22] Notably, patients aged 15 to 30 years have the highest incidence of IBD.[23]

Children who developed IBD typically have more extensive symptoms and more frequent and severe episodes than adults, and often carry the disease into later adulthood.[3,24] Common symptoms of IBD are diarrhea, bleeding and weight loss. Weight loss may lead to malnutrition or growth impairment (e.g., height) in patients with IBD, and this effect is especially important in children in puberty.[19] In addition, children with IBD are more likely to experience anxiety and depression, poor school functioning, and lower quality of life than children without IBD.[25]

The economic burden of UC and CD is substantial. In one study the average annual direct costs associated with CD was $8265 and was $5066 for UC (2004 US dollars), compared to controls without IBD.[26] In addition, the direct medical costs were higher in patients aged less than 20 compared to adults, inferring a greater economic burden in children and young adults with IBD.[26]

The Pediatric Crohn Disease Activity Index (PCDAI) is the disease activity index designed for pediatrics with CD. The PCDAI incorporates patient symptoms (abdominal pain, functioning, bleeding stool), physical examination, laboratory parameters and growth measures (height and weight).[27] The index is measured based on total points, ranging from 0 to 100 with 100 being the highest possible level of disease activity.

For children with UC, the Pediatric Ulcerative Colitis Activity Index (PUCAI) is used to determine the disease activity. The PUCAI has a rage of 0 to 85 points based on assessment of six components, including abdominal pain, rectal bleeding, stool consistency of most stools, number of stools per 24 hour, nocturnal stools (any episode causing wakening), and activity level.[28] The two disease activity indices are widely used in clinical trials for monitoring response to treatment. A higher score of PCDAI or PUCAI indicates a more severe disease activity of CD and UC, respectively. A clinical remission of CD is usually defined as PCDAI less than 10 points. Similarly in UC, patients with less than 10 points on PUCAI are considered to reach remission.

In children with active CD, exclusive enteral nutrition for 6-8 weeks is the first line therapy to induce remission. If the patient does not respond to enteral nutrition or if enteral nutrition is not an option, then oral corticosteroids are recommended.[29] For children with moderate to severe CD the recommendation is a prednisone equivalent of 1mg/kg once daily. However, corticosteroids should not be used as maintenance therapy for children due to adverse effects. Instead, azathioprine and 6-mercaptopurine are options for children with poor prognostic features that required maintenance therapy. Methotrexate can be used as primary maintenance therapy or for patients who have failed to respond to azathioprine or 6-mercaptopurine. Use of TNFIs (e.g., infliximab and adalimumab) is recommended for both induction and maintenance phase for children with moderate to severe active CD, or children with steroid refractory CD.[29] Induction doses and maintenance doses of TNFIs are shown in **TABLE II**.

For children with UC, oral and topical 5-aminosalicylic acid (5-ASA) (e.g., sulfasalazine, mesalazine) is the first line therapy in both induction and maintenance for remission.[30] Systematic use of corticosteroids is effective for inducing remission in children with moderate to severe disease or in children who fail 5-ASA therapy, but steroids should not be used in maintenance therapy. Thiopurines (e.g., azathioprine or 6-mercaptopurine) are added if patients are intolerant to 5-ASA, steroid-dependent, and frequently relapsing (2-3 relapse per year). However, if disease activity is not well controlled despite the treatment of thiopurines, TNFI infliximab should be considered (**TABLE II**).[30] Adalimumab can be used if patients fail infliximab. Last, surgery may be performed if the disease is still active despite all medication treatments.

In the treatment of JIA and IBD in children, TNFIs play a very important role. TNFIs are a relatively new treatment option for JIA and IBD, but have become a mainstay in the treatment strategy, particularly in moderate to severe JIA or IBD. TNFs are described in more detail in the following section.

TABLE II

DOSING OF TNFIS FOR IBD IN CHILDREN AND ADULTS

Drug	Indication	Induction dose	Maintenance dose
Infliximab	• Adult UC and CD • Pediatric UC and CD	5 mg/kg intravenous induction at 0, 2 and 6 weeks	5 mg/kg every 8 weeks
Etanercept	NA	NA (Does not have official pediatric indication for IBD)	
Adalimumab	Pediatric CD:17 kg (37 lbs) to < 40 kg (88 lbs)	• 80 mg on Day 1 (two 40 mg injections); and • 40 mg at week 2 (on Day 15)	20 mg every other week after week 4 (Day 29)
	• Pediatric CD: ≥ 40 kg (88 lbs) • Adult CD and UC	• 160 mg on Day 1 (four injections in one day or two 40 mg injections per day for two consecutive days); and • 80 mg on week 2 (on Day 15) (two 40 mg injections in one day)	40 mg every other week after week 4 (Day 29)
Certolizumab	Adult CD	400 mg (two subcutaneous injections of 200 mg) at 0, 2 and 4 weeks	400 mg every 4 weeks
Golimumab	Adult UC	• 200 mg subcutaneous injection at week 0 • 100 mg at week 2	100 mg every 4 weeks

1.2 Tumor Necrosis Factor-α Inhibitors

1.2.1 Role of Tumor Necrosis Factor-Alpha

Tumor necrosis factor-alpha (TNF-alpha) is a potent cytokine that modulates the early inflammatory process.[31] It is produced by activated macrophages and T-cells in response to immunological or infectious stimulants. The action of TNF-alpha occurs by binding to type 1 (p55) and type 2 (p75) TNF receptors. TNF receptor 1 can be found in most cell types and is responsible for inflammation initiation and apoptosis mediation. TNF receptor 2 is typically found in immune cells (e.g., lymphocytes) and facilitates antiviral immune response.[32-34] TNF-alpha transduces the proinflammatory signals and mediates an anti-apoptosis effect by activating additional cytokines and chemokines such as interleukin (IL)-1, IL-6, IL-8, granulocyte-macrophage colony-stimulating factor, and nuclear factor-κB.[32-35] In patients with RA, high concentrations of TNF-alpha are found in the rheumatoid joint, and TNF-alpha is also known to induce other immune and inflammatory cells to the joint.[32]

1.2.2 Type of Tumor Necrosis Factor-Alpha Inhibitors

TNFIs are biologic agents designed to bind to TNF-alpha and thus prevent its action on TNF receptors.[32] This then results in suppression of release of downstream inflammatory mediators, and thus exerts an anti-inflammatory effect.

The TNFIs include 1) monoclonal antibodies (infliximab, adalimumab, golimumab, and certolizumab) that mainly bind to TNF-alpha and 2) fusion protein (etanercept) that have equal affinity to both TNF-alpha and lymphotoxin-alpha (TNF-beta). Infliximab (Remicade®), the first TNFI (approved in 1998), is a chimeric immunoglobin (Ig) G1 human-murine protein antibody that has a high affinity to TNF-alpha.[32,34] Similarly, adalimumab (Humira®) and golimumab (Symponi®) are IgG1 antibodies, but both are recombinant humanized monoclonal antibodies. Certolizumab (Cimzia®) is a humanized IgG4 antigen-binding fragment (Fab) linked to

polyethylene glycol, which by design has longer half-life and lower clearance rate. Unlike other TNFIs, etanercept (Enbrel®) is a recombinant fusion protein that consists of the crystallizable fragment (Fc) domain of human IgG1 fused to an extracellular ligand-binding domain of TNF receptor 2 (p75). Etanercept binds to not only TNF-alpha but also lymphotoxin-alpha (also known as TNF-beta). Lymphotoxin-alpha is a cytokine involved in infections, tumor growth control and lymphoid organ development.[36-38] All of the TNFIs are administered subcutaneously except for infliximab which is given via intravenous infusion.

1.2.3 Efficacy of Tumor Necrosis Factor-Alpha Inhibitors

In clinical trials, TNFIs have demonstrated great efficacy in reducing disease activities as well as in improving quality of life in patients with autoimmune diseases such as RA, IBD, psoriasis, psoriatic arthritis, and ankylosing spondylitis. Here we focused on clinical trials of TNFIs in patients with RA, JIA, IBD and pediatric IBD.

In adults with RA, several large clinical trials have been conducted to assess the efficacy of TNFIs compared to standard care. For example, Keystone and others conducted a randomized controlled trial that included 619 RA patients who had previously experienced an inadequate response to methotrexate.[39] They observed a clinical response (ACR20) that was statistically higher in patients treated with 20 mg/week adalimumab plus methotrexate (63%) and 40 mg/every-other-week adalimumab plus methotrexate (61%), compared to placebo plus methotrexate (30%) at week 24.[39] Patients receiving adalimumab also experience at least a 10-point improvement from baseline in 5 out of 8 domains on SF-36 (physical function, physical role, body pain, vitality, and social function), as compared with 1 out of 8 domains in placebo group (physical role).

The efficacy of TNFIs has also been demonstrated in JIA. In a randomized controlled trial where 69 children with JIA were enrolled to receive open-label etanercept, 74% responded

to the treatment.[40] Among the 51 responders, children were subsequently randomly assigned to receive etanercept (0.4 mg/kg twice weekly) or placebo. The etanercept group had a greater disease improvement (ACR 30: 80% vs. 35%; ACR 50: 72% vs. 23%; ACR 70: 11% vs. 5%) and less disease flares (28% vs. 81%), compared to placebo group.[40] Additionally, elevated values of C-reactive protein, erythrocyte sedimentation rate, and white-cell and platelet counts at baseline shifted to normal values after treatment of etanercept. Moreover, 54% of patients who received etanercept reported a median improvement of their physical function ability measured by Childhood Health Assessment Questionnaire, compared to no change in the placebo group.

Two large randomized controlled trials—Active Ulcerative Colitis 1 and 2 (ACT 1 and ACT 2) demonstrated the efficacy of TNFIs in adults with UC.[41] In the ACT 1, 364 patients with UC were randomly treated with infliximab or placebo. The study found that 10mg/kg and 5mg/kg of infliximab improved clinical response (10mg/kg: 62%, 5mg/kg: 69%, placebo: 37%) and clinical remission (10mg/kg: 32%, 5mg/kg: 39%, placebo: 15%) compared to placebo.[41] Similar findings were observed in ACT 2. The clinical endpoints were measured based on the Mayo score—which is a summary score accounting for four aspects of clinical manifestations: stool frequency, rectal bleeding, endoscopic findings and physician's global assessment. A higher value of the Mayo score indicates a worse disease severity. A clinical response in the trial was defined as a decrease from baseline in the Mayo score by at least 30% and at least 3 points, with accompanying decrease of ≥1 point in rectal bleeding sub-score or an achievement of an absolute sub-score 1 or 0 in rectal bleeding. The clinical remission was defined as a Mayo score equal or less than 2 without any individual sub-score greater than 1.

Clinical trials of TNFIs have also been conducted in children with IBD. REACH was a randomized trial of 112 children with active CD who received induction treatment of infliximab at weeks 0, 2 and 6.[42] For children who responded to infliximab (99 out of 112) at week 10 were

subsequently randomly assigned to infliximab (5 mg/kg) every 8 weeks or every 12 weeks, in combination with oral immunosuppressant. In children with every 8-week dosing, 63.5% (compared to 33.3% in every 12-week dosing) achieved clinical response (a decrease of PCDAI score ≥ 15 points and a total PCDAI score no more than 30) and 55.8% (compared to 23.5% in every 12-week dosing) achieved clinical remission (a total PCDAI score of 10 points or lower). In addition, patients on the every 8-week regimen had a higher rate of discontinuation of corticosteroids (83% vs 56%), compared to every 12-week regimen.[42]

1.2.4 Utilization of Tumor Necrosis Factor-Alpha Inhibitors

Because of their significantly better effectiveness compared to other therapies, TNFIs have become a revolutionary therapy for many autoimmune and inflammatory diseases, especially for RA and IBD. More than 2 million people cumulatively have been treated with TNFIs for their rheumatoid diseases or IBD since 1998.[31,35] As a result, infliximab, adalimumab, and etanercept are among the top drugs in terms of total expenditures in the US, collectively surpassing $22 billion in sales in 2015.[43]

A study conducted by Lee and others used data from the Consortium of Rheumatology Researchers of North America (CORRONA) registry from 2002 to 2006 to examine the utilization patterns of TNFIs in 11,397 adults with RA.[44] The investigators found that use of TNFIs was growing at a rate of 2.8% per year in patients with established RA and 1.2% per year in those with early RA. According to the study, approximately one-third of RA patients received TNFIs.[44] A trend of increased use of biologics was also observed in patients with RA at Veteran Affairs Medical Centers—with 3.4% of patients in 1999 and 25% in 2009 receiving the drugs.[45]

Current guidelines suggest a “step-up” strategy in the treatment of JIA and IBD, reserving TNFIs as a later-line therapy for patients who failed to respond to traditional DMARDs or oral immunomodulators.[16,17,29,30,46] However, recent studies have suggested that early use of

TNFIs could improve remission rates, functional status, and slow disease progression.[47-51] This more aggressive "top-down" approach, which starts with a TNFI, is increasingly described in the primary literature.[52-55] However, the proportion of RA or IBD patients receiving TNFIs as the first-line therapy is still low in real-world clinical practice. For example, approximately 10% of patients with RA used TNFIs as the monotherapy based on data from the CORRONA registry,[44] and 6.7% of VA patients used biologics as the initial agent.[45]

1.3 Safety Issues Associated With Tumor Necrosis Factor-Alpha Inhibitors

Though effective and now commonly used, several safety concerns arose in the clinical trials and subsequently in post-marketing analyses of TNFIs.

In the aforementioned randomized controlled trial, where RA patients were treated with adalimumab or placebo, adalimumab was observed to have a significantly greater rate of serious infection (requiring hospitalization or antibiotics injection), 3.8%, compared to placebo group (0.5%) at week 52.[39] The incidence was reported to be 0.06/person-year for adalimumab 40 mg every other week, 0.03/person-year with 20mg adalimumab weekly, and 0.01/person-year in the placebo group. The serious infections that were observed in the adalimumab group included tuberculosis of the cervical lymph nodes, histoplasmosis infection, and encephalitis due to herpes zoster infection. In addition, four cases of cancer developed during the study period—including non-Hodgkin's lymphoma, adenocarcinoma, testicular seminoma, and breast cancer. Patients treated with adalimumab also had higher proportion of antinuclear antibodies (ANA) positive conversion (12.1% vs. 9.1%) and anti-double-stranded DNA (anti-dsDNA) antibodies (11.7% vs. 0%) compared to placebo.[39] A high proportion of ANA or anti-dsDNA can induce lupus-like syndromes.

Similar types of adverse events were observed in the ACT 1 and ACT 2 clinical trials in

patients with UC. Patients receiving 10 mg or 5 mg infliximab developed eight (6.6%) and three (2.5%) cases of serious infections, respectively, compared to five cases (4.1%) in placebo group in ACT 1.[41] In ACT 2, the rates of serious infections were reported to be 2.5%, 1.7%, and 0.8% in patients with 10 mg infliximab, 5mg infliximab, and placebo, respectively. These infections included a case of tuberculosis and a case of histoplasma pneumonia, which progressed to acute respiratory distress syndrome. Malignancy-related adverse events were also reported. A total of four patients were diagnosed with prostatic adenocarcinoma, colonic dysplasia, basal-cell carcinoma, and rectal adenocarcinoma in the infliximab groups, compared with one case of basal-cell carcinoma in the placebo group. In addition, three neurologic events mainly optic neuritis were reported. Higher proportions of ANA positive and anti-dsDNA antibodies were observed in infliximab treatments than placebo, with one patient developed lupus-like reaction.[41]

In the FDA Adverse Event Report Systems (FAERS) or MedWatch database, where post-marketing reports of drug adverse events are tracked, TNFIs were the number one drug class associated with adverse event reports. In total there were 461,929 case reports of TNF-associated events from January 2004 to June 2014.[56] Several post-marketing studies have reported adverse events from TNFIs, including infections, infusion reactions, autoimmune adverse events (e.g., lupus-like syndrome and drug-induced psoriasis), neurological adverse events (e.g., central nervous system/spinal demyelination), hematological adverse events (e.g., neutropenia, anemia, thrombocytopenia), interstitial lung disease, autoimmune hepatitis and abnormal elevated liver enzymes, and cancer—especially lymphoma and nonmelanotic skin cancer.[57,58]

Based on the findings from clinical trials and post-marketing studies, on September 4, 2008 the FDA required manufacturers of TNFIs to begin including a black-boxed warning in the product label.[59] The warning is for serious infections leading to hospitalization or death, including tuberculosis, histoplasmosis and invasive fungal infections. On August 4, 2009 the

FDA updated the boxed warning to add the risk of lymphoma and other cancer in children and adolescents. The addition was based on evidence from a post-marketing analysis of the FDA AERS database wherein 48 malignant cases were reported in children treated with TNFIs, and about half of the case reports were lymphoma.[60] In April 2011, FDA analyzed current evidence and incorporated in the black-box warning a rare type of lymphoma, Hepatosplenic T-Cell Lymphoma, in children treated with infliximab or adalimumab. This specific, rare type of lymphoma was observed primarily in children receiving TNFIs (infliximab or adalimumab) and/or other immunosuppressant azathioprine and 6-mercaptopurine for treatment of CD or UC.[61,62]

1.4 Infection Associated With Tumor Necrosis Factor-Alpha Inhibitors In Adults

Infections are the most frequently reported serious adverse event in adult patients treated with TNFIs, with an incidence of 2.2 to 8.16 cases per 100 person-years.[63-66] Post-marketing studies also found that infections were disproportionally reported in patients treated with TNFIs. A study analyzing data from the Portuguese Pharmacovigilance System database between 2009 and 2011 found that 'infections and infestations' were disproportionally associated with infliximab (reporting odds ratio (ROR) 2.95, 95%CI 2.16-4.02), etanercept (ROR 2.74, 95%CI 1.56-4.81), and adalimumab (ROR 6.65, 95%CI 4.50-9.83).[57] Wallis and colleagues examined the adverse events of infections related to TNFIs in the FAERS database from 1998 to 2002. They identified a total of 622 case reports of infections associated with infliximab and etanercept. Among these, tuberculosis was the mostly reported, with a reporting rate of 144 per 100,000 patients receiving infliximab and 35 per 100,000 patients receiving etanercept.[67] Separately, Keane and others reported that the rate of tuberculosis in RA patients who had received infliximab was greater than a background rate of 6.2 tuberculosis cases per 100,000 in patients with RA in the United States.[68] Cases of pneumonia, upper respiratory infections, soft tissue infections, Herpes zoster, and reactivation of hepatitis B virus were other types of infection that were associated with TNFIs in post-marketing studies. However, studies

using passive spontaneous reporting data can hardly provide causality assessment due to the nature of the data source and issues such as under-reporting, confounding effects by other factors, and the inability to estimate incidence.

In order to determine the existence of an association between infections and TNFI use, meta-analyses incorporating several clinical trials in adults were conducted. However, the results of these were conflicting (**TABLE III**). For example, one meta-analysis of 9 clinical trials including a total of 5,005 patients with RA found a 2-fold increased risk (OR 2.01, 95%CI 1.31-3.09) of serious infection with infliximab and adalimumab compared to placebo (all patients concomitantly used methotrexate).[69] However, two recent meta-analyses that included trials of etanercept found a non-significant increased risk of infection with TNFIs compared to placebo or traditional DMARDs,[70,71] although a 2-fold increased risk (OR 2.1, 95%CI 1.3-3.3) was observed in high dose group of TNFIs.[71] Conversely, a meta-analysis incorporating results from 7 observational studies (5 cohort studies and 2 nested-case control studies) found that TNFIs significantly increased the risk of serious infections in patients with RA (RR 1.37, 95%CI 1.18-1.60).[72] For patients with IBD, a meta-analysis was conducted that included 21 clinical trials of CD that totaled 3,341 patients in the TNFI group and 2,015 in the control group, with a median follow-up of 24 weeks (range 4 to 60 weeks). The study did not find a significant difference in the proportion of serious infections in TNFI group (2.09%) compared to control group (2.13%).[73] More recent meta-analyses were conducted and reported non-significant risk associated with TNFIs compared to placebo.[74,75] The conflicting results across these meta-analyses may be due to different criteria for inclusion of trials, different control drugs, and potential heterogeneity in the design of the clinical trials (e.g., dose of TNFIs and length of follow-up).

TABLE III
SUMMARY OF META-ANALYSES FOR EVALUATION OF THE TNFI-INFECTION ASSOCIATION IN ADULTS WITH RA AND IBD

Authors, published year	**Study cohort**	**Number of studies and study type**	**Treatment group**	**Control group**	**Main results [OR (95%CI) or incidence in %]**
Bongartz et al., 2006[69]	RA	9 clinical trials	Infliximab, adalimumab	DMARDs/ Placebo	2.0 (1.3-3.1)*
Alonso-Ruiz et al., 2008[70]	RA	13 clinical trials	Infliximab, adalimumab, etanercept	DMARDs/ Placebo	1.4 (0.8–2.2)
Leombruno et al., 2009[71]	RA	18 clinical trials	Infliximab, adalimumab, etanercept	DMARDs/ Placebo	1.2 (0.9-1.6)
Bernatsky et al., 2010[72]	RA	7 observational studies	Infliximab, adalimumab, etanercept	DMARDs/ non-TNFI	1.4 (1.2-1.6)*
Peyrin-Biroulet et al., 2008[73]	IBD	21 clinical trials	Infliximab, adalimumab, certolizumab	Placebo	2.09% vs 2.13%
Lichtenstein et al., 2012[74]	IBD	10 clinical trials	Infliximab	Placebo	4.7% vs 3.7%
Bonovas et al., 2016[75]	IBD	44 clinical trials	Infliximab, adalimumab, certolizumab, golimumab, natalizumab, vedolizumab	Placebo	0.89 (0.71-1.12)

* p value <0.05

In addition to meta-analyses, several registry-based studies and observational studies have also found mixed results. In a study analyzing data from the German Rheumatoid Arthritis-observation of Biologic Therapy registry, Listing and colleagues reported an unadjusted increased risk of serious infection for infliximab (RR 2.7, 95%CI 1.3-5.9) and etanercept (RR 2.8, 95%CI 1.4-5.9) compared to traditional DMARDs; however the statistically significant result did not persist after adjusting for the propensity to receive drug and several other important indicators of disease severity.[76] Another study using a UK registry called the British Society for Rheumatology Biologics Register and found that TNFIs as a group did not statistically increase the risk of serious infection based on adjusted incidence rate ratio estimates (IRR 1.35, 95%CI 0.99-1.85). However, when individual TNFIs were assessed, infliximab was found to increase the risk of infection by 40% (IRR 1.41, 95%CI 1.02-1.97).[77] Studies using registry data usually have follow-up time with long intervals (e.g., every 6 months), which may have limitations on collecting comprehensive information and adverse events. In addition, the results may be subject to recall bias if patients have to recall the occurrence of adverse events in the past few months.

Investigators have made efforts to overcome the limitations of meta-analysis and registry-based studies by using large claims databases with longer follow-up time. However, the differences in study population, and in the definitions of exposure and outcomes, have also resulted in discrepancies in the findings of these studies (**TABLE IV**). Several studies demonstrated an increased risk of infections associated with TNFIs. For example, Lane and colleagues analyzed 20,814 veterans with RA from 1995 to 2005, and found a 1.24-fold (95%CI 1.02-1.50) increased risk of serious infection requiring hospitalizations, compared to traditional DMARDs.[78] Another study conducted by Curtis et al using administrative data between 1998 and 2003 from a large a large health care organization (United Health Group) observed a HR of 1.90 (95%CI 1.3-2.8) in patients receiving TNFIs compared to methotrexate only.[79] In contrast,

many studies found no association between infections and TNFIs. A large observational cohort study analyzing patients from both commercial and national Medicaid/Medicare datasets in 1998-2007 failed to find an increased risk of infection-related hospitalizations associated with TNFIs in patients with RA (HR 1.05, 95%CI 0.91-1.21) and IBD (HR 1.10, 95%CI 0.76-1.45).[66] On the other hand, among studies conducted in IBD, the study findings were also conflicting. For example, Schnessweis and colleagues analyzed patients with CD or UC and reported no association between risk of serious infection and use of TNFIs (rate ratio 1.08, 95%CI 0.42-2.74) compared to use of methotrexate or thiopurines.[80] However, other studies using national registry or large disease registry found that TNFI use was associated with an increased risk of serious infection compared to non-TNFI users.[81,82]

In conclusion, the existence of an association between TNFIs and infection has been inconsistent across the literature. Moreover, most studies investigating this association were conducted in adults. However, children are a vulnerable population who are more likely to experience adverse drug events than adults.[83,84] More importantly, the immaturity of the immune system may put children at a higher risk for infection.[85] We conducted a post-marketing analysis using FDA AERS data from 2007-2012 and found that TNFIs (infliximab, etanercept and adalimumab) were among the top 20 commonly medications reported to cause an adverse event in children aged less than 18 years. Reports of pneumonia and clostridial infection associated with TNFIs were among on the top 10 adverse events resulting in serious outcomes.[86] This suggests the need for more objective evidence on the association between TNFIs and infection in children. However, evidence on the association between TNFIs and infection in children is relatively scarce. Below we give an overview of the current evidence on the TNFI-infection association specifically in children.

TABLE IV

SUMMARY OF OBSERVATIONAL STUDIES FOR EVALUATION OF THE TNFI-INFECTION ASSOCIATION IN ADULST WITH RA AND IBD

Authors, published year	**Study cohort**	**Data source and year of data**	**Control group**	**Main results [OR or HR (95%CI)]**
Curtis et al., 2007[79]	RA	United Health Group, 1998-2003	Methotrexate	1.94 (1.32-2.83)*
Schneeweiss et al., 2007 [65]	RA	Medicare database, 1995-2003	Methotrexate	1.01 (0.60-1.70)
Grijalva et al., 2011[66]	RA	Medicaid/Medicare database, 1998-2007	DMARDs	1.05 (0.91-1.21)
Lane et al., 2011[78]	RA	VA data, 1995-2005	DMARDs	1.24 (1.02-1.50)*
Schneeweiss et al., 2009[80]	IBD	British Columbia data, 2001-2006	Methotrexate, azathioprine, 6-mercaptopurine	1.08 (0.42-2.74)
Grijalva et al., 2011[66]	IBD	Commercial and Medicaid/Medicare database, 1998-2007	Azathioprine, 6-mercaptopurine	1.10 (0.76-1.45)
Lichtenstein et al., 2012[81]	CD	Crohn's Therapy, Resource, Evaluation, and Assessment Tool registry, 1999-2010	Non-infliximab users (immunomodulators or non-users)	1.43 (1.11-1.84)*
Nyboe Anderson et al., 2015[82]	IBD	Danish national registry, 2002-2012	Non-TNFI users (immunomodulators or non-users)	1.63 (1.01-2.63)*

* $p<0.05$

1.5 Infection Associated With Tumor Necrosis Factor-Alpha Inhibitors In Children

Clinical trials conducted in children with JIA or pediatric IBD typically have small sample sizes (no more than 200) and short follow-up periods, and therefore did not detect many cases of serious infections.[87-89] In a randomized controlled trial of infliximab plus methotrexate in 120 children with JIA, infections were found to occur in 41 of 60 (68.3%) patients receiving infliximab 3mg/kg compared to 28 of 60 (46.7%) receiving placebo.[90] Upper respiratory tract infection was the most commonly reported infection. However, most infections were mild and only 6 cases were serious infection in the infliximab group, with 4 cases of pneumonia and 1 case of varicella zoster infection. Even in a study with a long-term open-label extension of etanercept treated for children with JIA, a total of 8 out of 58 children developed serious infections requiring hospitalizations or antibiotic use over the 4-year study period.[88] In another clinical trial where 103 children with CD disease were treated with infliximab, only 7 serious infections were recorded, including cases of pneumonia, colitis, and enterocolitis.[42]

Several registry-based studies have followed children with JIA to evaluate the safety of TNFIs.[91-93] For example, a study using a Polish registry followed 188 children with JIA who are unresponsive or intolerant to methotrexate for 2 years. The most commonly reported adverse event was upper respiratory tract infection (2.94 per person year). Other adverse events of infections include herpes infections, urinary tract infections and varicella.[93] Again, these registry studies also ran into the issue of small number of cases of infections. In addition, the follow-up intervals were long (every 6 months or 12 months) and thus investigators may not capture all adverse events comprehensively.

A systematic review by Toussi and others summarized the incidence and etiology of infections in children with JIA or pediatric IBD who receive TNFIs.[94] The review included 30 prospective and 23 retrospective studies. Mild infection was reported at an incidence range of 8% to 97% in JIA and 3% to 77% in pediatric IBD across the studies. The wide range of

incidence was probably because of the differences in sample size and definition of infections used. Upper respiratory tract infection was the most common infection type among mild infection cases for both JIA and pediatric IBD. On the other hand, the incidence of severe infection was much lower, with a range between 0% to 9% in JIA and 0% to 10% in pediatric IBD. Respiratory tract infection and musculoskeletal infections were the most frequent severe infection type observed in JIA; while sepsis, gastrointestinal and soft tissue infections were the most commonly reported types of severe infection in pediatric IBD. The authors concluded that the most frequent infections were mild and of viral etiology; severe bacterial and fungal infections were less frequent, and may be associated with concomitant use of other immunosuppressants. However, most studies were small clinical trials, small observational studies or case series reports, with limited number of participants and short follow-up. As a result, no definitive association between TNFIs and infection was determined in children.

A few observational studies were conducted using data from relatively large electronic database or registry among children with JIA but again the results were mixed (**TABLE V**). One of these was a retrospective cohort study that analyzed a national Medicaid database in children with JIA from 2000 to 2005.[95] A total of 8,479 children with JIA were included and the risk of hospitalization due to bacterial infections was evaluated in those exposed compared to non-exposed to TNFIs. The crude incidence of hospitalizations due to bacterial infections was 3.5 per 100 person-years in patients receiving TNFIs, irrespective of methotrexate use, and was 3.3 per 100 person-years in methotrexate-only group. After adjusting for patients characteristics and important confounders such as infection episodes at baseline, TNFIs use was not associated with hospitalization due to bacterial infection (HR 1.2, 95%CI 0.8-1.8) compared to methotrexate use only. [95] However, two studies using data from registries reported contrasting findings. A UK study analyzed 1,112 children with JIA and found that etanercept was associated with a higher risk (HR 2.12, 95%CI 1.22-3.74) of medically significant infection than methotrexate. Another

German study identified 2,263 individuals with JIA and reported a higher risk of medically important infection associated with etanercept (RR 2.12, 95%CI 1.08-4.17) but not adalimumab (RR 0.88, 95%CI 0.18-4.28) compared to methotrexate.

The findings of the above observational studies conflicted with regard to the TNFI-infection association among children with JIA. The discrepancies in the findings may be attributable to selection bias associated with use of different types of data sources. For example, individuals enrolled in registries may have characteristics different from those who did not enroll. In addition, inconsistent definitions of infection across studies could have hindered arrival at valid conclusions regarding the association between TNFIs and infection. For children with IBD on the other hand, evidence of a TNFI-infection association was even scarcer. Therefore, more studies with large numbers of subjects and more rigorous designs are needed to provide more definitive evidence in order to confirm the FDA warning of TNFI-induced serious infection among children.

In addition to children with JIA and IBD, young adults with RA and IBD were often underrepresented in clinical trials and observational studies. Although adult studies usually included a full range of ages (e.g., ≥18 years), these studies tended to place more weight on middle-aged individuals, and thus the study findings were not fully generalizable to young adults. In addition, childhood-onset JIA or IBD usually extends to young adulthood, but this JIA/IBD population has rarely been examined. Given the limited evidence of the TNFI-infection association in young adults, additional studies for this population are also merited.

TABLE V

SUMMARY OF STUDIES FOR EVALUATION OF THE TNFI-INFECTION ASSOCIATION IN CHILDREN WITH JIA

Authors, published year	Study cohort	Data source and year of data	Treatment group	Control group	Outcome definition	Main results
Beukelman et al., 2014[95]	JIA	Medicaid data, 2000-2005	Etanercept, infliximab, adalimumab (+/- methotrexate)	Methotrexate or leflunomide	Hospitalized bacterial infections using diagnosis codes	1.2 (0.8-1.8)
Davies et al, 2015[96]	JIA	Paediatric and Adolescent Rheumatology Etanercept Cohort Study, since 2004	Etanercept	Methotrexate	Medically significant infections defined by consultant for any one of the reasons: 1) life-threatening, 2) caused significant disability, 3) caused death, 4) led to hospitalization, 5) required intravenous(IV) antibiotics or IV antivirals, or 6) was deemed “medically significant” by the consultant	1.36 (0.60-3.07)*
Klotsche et al, 2015[97]	JIA	Two German registries, 2005-2011	Etanercept, adalimumab	Methotrexate	Medically important infections: infections that led to hospitalization and/or required intravenous antibiotic treatment	ETA vs MTX: 2.12 (1.08-4.17)* ADA vs MTX: 0.88 (0.18-4.28)

* $p<0.05$

1.6 Gap In The Literature

From existing evidence we knew that the use of TNFIs has increased over the recent past; however, we did not have good information on medication usage patterns and trends in the use of TNFIs among children and young adults with JIA and IBD, especially after the FDA warning. Physicians may be more cautious when prescribing TNFIs because of the warning, and may even reduce the use of the drugs. On the other hand, the more aggressive treatment strategy and so-called “top-down” approach, was hypothesized to be more effective than “step-up” by improving the functional status and slowing the disease progression. The “top-down” approach may be particularly beneficial to children, because early use of TNFIs may decrease the use of corticosteroids and thus decrease the impact of adverse events on children’s pubertal growth. However, the TNFI utilization after the warning, especially early use of TNFIs, was not well studied among children and young adults in a real-world setting.

In addition, although the FDA warning applied to both adults and children exposed to TNFIs, studies evaluating the TNFI-infection association were primarily conducted in adults, and the findings were conflicting. Studies conducted in children and young adults were usually small and lacked statistical power needed to make a valid evaluation of the association. The need to confirm the TNFI-infection association in children is especially important, not only because children are more likely to experience adverse drug reactions, but also because of a lack of evidence in children to provide a thorough risk and benefit assessment. An adequately powered study is essential to accurately quantify the incidence of serious infections and the risk associated with exposure to TNFIs. Compared to randomized controlled trials or registry data, health claims data could provide much larger sample sizes and longer periods of follow-up. To date, observational studies conducted in children have found conflicting results for risk of serious infections associated with TNFIs. Therefore, more objective evidence on the evaluation

of the TNFI-infection association in children and young adults was needed to provide a more definite safety profile of TNFIs.

Moreover, the mechanism of action and structure are different among individual TNFI agents. Whether the risk of infections varied by specific TNFI or by route of administration was uncertain. Such analysis for the comparative safety among TNFIs has not been determined in children and young adults. However, this piece of information could better inform clinicians and patients in selecting a TNFI agent considering the comparative safety.

1.7 Purpose Of Dissertation

The goal of this dissertation work was to characterize the utilization of TNFIs and to examine the risk of serious infections associated with TNFIs among children and young adults. We developed four study aims to address the gaps in the evidence. These were (1) to characterize the utilization of TNFIs among children and young adults with JIA/RA; (2) to characterize the utilization of TNFIs among children and young adults with IBD; (3) to determine the association between TNFIs and serious infection in children with JIA; (4) to determine the association between TNFIs and serious infection and to examine the comparative risk of infection among TNFI agents in children and young adults with IBD.

1.8 Conceptual Framework

The conceptual framework of the dissertation work and the specific aims were illustrated in **FIGURE 1**. We used the Truven Health MarketScan® Commercial Claims and Encounters databases between 2009 and 2013 to accomplish these four aims. In the first two aims, we examined the prescribing patterns and the rate of early TNFI use (i.e., the top-down strategy) among children and young adults with JIA/RA (aim 1) and IBD (aim 2), respectively, in two separate cohort studies.

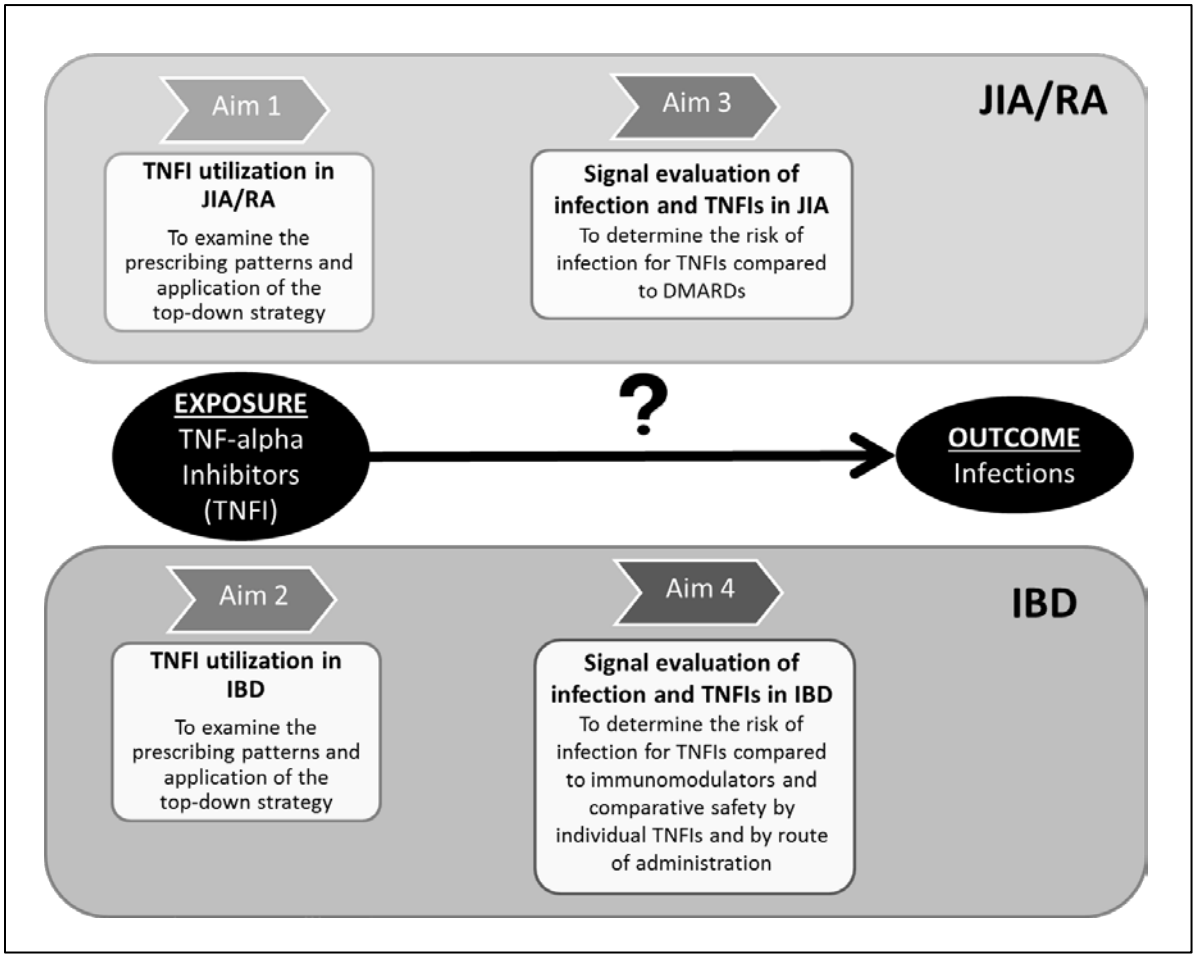

FIGURE 1. Conceptual framework

In aim 3, we evaluated the risk of serious infection associated with TNFIs compared to traditional DMARDs in a cohort of children with JIA. A directed acyclic graph (DAG) was used to describe the relationship between use of TNFIs and infection, along with potential confounders such as demographics, infection-related risk factors, health plan type, and disease severity, as shown in **FIGURE 2**.

In aim 4, we conducted a cohort study to determine the risk of infection associated with TNFIs compared to oral immunomodulators (i.e., thiopurines and methotrexate) among children and young adults with IBD. The same DAG (**FIGURE 2**) was applied to aim 4. In addition, we further examined the comparative risk of infection among individual TNFIs and by route of administration (**FIGURE 3**). The approach and research plan for each specific aim was elaborated on in the following chapters.

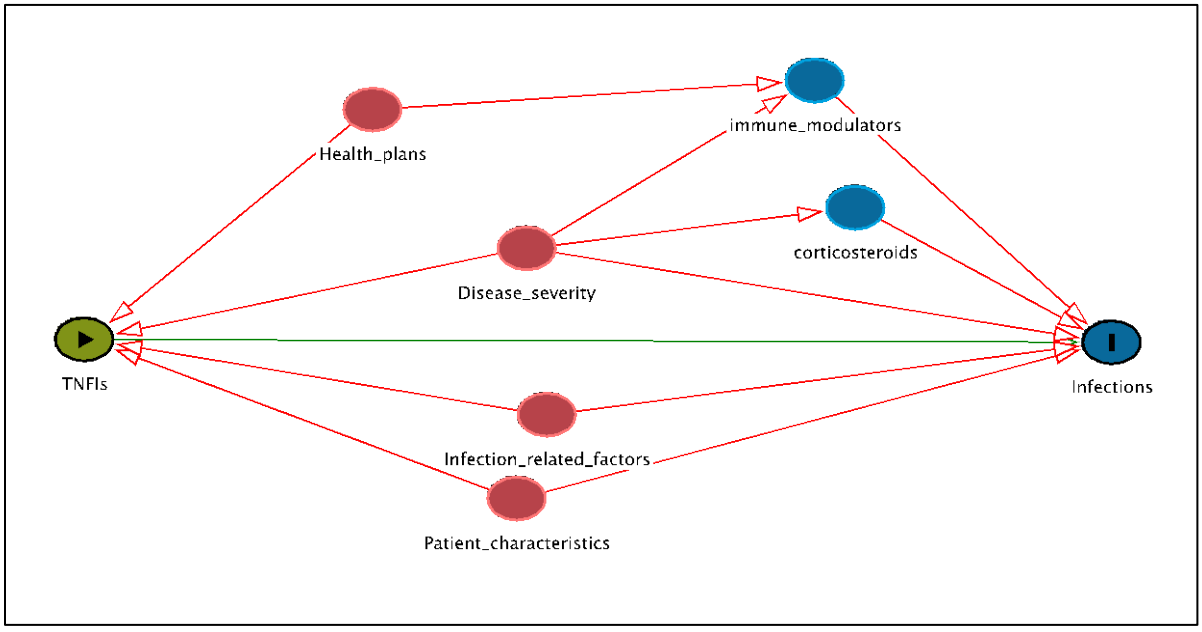

FIGURE 2. Directed acyclic graph of association between TNFIs and infections

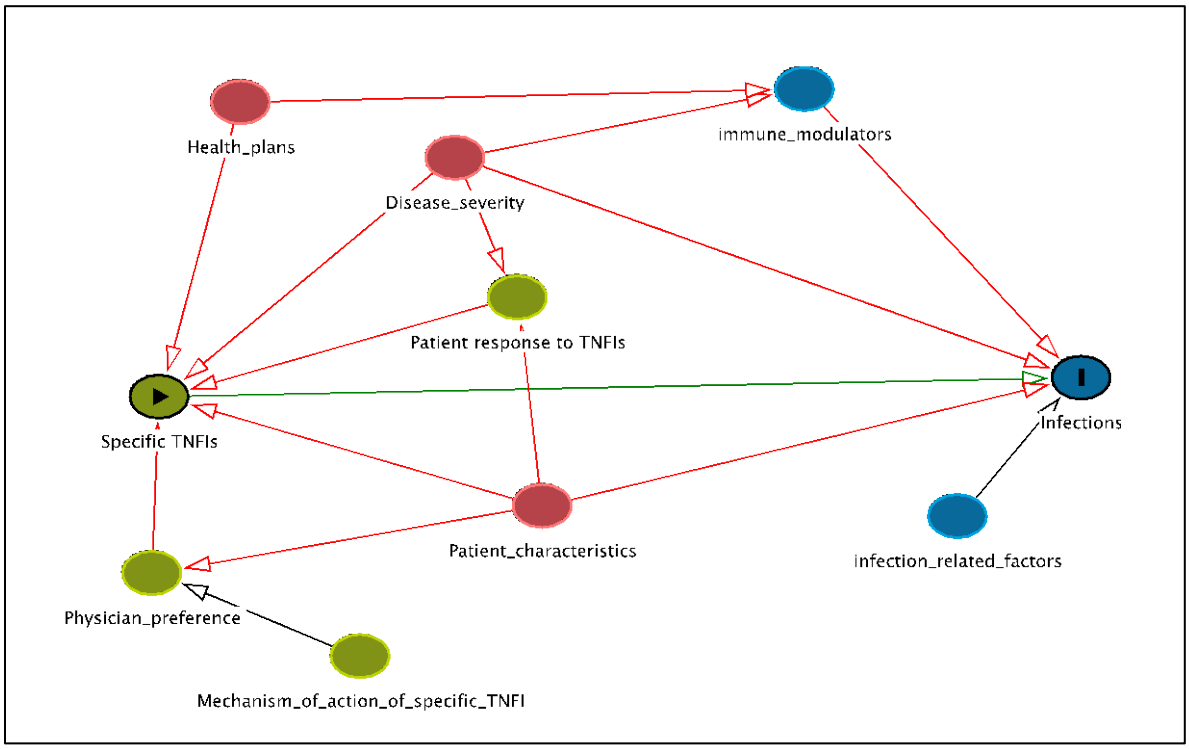

FIGURE 3. Directed acyclic graph of association between infections and specific TNFIs

2. UTILIZATION OF TUMOR NECROSIS FACTOR-ALPHA INHIBITORS IN CHILDREN AND YOUNG ADULTS WITH JUVENILE IDIOPATHIC ARTHRITIS OR RHEUMATOID ARTHRITIS

2.1 Preface

This chapter of the dissertation was accepted for publication as an article in the journal *Pharmacotherapy* on July 24, 2016. The paper is titled "Utilization of tumor necrosis factor-alpha inhibitors in children and young adults with juvenile idiopathic arthritis or rheumatoid arthritis." The article is now in press, and copyright permission will be requested once the article is published. Copyright permission for this use is described at http://onlinelibrary.wiley.com/journal/10.1002/(ISSN)1875-9114/homepage/Permissions.html. Included in this chapter is the pre-publication version. Partial study findings were also presented as a poster at the International Society of Pharmacoeconomics and Outcomes Research 21st Annual International Meeting in Washington DC.[98] This chapter describes the study conducted to address aim 1 of this dissertation.

2.2 Introduction

JIA is one of the most common chronic diseases in children in the United States.[99] The worldwide prevalence of JIA is approximately 150 per 100,000,[5,6] and the incidence is about 12 per 100,000 children.[7,8] The disease can have profound detrimental effects on quality of life and often results in absence from school.[9] In addition, severe JIA may lead to serious physical disability that can persist into adulthood.[10-12] As a result, the economic burden of JIA is substantial, and medications for JIA are a major component, accounting for 50% to 90% of the total medical costs.[9,13,100-103]

Treatment of JIA, as well as of RA in adults, includes NSAIDs, systemic corticosteroids, and DMARDs such as methotrexate and hydroxychloroquine. The treatment paradigm for JIA and RA has changed dramatically in recent years with the introduction of new biologic therapies such as TNFIs, interleukin inhibitors, and T-cell activation inhibitors.[39,40,104-106] Among these biologics, TNFIs are the most commonly used,[107] and they are recommended by the ACR for patients whose disease is not well controlled after having received traditional DMARDs for 3 to 6 months.[16] As a result, the use of TNFIs has increased over time in both the JIA and RA populations.[44,45,108]

Recent studies suggest that earlier use of TNFIs could improve patient remission rates and functional status as well as slow disease progression.[47-49] However, whether this more aggressive treatment approach is being implemented in current practice is not clear, especially for children with JIA and young adults with RA. Furthermore, although drug utilization studies have evaluated adults with RA, few studies have examined children and young adults with JIA and RA, especially with regard to common prescribing patterns, switching among TNFIs, adherence to TNFIs, and persistence with TNFI therapy. In addition, given that the JIA indication was approved for use for only two TNFIs (etanercept and adalimumab) in children, little is known about the degree of off-label use of TNFIs in children. Therefore, the objective of this study was to describe the current medication utilization patterns and use of TNFI therapy for children and young adults with JIA/RA.

2.3 Methods

2.3.1 Data Source

This retrospective cohort study examined the medication utilization patterns of TNFIs for children with JIA and young adults with RA. Data were obtained from the Truven Health MarketScan® Commercial Claims and Encounters database for the period from January 1,

2009, through December 31, 2013. The database contains private-sector health data collected from approximately 350 payers annually that include commercial insurance claims for over 180 million employees and their spouses and dependents since 1995. De-identified information on enrollment, healthcare encounters (e.g., outpatient, inpatient, and emergency room visits), and pharmacy records is included in the databases. Each claim included demographic information, date of encounter, disease diagnoses (using International Classification of Diseases, Ninth Revision, Clinical Modification [ICD-9-CM] code), medical procedures, and expenditures.[109]

2.3.2 Study Cohort

Patients aged ≤ 24 years with an incident diagnosis of JIA or RA during the period July 1, 2009, to June 30, 2013, were eligible for inclusion. A patient was confirmed to have JIA/RA if at least two claims included a code for JIA or RA (ICD-9-CM code 714.3x or 714) assigned by any physician within 1 year, or at least one claim coded by a pediatrician or rheumatologist.[110-112] The incident diagnosis was defined as no prior claims with a JIA/RA code and no JIA/RA medications recorded during the previous 6 months. The date of the first JIA/RA diagnosis claim was defined as the index date, and individual patients were followed from their index date to their health plan disenrollment date or the end of the study period (December 31, 2013), whichever came earlier.

Patients who had less than 6 months of continuous health plan enrollment before or after the index date were excluded. In addition, patients with a history of tuberculosis (ICD-9-CM code 011.xx – 018.xx) and/or use of medications for this disease during the 6 months before the index date were excluded because tuberculosis is a contraindication for use of TNFIs. Also excluded were patients who did not receive any medication therapy for JIA/RA during the follow-up period. This was done to help ensure more homogeneity in the cohort with respect to disease severity.

2.3.3 Outcomes

Medication use in the follow-up period was determined. Use of medications for JIA/RA was defined as any pharmacy record for NSAIDs, systemic corticosteroids, traditional DMARDs (methotrexate, hydroxychloroquine, sulfasalazine, and leflunomide), TNFIs (infliximab, etanercept, adalimumab, certolizumab, and golimumab), and other biologics (abatacept, anakinra, canakinumab, tocilizumab, and tofacitinib citrate). The patterns of use of TNFI monotherapy or combined use of TNFIs with traditional DMARDs were described, and the rate and patterns of switching among TNFI agents were identified.

The treatment approach in relation to TNFI use was defined as either “top-down” or “step-up.” The step-up approach was defined as the addition of a TNFI in a patient previously treated with a traditional DMARD. The top-down treatment approach was defined as a new prescription of TNFIs in a patient with newly diagnosed JIA/RA without a history of prior use of traditional DMARDs. Simultaneous use or later use of a traditional DMARD with the new TNFIs was also considered a top-down treatment strategy.

The time from JIA/RA diagnosis to the first use of TNFIs was measured and compared by year of JIA/RA diagnosis to examine changes over time. In addition, the time to discontinuation of TNFIs and persistence with TNFI therapy were assessed by TNFI agent. Continuous use of TNFIs was defined as the occurrence of consecutive claims (i.e., from the end of days supply of one prescription to the next prescription date) with a gap of less than 90 days. Adherence to TNFIs was measured using the proportion of days covered (PDC) for patients who had at least two TNFI prescriptions and who were persistent with TNFI treatment. The PDC was defined as the number of days using TNFIs over 180 days.[113]

Finally, off-label use of TNFIs was examined. Based on the FDA-labeled indications within the medication prescribing information, use of infliximab, certolizumab, and golimumab by children aged less than 18 years was considered “off-label use” of the TNFIs.[114]

2.3.4 Statistical Analysis

The demographic information and medication use patterns were assessed using frequencies (percentages) for categorical variables and means (standard deviations, SD) or medians (interquartile ranges [IQR]) for continuous variables. The proportion of newly prescribed TNFIs and the distribution of specific TNFIs were compared for three age groups: <12, 12-17, and 18-24 years, using a chi square test. A Kaplan-Meier plot was used to depict the proportion of patients who received TNFIs by the person time, and the log rank test was applied to examine the difference in year of diagnosis. We further stratified patients into those receiving diagnoses in 2012 to 2013 compared with those in 2009 to 2011, based on the similarity of the curves observed in the Kaplan-Meier plot. Cox proportional hazard models were used in the analysis of time to first TNFI treatment.

The proportion of patients treated with either the top-down or step-up approach was assessed by year of diagnosis and by age group. Adherence to TNFIs was measured by mean PDC and quartiles. A stratified analysis of PDC by age group was also conducted. Persistence with TNFI therapy was measured by the proportion of patients who continuously used TNFIs for 1, 3, 6, 12, 18, and 24 months. In sensitivity analyses, the definition of the gap between two consecutive claims was varied from 90 days to 30, 60, and 120 days. The calculation of PDC was re-defined as the number of days with TNFIs over 365 days in the sensitivity analysis.

Data extraction and data analyses were conducted using SAS statistical software version 9.4, Cary, North Carolina, USA, and STATA 12, College Station, Texas, USA. The

Institutional Review Board (IRB) determined this study was not human subject research and thus no IRB application and review were needed.

2.4 Results

A total of 6,962 children and young adults with a new diagnosis of JIA or RA were identified; 71.9% were female, and their mean age was 15 years. The median follow-up period was 670 (IQR 405-1,002) days. Among patients with JIA/RA, 73.9% and 56.1% received an NSAID or systemic corticosteroid, respectively, at some time during the follow-up period (**TABLE VI**). DMARDs were used by 43.5% of patients, with methotrexate and hydroxychloroquine being the most commonly used DMARDs. TNFIs were used by 18.6% of patients at some time during the follow-up period.

Etanercept (58.1%) was the most frequently prescribed TNFI, followed by adalimumab (28.0%) and infliximab (11.2%). Most patients (69.9%) treated with TNFIs also received one or more DMARDs (not necessarily concomitantly) during the follow-up period, while 30.1% received TNFI monotherapy.

Among TNFI users, 39.1% were treated with the top-down approach, varying from 36.8% in 2009, 35.0% in 2010, 44.3% in 2011, and 40.8% in 2012 to 33.0% in 2013 (based on year of diagnosis). The adoption of the top-down strategy seemed to be more frequent for young adults, although its adoption was not statistically different among age groups (36.5% in those <12, 38.2% in those 12-17, and 41.4% in those 18-24, p=0.32) (**TABLE VII**).

The proportion of patients receiving a specific TNFI therapy varied across age groups (**TABLE VII**). The proportion of patients receiving etanercept was 75.5% in those <12, 62.5% in those 12-17, and 44.4% in those 18-24 (p<0.0001). However, for adalimumab, the proportion of patients using the medication was higher in older age groups (age group <12: 16.4%; 12-17: 27.8%; 18-24: 35.0%, p<0.0001).

Infliximab, certolizumab, and golimumab were not indicated for children <18 years during the study period. However, 90 (12.1%) of 742 children who received TNFI therapy were prescribed one of these three off-label TNFIs, and 79 of the 90 children were prescribed off-label infliximab.

TABLE VI

PATIENT CHARACTERISTICS IN CHILDREN AND YOUNG ADULTS WITH INCIDENT JIA/RA

	Study cohort (N=6,929)	
Patient characteristics		
Age (year), mean (SD)	15.14	(6.34)
Female, n (%)	4,984	(71.93%)
Region, n (%)		
Northeast	1,614	(23.29%)
Midwest	1,522	(21.97%)
South	2,469	(35.63%)
West	1,191	(17.19%)
Unknown	133	(1.92%)
Medication use[a]		
NSAIDs, n (%)	5,117	(73.85%)
Corticosteroids, n (%)	3,888	(56.11%)
DMARDs, n (%)	3,016	(43.53%)
By initial agent[b] (N=3,016)		
Methotrexate	1,726	(57.23%)
Sulfasalazine	355	(11.77%)
Hydroxychloroquine	915	(30.34%)
Leflunomide	20	(0.66%)
Biologics other than TNFIs, n (%)	214	(3.09%)
TNFIs, n (%)	1,285	(18.55%)
By initial agent (N=1,285)		
Etanercept	746	(58.05%)
Adalimumab	360	(28.02%)
Infliximab	144	(11.21%)
Certolizumab	14	(1.09%)
Golimumab	21	(1.63%)
By regimen pattern (N=1,285)		
Monotherapy with TNFIs	387	(30.12%)
TNFI + any traditional DMARD[b]	898	(69.88%)
TNFI + 1 traditional DMARD	686	(76.39%)
TNFI + 2 traditional DMARDs	165	(18.37%)
TNFI + 3 traditional DMARDs	41	(4.57%)
TNFI + 4 traditional DMARDs	6	(0.67%)
By treatment strategy[c] (N=1,285)		
Top-down approach	503	(39.14%)
Step-up approach	782	(60.86%)

[a] Medication use was defined as presence of prescription claims during follow-up.
[b] Any prescription claims for TNFI and/or DMARDs measured during follow-up.
[c] Top-down treatment approach was defined as new TNFI use without prior use of DMARDs; step-up approach was defined as use of TNFIs with prior use of DMARDs.

TABLE VII
PERCENT OF CHILDREN AND YOUNG ADULTS WITH INCIDENT JIA/RA PRESCRIBED A TNFI, BY AGE AND AGENT

	Age <12 (N=1,833)		**Age 12-17 (N=2,173)**		**Age 18-24 (N=2,923)**		**P value[a]**
	n	(%)	n	(%)	n	(%)	
New TNFI use	318	(17.3%)	424	(19.5%)	543	(18.6%)	0.214
By agent							
Etanercept	240	(75.5%)	265	(62.5%)	241	(44.4%)	<0.0001
Adalimumab	52	(16.4%)	118	(27.8%)	190	(35.0%)	<0.0001
Infliximab	26	(8.2%)	35	(8.3%)	83	(15.3%)	<0.0001
Certolizumab	0	(0.0%)	4	(0.9%)	10	(1.8%)	0.037
Golimumab	0	(0.0%)	2	(0.5%)	19	(3.5%)	<0.0001
By treatment approach [b]							
Top-down approach	116	(36.5%)	162	(38.2%)	225	(41.4%)	0.316
Step-up approach	202	(63.5%)	262	(61.8%)	318	(58.6%)	

[a] P value was generated from chi-square tests.
[b] Top-down treatment approach was defined as new TNFI use without prior use of DMARDs; step-up approach was defined as use of TNFIs with prior use of DMARDs.

The time from JIA/RA diagnosis to receipt of the first TNFI therapy appeared to be shorter for patients diagnosed in more recent years. The proportion of patients who were taking TNFIs during the follow-up period is shown in **FIGURE 4**. Although no significant differences were found in the curves by year of diagnosis (log rank test p=0.36), the trend of shorter time to treatment with a TNFI is suggested in the figure. For example, in the cohort diagnosed in 2012, 20% of the patients used TNFIs within 720 days; however, it took more than 900 days to reach the same proportion (20%) in the cohorts diagnosed in 2009, 2010, and 2011. Because of the apparent differences observed in the graph, we further grouped patients into year 2012 to 2013 and year 2009 to 2011. Patients in year of diagnosis 2012-2013 had a higher rate of receiving a TNFI (HR 1.13, 95% confidence interval 1.00-1.28, p=0.044) than those in year 2009-2011.

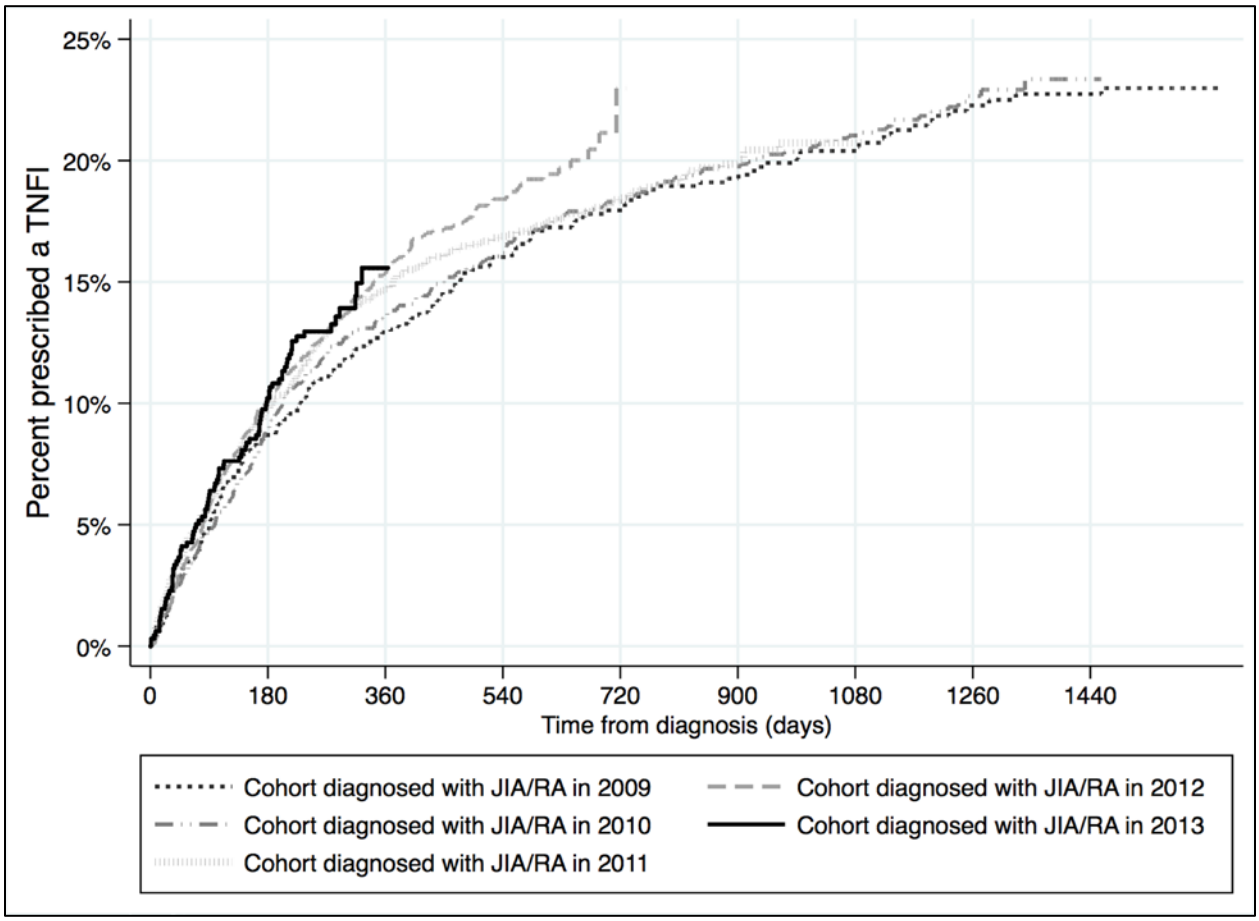

FIGURE 4 Kaplan-Meier plot of percentage of children and young adults with incident JIA/RA who initiated TNFI therapy, by the time from disease diagnosis to the start date of TNFI use.

During TNFI therapy, the proportion of patients who switched their initial medication to another TNFI ranged from 6.9% for infliximab and 17.2% for adalimumab to 28.6% for certolizumab (**TABLE VIII**). In patients who switched their TNFI therapy, a high proportion switched to adalimumab among those who started with etanercept (77.1%), golimumab (75.0%), and infliximab (60.0%). On the other hand, switching to etanercept was more common in patients who started with adalimumab (66.1%) and certolizumab (50.0%).

Mean PDC of TNFI therapy was highest for infliximab (93.2%), followed by adalimumab (89.6%), etanercept (88.9%), certolizumab (85.1%), and golimumab (70.4%) (**TABLE IX**). The results were similar when the PDC was assessed over a 365-day period, and no difference in adherence was found by age group (data not shown).

Time to discontinuation of the first prescribed TNFI ranged from 278 days for certolizumab to 347 days for etanercept (**TABLE X**). The proportion of patients who continuously used a TNFI was higher early but lower at time points further from TNFI initiation. For example, the proportion of patients who continuously took their TNFIs for 12 months was about 60% for etanercept, adalimumab, and infliximab, but the proportion was about 30% at 24 months. The results did not change appreciably when the gap employed to define continuous use was increased (e.g. from 90 to 120 days) or decreased (e.g. from 90 days to 60 or 90 day to 30 days).

TABLE VIII

SWITCHING AMONG TNFIS IN CHILDREN AND YOUNG ADULTS WITH INCIDENT JIA/RA

	Initial TNFI [a]									
	Infliximab (N=144)		**Etanercept (N=746)**		**Adalimumab (N=360)**		**Certolizumab (N=14)**		**Golimumab (N=21)**	
Any switch, n (%)	10	(6.9%)	157	(21.0%)	62	(17.2%)	4	(28.6%)	4	(19.0%)
1 switch	9	(90.0%)	134	(85.4%)	54	(87.1%)	4	(100.0%)	4	(100.0%)
≥2 switches	1	(10.0%)	23	(14.6%)	8	(12.9%)	0	(0.0%)	0	(0.0%)
Number of switches, mean (min-max)	1.1	(1-2)	1.2	(1-4)	1.1	(1-2)	1.0	(1-1)	1.0	(1-1)
First TNFI switched to [b], n (%)										
Etanercept	3	(30.0%)	NA	NA	41	(66.1%)	2	(50.0%)	1	(25.0%)
Adalimumab	6	(60.0%)	121	(77.1%)	NA	NA	0	(0.0%)	3	(75.0%)
Infliximab	NA	NA	19	(12.1%)	15	(24.2%)	1	(25.0%)	0	(0.0%)
Certolizumab	1	(10.0%)	6	(3.8%)	4	(6.5%)	NA	NA	0	(0.0%)
Golimumab	0	(0.0%)	11	(7.0%)	2	(3.2%)	1	(25.0%)	NA	NA

[a] Initial TNFI is the first prescribed TNFI.

[b] The TNFI prescribed after switch from the initial TNFI (i.e., first switch).

TABLE IX

ADHERENCE WITH FIRST PRESCRIBED TNFI AMONG CHILDREN AND YOUNG ADULTS WITH INCIDENT JIA/RA

	N[a]	Mean PDC	Minimum	First quartile	Median	Third quartile	Maximum
Etanercept	349	88.9%	32.0%	81.8%	94.0%	100.0%	100.0%
Adalimumab	177	89.6%	38.7%	84.5%	92.8%	98.9%	100.0%
Infliximab[b]	73	93.2%	33.1%	96.1%	100.0%	100.0%	100.0%
Certolizumab	5	85.1%	76.8%	77.3%	82.9%	91.2%	97.2%
Golimumab	6	70.4%	48.6%	63.0%	67.7%	78.5%	97.2%

[a] Only patients with more than two pharmacy claims and who did not switch TNFIs were included in the analysis.
[b] The adherence of infliximab was assessed using the service date for infliximab intravenous infusion.

TABLE X

TIME TO DISCONTINUATION AND PERSISTENCE WITH FIRST PRESCRIBED TNFI AMONG CHILDREN AND YOUNG ADULTS WITH INCIDENT JIA/RA

	Time to discontinuation (days), mean (median)	Persistence (%)[a,b]					
		1 month	3 months	6 months	12 months	18 months	24 months
Etanercept	347 (276)	91.3%	85.3%	76.7%	60.4%	45.1%	33.3%
Adalimumab	345 (254)	90.7%	85.6%	74.1%	60.6%	49.1%	32.4%
Infliximab	337 (266)	89.9%	83.8%	74.5%	62.7%	40.8%	34.5%
Certolizumab	278 (226)	90.0%	66.7%	62.5%	80.0%	100.0%	0.0%
Golimumab	326 (198)	64.7%	64.7%	40.0%	30.8%	30.0%	40.0%

[a] Only patients with more than two pharmacy claims and who did not switch TNFIs were included in the analysis.

[b] Patients were included in the analysis of persistence estimation if they had at least 1, 3, 6, 12, 18, and 24 months of follow-up, respectively. Persistence was defined as continuous claims with a gap less than 90 days.

2.5 Discussion

Our results shed new light on medication utilization patterns in children and young adults with JIA/RA. We found that TNFIs were used by 18.6% of children and young adults with new diagnoses of JIA/RA. This value is somewhat lower than other estimates of TNFI use in this population. For example, Beukelman and colleagues analyzed the Childhood Arthritis and Rheumatology Research Alliance (CARRA) Registry and found that of 2,748 children with prevalent JIA, 44% had ever used a TNFI.[115] In addition, a study conducted by Mannion and colleagues, who used national commercial claims data, reported that use of TNFIs increased from 13.6% in 2005 to 30.3% in 2012 among children with JIA.[108] Our lower estimate of TNFI use is attributable to differences in the populations and medications studied. Importantly, our study examined children with incident JIA who were newly prescribed TNFIs, while the other two studies assessed those with prevalent JIA who had ever used TNFIs.[108,115] In addition, unlike our claims data, the CARRA Registry was a convenience sample in which children with more severe arthritis may have been over-represented.

Etanercept was the most frequently used TNFI in children and young adults in our cohort, followed by adalimumab. Mannion and colleagues [108] also found that etanercept was the predominant TNFI agent used in children. In our study, adalimumab use increased with age, and this may be attributable to the approval of adalimumab for treating children with JIA in a later year (2008) than etanercept (2000). However, we found that switching from etanercept to adalimumab was the most common pattern when switching occurred. It has been suggested that many children who start therapy with etanercept and subsequently switch to adalimumab or infliximab are switching due to development of uveitis.[116] However, we examined the diagnosis of uveitis development (ICD-9-CM code 364) prior to the first switching and found that the proportions of uveitis were 7.6% (12 of 157) among patients starting with etanercept, 6.5% (4 of 62) among adalimumab initiators, and 30% (3 of 10) among infliximab initiators. Other reasons

for switching among TNFIs, such as occurrence of adverse events, development of anti-drug antibodies, medication intolerance, and history of chronic uveitis,[116,117] should be further investigated.

We observed that over the course of the study period, there was an increased earlier initiation of TNFIs in children and young adults. Otten and colleagues had similar findings. Using a Dutch national registry of children with JIA from 1999 to 2010, they found that disease duration before TNFI initiation decreased over time, from 6.9 to 2.2 years.[118] In our study, we found that the time from diagnosis to TNFI initiation had decreased to less than 1 year. In addition, we observed that about 40% of the TNFI users did not receive prior treatment with methotrexate or other traditional DMARDs before starting TNFI treatment (the top-down approach), while Mannion and colleagues reported that 57% of patients did not use methotrexate prior to their new TNFI use.[108] However, we may have overestimated the frequency of use of the top-down strategy because a relatively short period was used to examine the medication history. That is, patients who used traditional DMARDs more than 6 months prior to their first disease diagnosis may not have been identified and thus may have been incorrectly classified as “top-down” when they started TNFIs.

The top-down approach is not consistent with ACR guidelines published in 2011, which suggest that TNFIs should be used only after patients fail to respond to traditional DMARDs.[16] Nonetheless, use of this more aggressive strategy was promoted by recent studies which reported that earlier use of TNFIs in combination with methotrexate for patients with RA or JIA was associated with better short-term clinical outcomes and functional status.[47-49,119,120] However, a high proportion of early TNFI users in our study (387 of 503, 77%) and the study by Mannion and colleagues (174 of 195, 89%) [108] did not use concomitant traditional DMARDs. Along with the findings of other researchers, our observation of a shift in the use of TNFIs to earlier in the disease course should motivate further evaluation of the long-term safety and effectiveness of the top-down treatment approach, especially for the early use of TNFI monotherapy.

We found that the rate of adherence (PDC) was highest for infliximab (93.2%), followed by adalimumab (89.6%) and etanercept (88.9%). To the best of our knowledge, this is the first study to estimate adherence to TNFI therapy among children and young adults with JIA/RA. Our estimates of adherence to TNFIs were similar to or higher than the adherence observed in older adults with RA.[121-123] However, because of differences across studies in the methods used to measure adherence, and because of lack of control for the impact of specialty pharmacies, a true comparison of adherence may be difficult. Notably, one major difference is that children need assistance in administering the injectable TNFIs, and thus family members or other caregivers play an important role in children's adherence. Several additional factors have been associated with non-adherence to JIA medications, such as low socioeconomic status, lack of family support, the occurrence of adverse events, and high complexity and costs of treatment regimens.[124,125] As was found in studies of adults,[121,122] infliximab had the highest estimate of adherence in children and young adults. However, infliximab is administered through intravenous infusion, and we imputed the "days supply" for infliximab using the service dates. Because of the differences in delivery mechanisms and in the ways to calculate the days supply, it may not be appropriate to directly compare adherence to physician-administered versus self-administered TNFIs. In addition, patients may more readily comply with a treatment regimen involving physician visits or use of an infusion center than with one involving injecting medications at home.

Our study had limitations that are common to research based on administrative claims data. First, it is possible that disease diagnoses were incorrectly coded and patients were misclassified as having JIA/RA. In addition, JIA is not a single disease but rather consists of many types of arthritis; for example, psoriatic arthritis and spondyloarthritis may be considered JIA and were not captured in our algorithm for JIA identification. However, we attempted to minimize these issues by using a previously validated algorithm to identify patients with JIA and RA,[110-112] and all the patients received at least one medication related to JIA/RA treatment.

Second, due to lack of clinical measurements such as number of joints with pain and laboratory test results in the data, varying disease severity (e.g., systemic JIA or oligoarthritis) could not be distinguished and considered in our analyses. Third, caution is needed when interpreting measures of medication adherence using administrative data. Medication claims are simply records of filled prescriptions, and we could not determine whether patients actually took their medications as directed. However, previous literature has validated use of prescription claims for adherence measurement.[126,127] Finally, the adoption of the top-down and step-up treatment strategies may be influenced by the policies of individual insurance companies, such as a requirement for prior authorization of TNFI prescriptions based on previous use of DMARDs. However, we could not identify decision-making factors driving such policies in insurance companies.

2.6 Conclusion

In summary, this study characterized the use of TNFIs in children and young adults with JIA/RA. Etanercept was the most commonly used TNFI, especially in children and adolescents, while adalimumab was most frequently used by young adults. In contrast with ACR guideline recommendations, both earlier use of TNFIs and TNFI monotherapy were observed in clinical practice. Future studies should investigate the long-term effectiveness and safety of TNFI use as well as the reasons for TNFI discontinuation.

3. TOP-DOWN VERSUS STEP-UP PRESCRIBING STRATEGIES FOR TUMOR NECROSIS FACTOR-ALPHA INHIBITORS IN CHILDREN AND YOUNG ADULTS WITH INFLAMMATORY BOWEL DISEASE

3.1 Preface

This chapter of the dissertation has been published as an article in the journal *Inflammatory Bowel Disease*. The paper is titled "Top-down versus step-up prescribing strategies for tumor necrosis factor-alpha inhibitors in children and young adults with inflammatory bowel disease." The full citation is provided in the Cited Literature section,[128] and as required by the journal, the citation is listed here as Inflamm Bowel Dis: October 2016 - Volume 22 - Issue 10 - p 2410–2417. Wolters Kluwer Health Lippincott Williams & Wilkins©. Copyright permission is included in the Appendix. Included here is the pre-publication version. Partial study findings were also presented as a poster at the International Conference on Pharmacoepidemiology & Therapeutic Risk Management 32nd Annual Meeting, Dublin, Ireland, 2016.[129] This chapter describes the study conducted to address aim 2 of this dissertation.

3.2 Introduction

IBD is an immune-mediated disorder characterized by chronic inflammation in the gastrointestinal tract and includes both CD and UC.[18] Children account for about 30% of all cases of IBD.[20] The incidence of IBD in children aged 1 to 17 years is 4.6 per 100,000 for CD[20,21] and 2.1 per 100,000 for UC and has been increasing globally.[22] In most cases, children with IBD carry the disease into later adulthood. Notably, adolescents and young adults aged 15 to 29 years have the highest incidence of both CD and UC.[23] Childhood-onset IBD typically has more extensive symptoms and more frequent and severe episodes than adult-onset IBD.[3,24] In addition, children with IBD are more likely to experience anxiety and depression, poor school

functioning, and lower quality of life than children without IBD.[25]

Drug treatment for IBD includes corticosteroids, 5-ASA, thiopurines, methotrexate, immunosuppressants (e.g., cyclosporine and tacrolimus), and TNFIs. Among these drugs, TNFIs are generally considered the most effective, and as a result, use of TNFIs for IBD has increased over time.[41,42,130] However, some controversy exists about when in the disease course TNFIs should be used.

According to the recommendations of the North American Society for Pediatric Gastroenterology Hepatology and Nutrition (NASPGHAN), the European Crohn's and Colitis Organisation (ECCO), and the European Society for Paediatric Gastroenterology Hepatology and Nutrition (ESPGHAN), TNFIs can be considered in both the induction and maintenance phases of treatment.[29,30,46] Under the conventional step-wise treatment approach, or the “step-up” approach, the use of systemic corticosteroids and/or immunomodulators is recommended before initiating TNFIs. However, a newer treatment strategy called the “top-down” approach has recently emerged. In this approach, patients are treated more aggressively by using TNFIs, often combined with immunomodulators, as initial therapy. Recent evidence suggests that use of TNFIs earlier in the disease course may improve clinical outcomes.[50,51,53-55] The “top-down” approach may be particularly beneficial to children because early use of TNFIs may decrease or avoid the use of corticosteroids, which are associated with adverse effects on pubertal growth.

The rate of adoption of the top-down treatment approach in current clinical practice has not been examined in children and young adults with IBD. In addition, little is known about how the step-up and top-down treatment strategies differ in terms of switching, adherence, and persistence with TNFI therapy in real-world settings. Therefore, this study aimed to examine the use of the top-down approach for children and young adults with IBD and more specifically to compare medication utilization between the step-up and top-down strategies.

3.3 Methods

3.3.1 Data Source

Health insurance claims from January 1, 2009, to December 31, 2013, were obtained from the Truven Health MarketScan® Commercial Claims and Encounters databases. These databases contain health care claims for about 180 million people across the U.S. who were commercially insured, mainly through employer-based coverage. All data were de-identified and include information on health plan enrollment, medical service utilization, and prescription records. Each claim contained longitudinal information on patient demographics, type of encounter (e.g., outpatient, inpatient, or emergency room visits), date of encounter, physician specialties, disease diagnoses, medical procedures, and expenditures.[109]

3.3.2 Study Cohort

Patients were eligible to be included in the study if they had a new diagnosis of IBD (ICD-9-CM code 555.xx or 556.xx) at an age of ≤24 years during the study period. The algorithm for identification of confirmed IBD was two diagnoses within 1 year or at least one IBD diagnosis coded by a pediatrician or gastroenterologist.[131] A new diagnosis was defined as the absence of an IBD diagnosis in the 6-month period prior to the first confirmed IBD identified. The date of the new diagnosis was marked as the index date. For eligible subjects, at least 6 months of continuous enrollment was required before and after the index date. In addition, eligible patients had to have received at least one IBD medication during the follow-up period. However, we excluded patients with a history of tuberculosis and/or medications for tuberculosis, which is a contraindication for TNFI use. The study cohort was followed from the index date until the health plan disenrollment date or the end of the study period, whichever came first.

Medications used for IBD consisted of systemic corticosteroids, 5-ASA (sulfasalazine, mesalazine), thiopurines (azathioprine and 6-mercaptopurine), methotrexate, TNFIs (infliximab,

adalimumab, certolizumab, and golimumab), and other immunosuppressants (tacrolimus, cyclosporine, rituzumab, and vedolizumab). Patients who used TNFIs in the follow-up period were further categorized as having received the top-down or step-up approach based on the order of their treatment regimen. The top-down approach was defined as a dispensing of a new TNFI prescription within 30 days of the first medication prescription for IBD (i.e., 5-ASA, systemic corticosteroids, thiopurines, and/or immunosuppressants), while the step-up approach was defined as TNFI initiation more than 30 days after the first IBD medication prescription.[55]

3.3.3 Outcomes

We assessed the use of IBD medications during the follow-up period in the study cohort. The time from IBD diagnosis to first TNFI prescription was calculated. Any switch from the initial TNFI (the first TNFI agent) to another TNFI within 1 year was identified, and the pattern of switching was described.

Persistence and adherence with TNFI therapy was also assessed. Persistence was defined as continuous use of TNFIs among patients who had at least two prescriptions and who did not switch from their initial TNFI. Any gap between two consecutive TNFI claims was calculated, and a gap of ≤90 days was defined as continuous use. The period of continuous use (or time to discontinuation) was calculated as the time from the first TNFI prescription date to the last prescription date before a gap >90 days plus half the days supply for the last prescription. Adherence to TNFI was defined as the PDC over a 180-day period among patients who continuously took TNFIs for ≥180 days. The total number of days supply of TNFIs was calculated, with adjustment of overlapping days due to early refills. PDC was calculated as adjusted total days of supply of TNFIs divided by 180 days and multiplied by 100.[113]

3.3.4 Statistical Analysis

We described baseline demographic information and medication use patterns for the overall study cohort, the top-down approach, and the step-up approach as well as for non-TNFI users. Use of individual TNFI agents by age group (<12, 12-17, and 18-24 years) was compared between the top-down and step-up approaches using chi-square tests.

Among TNFI users, the time from IBD diagnosis to first TNFI prescription was compared by year of diagnosis using a log-rank test. A Kaplan-Meier plot was used to illustrate the proportion of patients prescribed a TNFI by the time followed from the diagnosis. We also used Cox hazard models to examine the HR and 95% CI of TNFI use for patients in different year of diagnosis, compared to year of 2009.

We assessed the time from first TNFI use to discontinuation by individual TNFI agent. The proportions of patients who continuously took TNFIs for 1, 3, 6, 12, 18, and 24 months were then compared between the top-down and step-up approaches using a log-rank test. As a sensitivity analysis for persistence, we varied the gap from 90 days to 30, 60, and 120 days in order to define continuous use of TNFIs. Adherence was described in mean PDC with quartile, minimum, and maximum values. A stratified analysis was conducted to examine whether the adherence varied by age group. In addition, we performed a sensitivity analysis of the PDC using a 365-day period.

The statistical software SAS version 9.4 (Cary, North Carolina, USA) and STATA 12 (College Station, Texas, USA) were used for data cleaning, extraction, and analysis. A university IRB determined that this study did not involve human subject research, and thus no IRB application and review were necessary.

3.4 Results

A total of 11,962 patients with incident IBD were followed for a median of 657 days (IQR 409-1,000 days); their mean age was 17.3 years (SD 5.0), and 51% were males. Of the overall

cohort, 3,300 (27.6%) used TNFIs and 8,662 (72.4%) were treated with other agents (**TABLE XI**). No differences were found in the proportions of geographic location and corticosteroid use between TNFI and non-TNFI users. However, TNFI users included a greater proportion of patients who were in the 12-17 year age group (38.7% vs 29.6%, p<0.0001), males (54.1% vs 49.8%, p<0.0001), methotrexate users (11.7% vs 2.3%, p<0.0001), and thiopurine users (38.6% vs 25.4%, p<0.0001) compared to non-TNFI users but exhibited a lower rate of 5-ASA use (52.4% vs 79.3%, p<0.0001).

Among patients taking TNFIs, 1,298 (39.3%) were treated with the top-down and 2,002 (60.7%) with the step-up approach. Under top-down treatment, TNFI therapy was the first treatment in 76.7% of patients (i.e., there was no prior use of other IBD medications prior to TNFI initiation). The proportion of patients receiving top-down treatment increased over the study period (31.4%, 37.5%, 39.0%, 42.2%, and 49.8% for the years 2009 to 2013, respectively; p for trend <0.0001). Patients who received top-down treatment were less likely to use corticosteroids (32.5% vs 94.2%, p<0.0001), 5-ASA (17.3% vs 75.1%, p<0.0001), methotrexate (7.2% vs 14.6%, p<0.0001), or thiopurines (13.5% vs 54.8%, p<0.0001) compared to step-up patients.

Infliximab was the most commonly used TNFI across different age groups (**TABLE XII**). However, the proportion of patients administered infliximab as their initial TNFI therapy was lower among those 18-24 years of age (55.1%) compared to those <12 years old (89.2%) and 12-17 years old (82.3%) while a contrasting pattern was observed for adalimumab (37.9%, 16.6%, and 10.6% among those 18-24, 12-17, and <12 years of age, respectively). In addition, a consistent pattern of infliximab and adalimumab use was observed between the top-down and step-up strategies across the three age groups: the rate of infliximab use was higher in the top-down strategy, while the rate of adalimumab use was higher in the step-up strategy.

The time from IBD diagnosis to TNFI initiation was shorter for patients who were diagnosed more recently (log-rank test p<0.001), as shown in **FIGURE 5**. For example, among

those diagnosed with IBD in 2009, it took almost 2 years for 20% of the patients to start TNFI therapy, while for those diagnosed in 2010, 2011, 2012, and 2013, it took about 1.5, 1, 0.6, and 0.5 years, respectively. Compared to the 2009 diagnosis group, the HR (95% CI) for receiving TNFIs was 1.18 (1.05-1.32), 1.35 (1.20-1.52), 1.76 (1.56-1.99), and 2.01 (1.72-2.35) for patients diagnosed in 2010, 2011, 2012, and 2013, respectively.

TABLE XI

DEMOGRAPHIC CHARACTERISTICS AND MEDICATION UTILIZATION IN CHILDREN AND YOUNG ADULTS WITH IBD

	Overall cohort (N=11,962)		Non-TNFI users (N=8,662)		TNFI users					
					Overall TNFI users (N=3,300)		Top-down strategy [a] (N=1,405)		Step-up strategy [a] (N=1,895)	
	n	%	n	%	n	%	n	%	n	%
Age group (years)										
Age <12	1,594	13.3%	1,188	13.7%	406	12.3%	155	11.9%	251	12.5%
Age 12-17	3,839	32.1%	2,563	29.6%	1,276	38.7%	533	41.1%	743	37.1%
Age 18-24	6,529	54.6%	4,911	56.7%	1,618	49.0%	610	47.0%	1,008	50.4%
Male	6,096	51.0%	4,310	49.8%	1,786	54.1%	730	56.2%	1,056	52.8%
Region										
Northeast	2,941	24.6%	2,175	25.1%	766	23.2%	322	24.8%	444	22.2%
Midwest	2,894	24.2%	2,050	23.7%	844	25.6%	316	24.4%	528	26.4%
South	3,974	33.2%	2,869	33.1%	1,105	33.5%	413	31.8%	692	34.6%
West	1,916	16.0%	1,386	16.0%	530	16.1%	215	16.6%	315	15.7%
Unknown	237	2.0%	182	2.1%	55	1.7%	32	2.5%	23	1.2%
Medication use [b]										
Corticosteroids	8,300	69.4%	5,992	69.2%	2,308	69.9%	422	32.5%	1,886	94.2%
Thiopurines	3,471	29.0%	2,199	25.4%	1,272	38.6%	175	13.5%	1,097	54.8%
Azathioprine	1,777	51.2%	1,114	50.7%	663	52.1%	98	7.6%	565	28.2%
6-mercaptopurine	1,694	48.8%	1,085	49.3%	609	47.9%	77	5.9%	532	26.6%
Methotrexate	588	4.9%	201	2.3%	387	11.7%	224	17.3%	1,504	75.1%
5-ASA	8,599	71.9%	6,871	79.3%	1,728	52.4%	94	7.2%	293	14.6%
TNFIs	3,300	27.6%	NA	NA	3,300	100.0%	1,298	100.0%	2,002	100.0%
Infliximab	2,303	69.8%	NA	NA	2,303	69.8%	1,034	79.7%	1,269	63.4%
Adalimumab	869	26.3%	NA	NA	869	26.3%	220	17.0%	649	32.4%
Certolizumab	123	3.7%	NA	NA	123	3.7%	44	3.4%	79	4.0%
Golimumab	5	0.2%	NA	NA	5	0.2%	0	0.0%	5	0.3%
Other immunosuppressants	55	0.5%	44	0.5%	11	0.3%	0	0.0%	11	0.6%

[a] Top-down treatment approach was defined as new TNFI use without prior use of thiopurines or 5-ASA; step-up approach was defined as new TNFI use after previous use of thiopurines or 5-ASA.

[b] Medication use was defined as presence of prescription claims during the follow-up period.

TABLE XII

PERCENT OF CHILDREN AND YOUNG ADULTS WITH INCIDENT IBD PRESCRIBED A TNF INHIBITOR, BY AGE AND AGENT

	Overall TNFI users		Top-down strategy [a]		Step-up strategy [a]		P value [b]
	n	%	n	%	n	%	
Age <12							
New TNFI use	406	100.0%	155	100.0%	251	100.0%	
By agent							
Infliximab	362	89.2%	146	94.2%	216	86.1%	0.010
Adalimumab	43	10.6%	9	5.8%	34	13.5%	0.014
Certolizumab	1	0.2%	0	0.0%	1	0.4%	1.000
Golimumab	0	0.0%	0	0.0%	0	0.0%	NA
Age 12-17							
New TNFI use	1,276	100.0%	533	100.0%	743	100.0%	
By agent							
Infliximab	1,050	82.3%	490	91.9%	560	75.4%	<0.0001
Adalimumab	212	16.6%	40	7.5%	172	23.1%	<0.0001
Certolizumab	13	1.0%	3	0.6%	10	1.3%	0.258
Golimumab	1	0.1%	0	0.0%	1	0.1%	1.000
Age 18-24							
New TNFI use	1,618	100.0%	610	100.0%	1008	100.0%	
By agent							
Infliximab	891	55.1%	398	65.2%	493	48.9%	<0.0001
Adalimumab	614	37.9%	171	28.0%	443	43.9%	<0.0001
Certolizumab	109	6.7%	41	6.7%	68	6.7%	0.985
Golimumab	4	0.2%	0	0.0%	4	0.4%	0.304

[a] Top-down treatment approach was defined as new TNFI use without prior use of thiopurines or 5-ASA; step-up approach was defined as new TNFI use after previous use of thiopurines or 5-ASA.

[b] P value was generated from chi-square test for top-down versus step-up strategy.

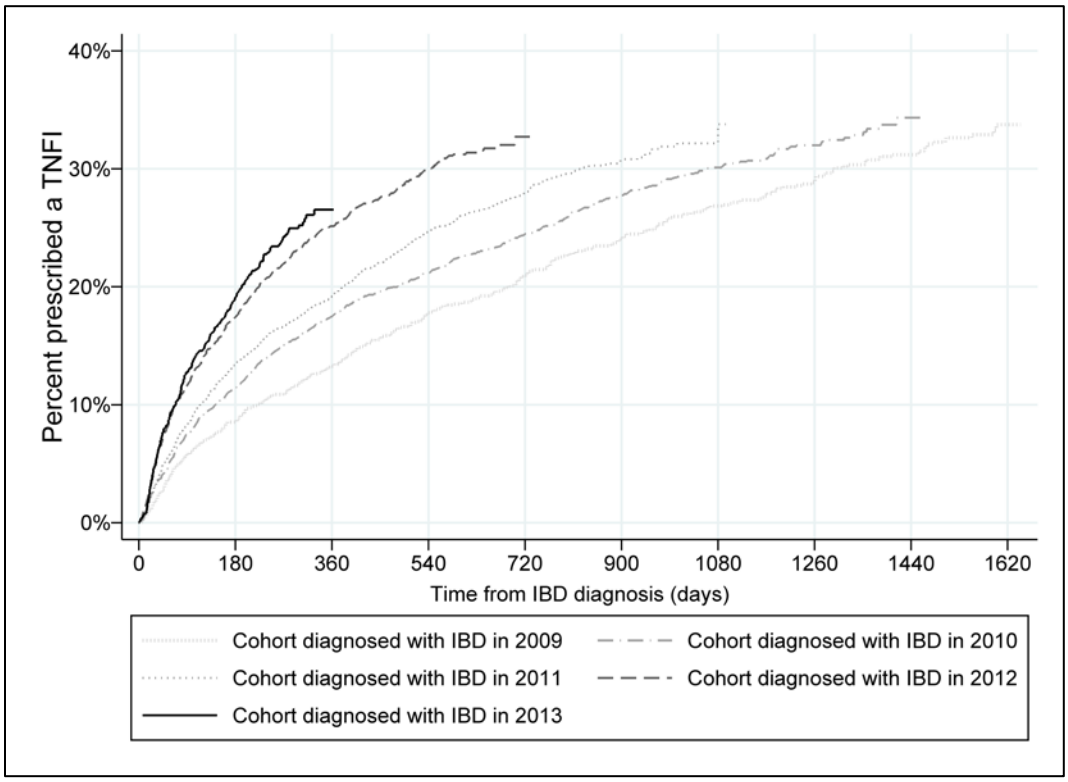

FIGURE 5. Kaplan-Meier plot of percentage of children and young adults with incident IBD who initiated TNFI therapy, by the time from disease diagnosis to the start date of TNFI use

Among TNFI users overall, the rate of switching from one TNFI to another within 1 year was 6.7% (**TABLE XIII**). The one-year switching rate was similar between the top-down (5.7%) and step-up strategies (7.4%). The mean time to switching after the initial TNFI prescription was 172 days for the step-up strategy and 191 days for the top-down strategy. When switching occurred, switching from infliximab to adalimumab was the most common pattern.

As for patients who did not switch their initial TNFIs, their persistence with TNFI therapy is shown in **TABLE XIV**. The median time to discontinuation was about 300 days for infliximab, adalimumab, and certolizumab. Depending on the individual TNFI used, a range of 77.8% to 86.1% of patients persistently received TNFI therapy for 6 months, and 67.8% to 74.8% underwent continuous 12-month TNFI therapy. However, discontinuation of TNFI therapy was higher in patients receiving the top-down compared to the step-up strategy (log-rank test p=0.034). The results did not change substantially when the gap used to define continuous use was varied from 90 days to 30, 60, or 120 days.

Among patients who continuously took their TNFIs without switching their initial TNFI therapies, the adherence to TNFIs was high (**TABLE XV**). The mean PDC was highest for infliximab (95.4%), followed by adalimumab (91.0%) and certolizumab (83.7%). No patients in the golimumab group could be followed for ≥180 days. We found no differences in the PDC estimates between the top-down and step-up strategies. Adherence to individual TNFIs did not vary by age group. The results were similar when PDC was calculated using a 365-day period.

TABLE XIII

ONE-YEAR TNFI SWITCH RATE BY TREATMENT STRATEGY IN CHILDREN AND YOUNG ADULTS WITH INCIDENT IBD

	Overall TNFI users			Top-down strategy [c]			Step-up strategy [c]			
Initial TNFI therapy [a]	**Total users**	**No. patients switched [b]**	**Switch rate**	**Total users**	**No. patients switched [b]**	**Switch rate**	**Total users**	**No. patients switched [b]**	**Switch rate**	**P-value [d]**
Any TNFI	3,300	222	6.7%	1,298	74	5.7%	2,002	148	7.4%	0.0581
Infliximab	2,303	140	6.1%	1,034	54	5.2%	1,269	86	6.8%	0.1204
Adalimumab	869	64	7.4%	220	15	6.8%	649	49	7.6%	0.7195
Certolizumab	123	17	13.8%	44	5	11.4%	79	12	15.2%	0.7859
Golimumab	5	1	20.0%	0	0	NA	5	1	20.0%	NA

[a] Initial TNFI is the first prescribed TNFI.

[b] Only patients who switched their TNFIs in the first year after initiation were included.

[c] Top-down treatment approach was defined as new TNFI use without prior use of thiopurines or 5-ASA; step-up approach was defined as new TNFI use after previous use of thiopurines or 5-ASA.

[d] P value was generated from chi-square test for top-down versus step-up strategy.

TABLE XIV
TIME TO DISCONTINUATION AND PERSISTENCE WITH FIRST PRESCRIBED TNFI AMONG CHILDREN AND YOUNG ADULTS WITH INCIDENT IBD

	Duration (days), mean (median)	Persistence (%) [a]					
		1 month	3 months	6 months	12 months	18 months	24 months
Overall TNFI users							
Infliximab	405 (320)	98.2%	93.2%	82.4%	71.0%	64.1%	59.7%
Adalimumab	400 (307)	98.5%	92.3%	86.1%	74.8%	68.5%	63.3%
Certolizumab	413 (316)	97.8%	94.4%	77.8%	67.8%	61.7%	60.0%
Golimumab [b]	167 (167)	100.0%	100.0%	0.0%	0.0%	0.0%	0.0%
Top-down strategy [c]							
Any TNFIs	418 (338)	97.3%	92.5%	80.8%	70.2%	61.5%	56.8%
Infliximab	411 (336)	97.3%	92.3%	80.1%	69.2%	60.1%	55.6%
Adalimumab	442 (349)	97.3%	93.4%	85.7%	73.7%	66.7%	60.0%
Certolizumab	471 (454)	97.1%	91.2%	71.9%	79.2%	70.6%	66.7%
Golimumab [b]	NA	NA	NA	NA	NA	NA	NA
Step-up strategy [c]							
Any TNFIs	393 (301)	98.9%	93.5%	85.0%	73.0%	67.7%	63.9%
Infliximab	399 (308)	98.9%	94.1%	84.6%	72.7%	67.9%	64.0%
Adalimumab	385 (289)	98.9%	91.9%	86.3%	75.3%	69.2%	64.8%
Certolizumab	380 (298)	98.3%	96.4%	81.6%	60.0%	56.7%	53.8%
Golimumab [c]	167 (167)	100.0%	100.0%	NA	NA	NA	NA

[a] Persistence was defined as continuous claims with a gap less than 90 days.
[b] Only four patients (zero in the top-down strategy and four in the step-up strategy) were included in the analysis and none of them had enough follow-up for more than 3 months.
[c] Top-down treatment approach was defined as new TNFI use without prior use of thiopurines or 5-ASA; step-up approach was defined as new TNFI use after previous use of thiopurines or 5-ASA.

TABLE XV

ADHERENCE WITH FIRST PRESCRIBED TNFI AMONG CHILDREN AND YOUNG ADULTS WITH INCIDENT IBD

	Overall TNFI users				Top-down strategy [b]				Step-up strategy [b]			
	N	Mean	Median (IQR)	Min-Max	N	Mean	Median (IQR)	Min-Max	N	Mean	Median (IQR)	Min-Max
Infliximab [a]	1323	95.4%	99.5% (95.6-100.0)	51.4-100.0%	625	95.5%	99.4% (95.6-100.0)	51.4-100.0%	698	95.3%	99.4% (95.0-100.0)	53.0-100.0%
Adalimumab	497	91.0%	95.0% (86.2-99.5)	48.6-100.0%	144	90.2%	95.0% (85.9-99.7)	50.8-100.0%	353	91.3%	95.6% (86.7-99.4)	48.6-100.0%
Certolizumab	63	83.7%	84.5% (77.4-92.8)	43.1-100.0%	23	83.4%	81.2% (77.3-95.6)	55.8%-100.0%	40	83.9%	85.4% (77.1-92.8)	43.1-100.0%

[a] The adherence of infliximab was assessed using the service date for infliximab intravenous infusion.

[b] Top-down treatment approach was defined as new TNFI use without prior use of thiopurines or 5-ASA; step-up approach was defined as new TNFI use after previous use of thiopurines or 5-ASA.

3.5 Discussion

In this analysis, we examined the employment of the top-down and step-up strategies in children and young adults with IBD. This study followed IBD children and young adults for 5 years and found that 27.6% were treated with TNFIs. Childhood-onset IBD usually has more extensive symptoms and more severe disease progression than adult-onset IBD.[3,24] As a result, children have been reported to require pharmacotherapy more often than adults. For example, Goodhand and colleagues analyzed 200 adolescents and adults with IBD in a case-control study and found that biological therapy (i.e., infliximab) was used more frequently in adolescents (20%) than in adults (8%).[132] Similarly, we found that 27.6% of children and young adults used TNFIs. Our study provided additional detail on the types of TNFIs used (including the newer agents adalimumab, certolizumab, and golimumab) and the use of these agents within age groups. While infliximab was the dominant agent used across patients aged <12, 12-17, and 18-24 years, the use of adalimumab increased with age.

Infliximab and adalimumab have similar efficacy and safety profiles in adults with IBD.[133,134] In addition, a recent network meta-analysis of 17 randomized controlled trials involving adults with moderate to severe CD reported that infliximab and adalimumab were the most effective therapies for inducing remission in the induction and maintenance phases, respectively.[135] Moreover, in the Gauging Adalimumab efficacy in Infliximab Non-responders (GAIN) trial, adalimumab induced remission in 21% of adults with CD who were either intolerant of or nonresponsive to infliximab.[136] Thus, adalimumab is often used as a second-line treatment for patients who stop responding to infliximab. However, we found that 28.0% of IBD patients aged 18-24 were prescribed adalimumab as the initial treatment in the top-down strategy. Similarly, using the Stanford Translational Research Integrated Database, Park and colleagues found a trend of increasing adalimumab use between 2007 and 2012 for both adult and pediatric patients with IBD.[130] One reason for this finding may be that the costs of infliximab as

the first-line therapy were significantly higher than the costs of adalimumab, with the higher infliximab costs driven by both a higher drug cost and the additional cost of administration.[137] In addition, factors such as availability, patient preference, route of administration (subcutaneous for adalimumab and intravenous infusion for infliximab), and the reimbursement policies of individual insurance companies may have affected the prescribing decisions made by physicians.

We found that children and young adults with IBD were treated with TNFIs more aggressively during the time period we studied. Specifically, of TNFI users, 42.6% were treated earlier with TNFIs (the top-down strategy), and this proportion increased from 31.4% to 49.8% from 2009 to 2013. In addition, the time from IBD diagnosis to TNFI initiation became shorter for patients diagnosed in more recent years. In clinical studies, the top-down strategy was associated with a higher remission rate in both adults and children with CD.[50,51,53] Furthermore, Rubin and colleagues found that the top-down strategy was associated with lower concomitant use of corticosteroids and discontinuation or switching of TNFIs in adults.[55] Our findings also revealed lower rates of corticosteroid use in children and young adults under the top-down strategy. However, we did observe a higher rate of discontinuation of TNFIs in patients treated with the top-down strategy. Reasons for this are unknown. ECCO and ESPGHAN guidelines do not specify a duration for TNFI use in patients with IBD. It is possible that the top-down strategy, a more aggressive treatment approach, is related to some causes for discontinuation, such as occurrence of adverse events or development of anti-drug antibodies (which leads to ineffectiveness of TNFIs), and thus more studies are needed to confirm our findings and identify the reasons for discontinuation.

Among IBD patients treated with the top-down strategy, we found that most used TNFI monotherapy; only 25.8% initiated 5-ASA or thiopurines, either concomitantly or as augmentation to TNFIs. In the Study of Biologic and Immunomodulator Naive Patients in Crohn's Disease (SONIC) trial, the combination of infliximab and azathioprine showed a greater

corticosteroid-free remission rate (56.8%) than use of infliximab (44.4%) or azathioprine (30.0%) alone.[138] In addition, whereas one study found that up to 61% of CD patients developed antibodies to infliximab,[139] the combination of TNFIs and immunomodulators has been associated with a lower risk of anti-drug antibody development.[138,140] However, TNFIs were reported to be associated with an increased risk of lymphoma in children, especially when combined with thiopurines.[60,141] Prescribing of a TNFI alone as opposed to in combination with other immunomodulators remains controversial. In our study, due to the limitations of the claims data, we were unable to identify the reasons for physicians' prescribing decisions or to examine development of anti-drug antibodies in patients receiving TNFI therapy. Future studies are needed to evaluate the effectiveness of TNFI monotherapy as opposed to combined therapy as well as the associated clinical consequences in children and young adults with IBD.

Several limitations of our study merit discussion. First, included patients may have been misclassified as having IBD if the disease diagnoses were coded inaccurately. However, we made every effort to identify the IBD cohort by using an algorithm that was validated previously[131]. In addition, any misclassification that may have occurred was likely nondifferential between the top-down and step-up strategies, and would bias our results toward to the null. Second, due to the absence of some clinical information in the claims database, such as gastrointestinal symptoms and endoscopy results, we were unable to accurately account for the effect of disease severity on TNFI utilization. Third, our findings for TNFI adherence should be interpreted with caution. The claims data provided only the dates and days supply of prescription fills, and thus we could not determine whether patients actually took the medications. However, adherence measurement using prescription records has been validated previously.[126,127] In addition, it may not be appropriate to compare adherence to infliximab (by intravenous infusion) with adherence to other TNFI agents (by subcutaneous injection) because of their different routes of administration. Furthermore, the effect of specialty pharmacy management on adherence to TNFIs was difficult to identify and control for in our analysis.

3.6 Conclusion

In summary, this study characterized utilization of TNFIs in children and young adults with IBD. Employment of the top-down strategy increased over time and the time to TNFI initiation became shorter during the study period, indicating that a more aggressive treatment approach has emerged for children and young adults with IBD. However, higher rates of TNFI monotherapy and discontinuation were observed with the top-down strategy. Future studies should evaluate the long-term benefits and risks of the top-down treatment approach to ensure the effectiveness and safety of this emerging aggressive treatment approach for children and young adults.

4. RISK OF SERIOUS BACTERIAL INFECTION ASSOCIATED WITH TUMOR NECROSIS FACTOR-ALPHA INHIBITORS IN CHILDREN WITH JUVENILE IDIOPATHIC ARTHRITIS

4.1 Preface

This chapter of the dissertation is being considered for publication as an article in the journal *Rheumatology*. The paper is titled "Risk of serious bacterial infection associated with tumor necrosis factor-alpha inhibitors in children with juvenile idiopathic arthritis." The manuscript has been reviewed by journal personnel and is currently being revised for resubmission. Included here is the unrevised version. This chapter describes the study conducted to address aim 3 of this dissertation.

4.2 Introduction

TNFIs, including monoclonal antibodies (e.g., infliximab and adalimumab) and fusion proteins (etanercept), are biological agents used to treat RA and JIA. TNFIs are highly effective for RA and JIA and have been shown in clinical trials to induce disease remission, improve quality of life, and enhance physical functioning.[39,40,106] The ACR recommends use of TNFIs if RA or JIA is uncontrolled after a treatment course of traditional DMARDs (e.g., methotrexate or leflunomide).[16,142] These traditional drugs are referred to simply as DMARDs hereafter. In addition, earlier use of TNFIs has been shown to improve short-term clinical outcomes in both RA and JIA.[47,49] As a result, TNFI use has increased over the past decade.[44,108]

Although TNFIs are generally safe, growth in their use has resulted in more reports of adverse events. In particular, infections have been the most frequently reported serious adverse event in adult RA patients.[63,65,66] Observational studies[65,66,76-79,143] and meta-analyses[69,70,72] have been conducted to evaluate the association between TNFIs and infection among adult RA

patients, but the findings were mixed. Some studies reported increased risk of infection compared to DMARDs,[69,72,78,79,143] whereas others found no elevated risk.[65,66,70,76,77] Nevertheless, in 2008, theFDA required TNFI manufacturers to include a black box warning in the product label for serious infections leading to hospitalization or death.[66]

The warning applies to both adults and children, yet most studies evaluating the TNFI-infection association were conducted in adults with RA. Children are a vulnerable population more likely to experience adverse drug events than adults.[84] In addition, the immaturity of their immune system may put children at a higher risk for infection.[144] Unfortunately, clinical and observational studies involving JIA patients have had limited numbers of participants and short follow-up periods.[40,87,92,93,106]

More definitive evidence is needed for the association between TNFIs and infection in children. This study aimed to examine the risk of serious bacterial infection associated with TNFIs in children with JIA.

4.3 Methods

4.3.1 Data Source

In this retrospective cohort study, we analyzed data from the Truven Health MarketScan® Commercial Claims and Encounters database for the period January 1, 2009 through December 31, 2013. The database contains employer-based health insurance claims for over 180 million enrollees and their dependents across the US since 1996. Administrative data on patient enrollment; healthcare utilization, including hospitalizations and visits to outpatient clinics and emergency departments; medical procedures; costs of services; and pharmacy records are available in the database and for research use.[109]

4.3.2 Study Cohort

The analytic cohort was developed by first identifying children (age <16 years) who had a diagnosis of JIA and had at least one prescription for a TNFI or DMARD during the study period. We used a previously validated algorithm to identify patients with JIA that included ICD-9-CM codes 714.xx (RA and JIA), 696.0 (psoriatic arthritis), and 720.xx (ankylosing spondylitis).[8] Included children were required to have two or more JIA diagnoses within 1 year or one JIA diagnosis coded by a pediatrician or rheumatologist. The date of the first new prescription for either a TNFI or DMARD was defined as the index date. Patients were excluded if they met any of the following criteria during the 6 months prior to the index date: (1) a previous prescription for either a TNFI or DMARD; (2) less than 6 months of continuous enrollment in the health plan; (3) a history of tuberculosis (ICD-9-CM code 011.xx - 018.xx) and/or use of medications for tuberculosis; or (4) a history of cancer, transplantation, and/or HIV infection.

4.3.3 Exposures

Exposures to TNFIs and DMARDs were identified using National Drug Codes and Healthcare Common Procedure Coding System. DMARDs included methotrexate, hydroxychloroquine, sulfasalazine, and leflunomide, and TNFIs included etanercept, adalimumab, infliximab, certolizumab, and golimumab. Each included patient was followed from the index date to the first occurrence of infection, disenrollment from the health plan, discontinuation of treatment, or a switch between a TNFI and DMARD or to the end of the study period (December 31, 2013). Discontinuation of medication was defined as a gap of more than 92 days between the end of one prescription’s days supply and the next prescription date.

4.3.4 Outcomes

The outcome of interest was a serious bacterial infection, which was defined as an infection requiring hospitalization identified using ICD-9-CM diagnosis codes at any diagnosis position in the inpatient claims. We applied a previously validated algorithm that incorporated 27 sites of infections,[145] including sites in the skin and skin structure, digestive system, respiratory tract, and genitourinary system. If more than one infection was identified for a given patient, then only the first occurrence was used. If an individual was diagnosed as having an infection at two or more sites on the same date, the major site of infection was identified based on the severity of infection, concomitant diagnoses, and procedures recorded. Only 14% of cases of serious infections had more than one site of infection.

4.3.5 High-Dimensional Propensity Score Models

We used an hdPS to identify and adjust for a large number of covariates that could confound the association between the exposure and infections.[146,147] Variables were grouped in "dimensions" that included diagnoses and procedures in both the inpatient and outpatient settings and outpatient medication use during the 6 months before the index date. The hdPS algorithm first selected the 200 variables that were most frequent in each data dimension and then calculated a measure of confounding bias for each variable. All variables were then ranked by the confounding bias, and the top 500 were included in the propensity score model. Along with the 500 empirical variables, we included demographic variables (age, gender, geographic location, calendar year of medication use, and type of health plan on the index date) and healthcare utilization variables (the number of visits to outpatient, inpatient, and emergency departments during the 6 months before the index date) in the logistic regression model to calculate the probability of receiving TNFIs (i.e., the propensity score) for every individual in the study cohort.

4.3.6 Statistical Analysis

Demographic information, healthcare utilization, comorbidities, and concomitant medication use were compared between the TNFI and DMARD groups using a t-test, a chi square test, or Fisher's exact test, as appropriate. Crude rates of serious infection were calculated as the number of events per 100 person-years, and the 95% CI were computed using the Poisson exact method. The 3-year cumulative rate function was plotted and a log-rank test was used to examine the rate of serious infection for the two groups over time. Specific infection sites were described in the two exposure groups. Cox proportional hazard models were employed to estimate the HR for serious infection associated with use of TNFIs compared to DMARDs. The tertile of the propensity score and time-varying corticosteroid use were included in the final Cox model. Corticosteroid use during follow-up was examined monthly in a time-varying manner. Analyses stratified by gender were also performed.

We also performed several sensitivity analyses to examine the robustness of our findings. First, because TNFIs are indicated for children aged 2 years and older with active JIA, we restricted our analysis to children ≥2 years of age. Second, we were concerned that in some patients, symptoms of infection may have resulted in discontinuation of treatment before confirmation of infection. Because we censored patients at treatment discontinuation, we could not include such cases. Therefore, we performed a sensitivity analysis in which the observation period was extended by 30 days and 90 days beyond discontinuation of medication use. Third, in the primary analysis, we allowed a gap of up to 92 days before defining the treatment as discontinued, as described above. This approach was based on an assumed long duration of effect of the TNFIs;[23,40] however, if the duration was shorter, then this approach could have misclassified an event as occurring during an exposure period. We tested the assumption by using a shorter (31-day) gap in our sensitivity analysis.

All analyses were performed using SAS statistical software version 9.4 (Cary, North Carolina, USA) and STATA 12 (College Station, Texas, USA). The Institutional Review Board determined this study to be non-human subject research.

4.4 Results

We identified 5,497 children with JIA who were prescribed either a TNFI or DMARD during the study period (**FIGURE 6**). After excluding children with prevalent use of TNFIs or DMARDs (24.6%), those without 6 months of continuous enrollment (26.5%), and other exclusion characteristics, the final study cohort consisted of 2,495 individuals; including 2,013 new DMARD users and 482 new TNFI users.

Baseline characteristics were compared between the TNFI and DMARD groups (**TABLE XVI**). TNFI initiators were slightly older than DMARD initiators (mean age: 10.4 vs 9.9 years); less likely to be female (62.9% vs 70.6%); more likely to have uveitis (12.7% vs 8.8%), asthma (9.1% vs 6.5%) or inflammatory bowel disease (9.8% vs 1.4%); and more likely to have a hospitalization due to infection (3.1% vs 1.7%) in the 6 months preceding the index date. However, the DMARD group had higher proportions of patients with a history of systemic lupus erythematosus (1.7% vs 0.4%), nonsteroidal anti-inflammatory drug use (60.5% vs 42.7%), corticosteroid use (27.9% vs 23.4%), and antibiotic use (38.7% vs 31.1%).

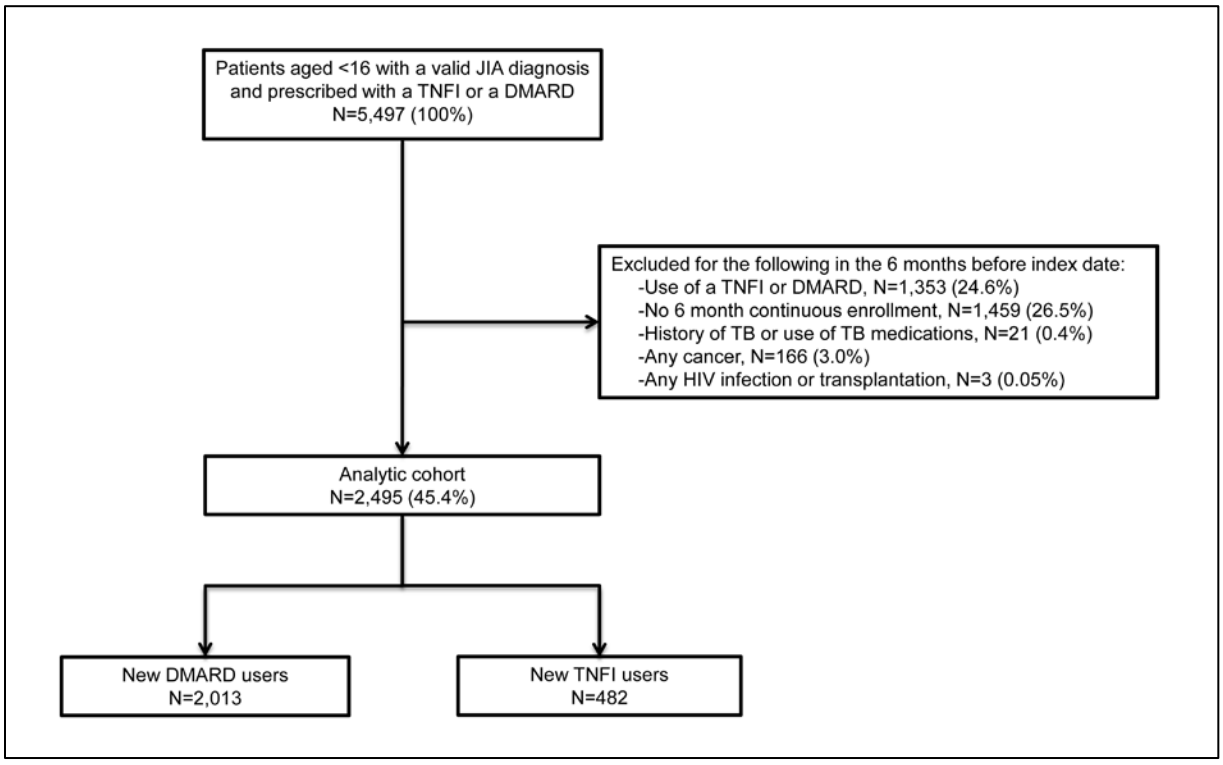

FIGURE 6. Selection criteria for analytic study cohort in children with JIA

TABLE XVI
PATIENT CHARACTERISTICS IN DMARD AND TNFI USERS

	DMARDs (N=2,013)		TNFIs (N=482)		P value
Patient characteristics[a]					
Age, mean (SD)	9.9	(4.2)	10.4	(4.0)	0.018
Gender, n (%)					
Male	592	(29.4)	179	(37.1)	0.001
Female	1,421	(70.6)	303	(62.9)	
Region, n (%)					
Northeast	407	(20.2)	104	(21.6)	0.600
Midwest	530	(26.3)	111	(23.0)	
South	661	(32.8)	170	(35.3)	
West	366	(18.2)	86	(17.8)	
Unknown	49	(2.4)	11	(2.3)	
Capitated health plan type, n (%)					
Non capitalized plan	1,575	(78.2)	379	(78.6)	0.582
Capitalized plan	296	(14.7)	75	(15.6)	
Unknown	142	(7.1)	28	(5.8)	
Year of medication use, n (%)					
2009	277	(13.8)	52	(10.8)	0.007
2010	476	(23.6)	97	(20.1)	
2011	509	(25.3)	110	(22.8)	
2012	524	(26.0)	161	(33.4)	
2013	227	(11.3)	62	(12.9)	
Healthcare utilization[b], n (%)					
Number of outpatient visit					
0-2 times	528	(26.2)	122	(25.3)	0.131
3-4 times	612	(30.4)	128	(26.6)	
≥5 times	873	(43.4)	232	(48.1)	
Number of inpatient visit					
0	1,873	(93.0)	439	(91.1)	0.137
≥1	140	(7.0)	43	(8.9)	
Number of ED visit					
0	1,595	(79.2)	370	(76.8)	0.233
≥1	418	(20.8)	112	(23.2)	
RA surgery	16	(0.8)	1	(0.2)	0.223
Comorbidities[b], n (%)					
Charlson Comorbidity Index					
0	1,534	(76.2)	361	(74.9)	0.546
≥1	479	(23.8)	121	(25.1)	
Asthma	131	(6.5)	44	(9.1)	0.043
Diabetes	14	(0.7)	5	(1.0)	0.392
Systemic lupus erythematosus	35	(1.7)	2	(0.4)	0.033
Sjogren's syndrome	8	(0.4)	0	0.0	0.367
Psoriasis	47	(2.3)	18	(3.7)	0.109
Inflammatory bowel disease	29	(1.4)	47	(9.8)	<0.0001
Uveitis	178	(8.8)	61	(12.7)	0.011

TABLE XVI (continued)
PATIENT CHARACTERISTICS IN DMARD AND TNFI USERS

	DMARDs (N=2,013)		TNFIs (N=482)		p value
Medication use[b], n (%)					
NSAIDs	1,217	(60.5)	206	(42.7)	<0.0001
Corticosteroids	561	(27.9)	113	(23.4)	0.049
Antibiotics	780	(38.7)	150	(31.1)	0.002
Anakinra	10	(0.5)	3	(0.6)	0.725
Azathioprine	3	(0.1)	5	(1.0)	0.009
Cyclosporine	3	(0.1)	1	(0.2)	0.577
Mercaptopurine	4	(0.2)	6	(1.2)	0.005
Mycophenolate	2	(0.1)	0	(0.0)	1.000
Tacrolimus	5	(0.2)	2	(0.4)	0.627
Previous infections[b], n (%)					
Any previous infections	849	(42.2)	229	(47.5)	0.034
Outpatient visit for infections	736	(36.6)	203	(42.1)	0.024
Hospitalizations for infections	34	(1.7)	15	(3.1)	0.043

[a] Patient characteristics were measured on the index date (i.e., new use of TNFIs or DMARDs).
[b] The covariates were measured in the 6 months prior to the index date.

The mean follow-up time was 255 days for the DMARD group and 307 days for the TNFI group. We observed 18 and 11 serious infections in 1,405.4 and 404.9 total person-years for the DMARD and TNFI groups, respectively; this resulted in crude rates of 1.28 (0.76-2.02) and 2.72 (1.36-4.86) serious infections per 100 person-years for these groups (**TABLE XVII**). The TNFI group had 1.44 more serious infections per 100 person-years than the DMARD group. The crude rate ratio for infection was 2.12 (95%CI 0.91-4.74) for TNFIs compared to DMARDs. The higher rate of TNFI-associated serious infection was also reflected in the crude cumulative hazard estimates (log rank test p=0.0357) (**FIGURE 7**). In addition, among the patients with infections, the median time to infection was 86 days (IQR 37-198) for the DMARD group and 91 days (IQR 21-207) for the TNFI group.

TABLE XVII

CRUDE RATES OF SERIOUS INFECTIONS ASSOCIATED WITH TNFIS AND DMARDS

	Total N	**Total person-years**	**Number of serious infections**	**Crude rate of infection, event/100 person-years (95% CI)**
DMARDs	2013	1405.4	18	1.28 (0.76-2.02)
TNFIs	482	404.9	11	2.72 (1.36-4.86)

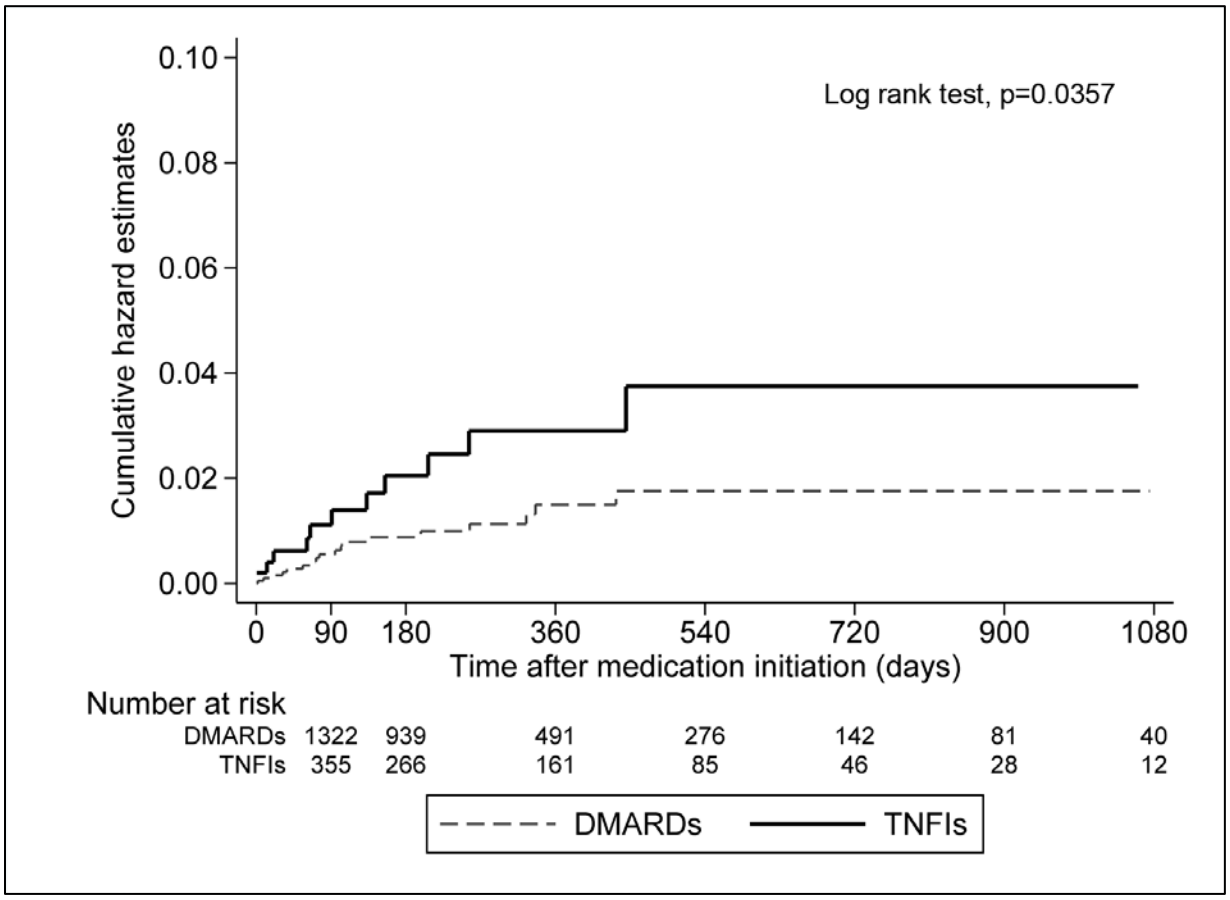

FIGURE 7. Three-year cumulative hazards of serious infections in children with JIA.

TABLE XVIII shows specific sites of infection in the TNFI and DMARD users. For both the TNFI and DMARD groups, infections were most commonly observed in the respiratory tract (36.4% and 33.3%), followed by the digestive system (27.3% and 22.2%), “other” organ systems (which included blood and device-related infections) (18.2% and 22.2%), skin and skin structure (9.1% and 16.7%), and genitourinary system (9.1% and 5.6%).

TABLE XVIII
SITE OF INFECTIONS IN JIA CHILDREN WITH SERIOUS INFECTION

	DMARDs		**TNFIs**	
	N	**(%)**	**N**	**(%)**
Number of patients with serious infection[a]	18	(100.0)	11	(100.0)
Respiratory tract system	6	(33.3)	4	(36.4)
Upper respiratory tract infection	4	(22.2)	2	(18.2)
Pneumonia	2	(11.1)	2	(18.2)
Digestive system	4	(22.2)	3	(27.3)
Abdominal abscess	2	(11.1)	1	(9.1)
Cholecystitis	1	(5.6)	1	(9.1)
Gastroenteritis	1	(5.6)	1	(9.1)
Others	4	(22.2)	2	(18.2)
Bacteremia/septicemia	4	(22.2)	1	(9.1)
Device-associated infections	0	(0.0)	1	(9.1)
Skin and skin structure	3	(16.7)	1	(9.1)
Cellulitis	2	(11.1)	0	(0.0)
Necrotizing fasciitis	0	(0.0)	1	(9.1)
Septic arthritis	1	(5.6)	0	(0.0)
Genitourinary system	1	(5.6)	1	(9.1)
Pyelonephritis/urinary tract infection	1	(5.6)	1	(9.1)

[a] Patients could have diagnoses of infections at more than one site at their event hospitalization, and the major site of infection was used based on clinical expert opinion.

Compared to DMARDs, use of TNFIs was associated with an increased risk of serious bacterial infection (HR 2.72, 95%CI 1.08-6.86) after adjusting for the tertile of the hdPS and time-varying corticosteroid use (**TABLE XIX**). In the gender-stratified analysis, an increased risk was observed (HR 2.99, 95%CI 1.04-8.61) in female patients who initiated TNFIs. The point estimate was also elevated in the males (HR 2.03, 95%CI 0.33-12.61) but was not statistically significant.

Our sensitivity analyses did not change the direction of our findings. When we restricted the study cohort to 2 years of age and older (and <16 years), the HR did not change significantly (HR 2.62, 95%CI 1.00-6.82, p=0.0494). Similarly, when we extended the observation period by 30 days (HR 2.70, 95%CI 1.09-6.72) and 90 days (HR 2.76, 95%CI 1.11-6.85) beyond treatment discontinuation, we found no change in the association. However, when the gap for defining treatment discontinuation was reduced to 31 days, we observed a greater magnitude of infection risk for TNFIs (HR 3.61, 95%CI 1.32-9.87).

TABLE XIX
RISK OF SERIOUS BACTERIAL INFECTIONS ASSOCIATED WITH TNFIS COMPARED TO DMARDS

	N	No. of events	Crude HR (95% CI)	Adjusted HR (95% CI) [a]
Main analysis				
DMARDs	2,013	18	1.00 (reference)	1.00 (reference)
TNFIs	482	11	2.27 (1.07-4.80)	2.72 (1.08-6.86)
Stratified by gender				
Male				
DMARDs	592	3	1.00 (reference)	1.00 (reference)
TNFIs	179	3	2.91 (0.59-14.50)	2.03 (0.33-12.61)
Female				
DMARDs	1,421	15	1.00 (reference)	1.00 (reference)
TNFIs	303	8	2.20 (0.93-5.19)	2.99 (1.04-8.61)

[a] Adjusted for high-dimensional propensity score (tertile), and use of systemic corticosteroids as a time-varying variable in the model.

4.5 Discussion

In a population of commercially insured children with JIA, we found that new use of TNFIs was associated with a 2.7-fold increase in risk of serious bacterial infection compared to new use of DMARDs. This increased risk estimate is consistent with the findings of some RA studies in adults.[78,79] However, previous studies examining the association between TNFIs and infection in children with JIA had conflicting results. For example, Beukelman and colleagues analyzed US national Medicaid data from 2000 through 2005 and found no difference between TNFIs and methotrexate in the rate of hospitalization for bacterial infections (adjusted HR 1.2, 95%CI 0.8-1.8).[95] Similarly, an analysis performed by Davies and colleagues using data from the British Society for Paediatric and Adolescent Rheumatology Etanercept Cohort Study revealed no increased risk for serious infections requiring hospitalization and/or intravenous antibiotic use (adjusted HR 1.36, 95%CI 0.60-3.07) associated with etanercept compared to methotrexate[96] On the other hand, Klotsche and colleagues examined a set of German registries for the period 2005 to 2011 and found that the risk of infection leading to hospitalization was higher (RR 2.12, 95%CI 1.08-4.17) in patients receiving etanercept compared to methotrexate.[97]

In contrast to the abovementioned studies, we adopted a new-user design, excluded the effect of methotrexate or other DMARDs in the TNFI exposure group, and employed a comparison group of biologic-naïve DMARD initiators. Although TNFIs are usually recommended for use in combination with DMARDs, studies have shown that TNFIs are increasingly used early in the JIA disease course[98,118] and as monotherapy.[98,108] This new treatment paradigm facilitated our comparison of the two groups, as both consisted of new initiators of therapy. Notably, the black box warning for TNFIs stated that most infections developed when the drugs were used in combination with other immunosuppressants, such as DMARDs or corticosteroids.[7,148] However, our study provides evidence that TNFI monotherapy is also associated with an increased risk of infection compared to DMARDs while controlling for

corticosteroid use and other confounders. In addition, the FDA warning for TNFI-induced infection was based on evidence from RA studies in adults. Our study further confirms the risk of infection associated with TNFI use in children with JIA.

The likely mechanism by which TNFIs increase the risk of infection is related to the role of the TNF-alpha in immune response.[149] Activation of macrophages and fibroblasts stimulates the release of TNF, which activates additional chemokines and proinflammatory signals, initiating downstream immune response.[33] By inhibiting the action of TNF, TNFIs prevent the immune response to foreign pathogens, increasing risk for infections. In our study, the rates of infection in the TNFI (2.27/100 person-years) and DMARD groups (1.28/100 person-years) were consistent with those observed in other studies of JIA.[96,150,151]

The time to infection (median of about 90 days) was short in our study and was similar to findings of previous studies. For example, in the analysis by Davies and colleagues, 44% (24 of 54) of cases developed a serious infection requiring hospitalization within 6 months of etanercept initiation in children with JIA.[96] A study of adults with RA also reported that the adjusted incidence rate ratio was 4.6 (95% CI 1.8-11.9) for TNFIs compared to DMARDs in the analysis of restricting the follow-up time to the first 90 days.[77] These findings are consistent with the pharmacodynamic properties of TNFIs. The time to therapeutic effect of TNFIs varies by individual patient but is typically rapid; symptom improvement can be seen after two or three doses, and additional improvements over 3 to 6 months have been reported. Given these findings, healthcare professionals should be vigilant in monitoring for symptoms of infection, especially in the first 6 months of treatment.

While our results suggest increased risk for infections associated with TNFIs compared to DMARDs, clinicians and patients should consider this risk in light of the benefits of TNFIs. Specifically, TNFIs are highly effective drugs that have been shown to improve symptoms, physical functioning, radiographic progression, and quality of life.[39,40,106] In order to balance the risks and benefits associated with TNFIs, both the US FDA and European Medicines Agency

have developed risk mitigation strategies for these biologics, but risk management guidance for children is lacking.[91,92] Our findings provide evidence that these agencies could use to adapt risk management plans for children under TNFI treatment. Such plans could incorporate appropriate screening, monitoring, and even withholding of treatment to mitigate the potential harm of TNFIs to children with JIA.

The strengths of our study include its use of relatively recent data (2009 through 2013), employment of a new-user design, and use of an hdPS approach. However, our findings should be interpreted with consideration of the limitations noted below. In particular, our results are subject to limitations common to studies using administrative claims databases, including potential misclassification of outcomes and exposure. However, we minimized this potential issue by using previously validated algorithms to identify infections and JIA.[8,145] We also used comprehensive pharmacy records and intervention procedure codes to examine exposure, although we could not confirm that the patients actually administered the medications as directed. In addition, because administrative data are not designed for research purposes, clinical data for health status in JIA (e.g., disease activity score, JIA subtype, and number of involved joints) were not available for our analysis. Confounding from these and other unmeasured variables cannot be completely ruled out and may have biased our results.

Specifically, an important unmeasured confounder in our study is the relationship between the autoimmune disease itself and infection. Beukelman and colleagues found JIA to be associated with a doubled risk of infection compared to attention deficit hyperactivity disorder (ADHD).[95] In adult RA studies, a relationship between the autoimmune disease and infection was also observed.[152,153] Immunological abnormalities, including T cell circulation and impaired thymic function, are possible reasons for the observed risk of infection attributable to JIA or RA.[153,154] Our findings may have overestimated the TNFI-infection relationship if JIA severity was higher in the TNFI group. TNFIs are indicated for moderately to severely active polyarticular JIA, and thus children who receive TNFIs may have more severe JIA than those who receive

DMARDs alone. Recognizing this possibility, we applied an hdPS approach that used a great amount of information in the database to account for the potential channeling bias. The hdPS approach controlled for a large number of proxy indicators that indirectly reflected disease severity, and several simulation studies have demonstrated the effectiveness of this method.[146,147] Nonetheless, residual confounding of the JIA-infection relationship may remain.

Another potential limitation of our study is insufficient statistical power. Children with rheumatological conditions constitute a smaller population than adults. Although the rate of TNFI-related infection in our study was not extremely low at about 1 to 3 serious infections per 100 person-years, it is still challenging for any study of children to obtain a large enough sample size to adequately examine safety outcomes, especially in subgroup analyses. As a result, our estimates had wide confidence intervals, and we could not perform additional analyses such as evaluating the infection risk for individual TNFI agents. To facilitate studies of drug safety for children, it would be beneficial to incorporate relevant data into a national- or international-scale surveillance system. As one example, the European registry called Pharmachild is a pharmacovigilance project that aims to observe long-term adverse events associated with use of DMARDs and biologics in children with JIA across 50 participating countries.[155] In the US, the FDA Sentinel Initiative is a national electronic surveillance system designed to proactively monitor and examine the safety of medications and biologics.[89] In future studies, data from such a system would support a more thorough examination of potentially serious adverse events related to TNFIs.

Finally, the FDA-required black box warning may have impacted the observed association between TNFIs and infection. The FDA warning may have encouraged healthcare professionals to check for infections more often in TNFI users than in DMARD users. Therefore, a differential detection bias may exist between the two exposure groups, which may have resulted in overestimation of infection rates. On the other hand, the FDA warning may have caused physicians to avoid use of TNFIs for children who were susceptible to infection, and

these children may have been channeled to DMARD treatment instead of TNFI treatment. In this case, individuals in the DMARD group would appear to have higher risks for infection than those in the TNFI group, introducing a selection bias. This bias would have resulted in underestimation of the relationship between TNFIs and infection. In our study, the influence of the timing of the FDA warning was likely minimal because we used data only for years after the issuance of the 2008 FDA warning. However, we were unable to control for the potential behavior change of healthcare professionals due to the warning.

4.6 Conclusion

In summary, our study demonstrated a higher risk of serious bacterial infection associated with use of TNFIs compared to DMARDs in children with JIA. Our analysis supports the FDA warning about TNFI-associated infection in children with JIA and also provides a comparison between use of DMARDs and TNFIs alone. Future studies employing a larger cohort of children with JIA would help to confirm our findings and further characterize the risk of infection across individual TNFI agents. In the meantime, clinicians and patients need to balance the benefits of these highly effective drugs against the risk for infection they pose.

5. RISK OF SERIOUS BACTERIAL INFECTION ASSOCIATED WITH TUMOR NECROSIS FACTOR-ALPHA INHIBITORS IN CHILDREN AND YOUNG ADULTS WITH INFLAMMATORY BOWEL DISEASE

5.1 Preface

This chapter of the dissertation has been submitted for consideration for publication as an article in the journal *American Journal of Gastroenterology*. The paper is titled "Risk of serious bacterial infection associated with tumor necrosis factor-alpha inhibitors in children and young adults with inflammatory bowel disease." This chapter describes the study conducted to address aim 4 of this dissertation.

5.2 Introduction

TNFIs are effective biologics that have revolutionized the treatment of IBD, including CD and UC. TNFIs approved by the FDA for IBD treatment include infliximab, adalimumab, certolizumab pegol, and golimumab. These drugs have been shown in clinical trials to hasten clinical remission, increase health-related quality of life, and reduce the need for corticosteroids.[41,42] Among the IBD treatment options, TNFIs are considered the most effective, and as a result their use has increased.[130]

As the utilization of TNFIs has increased, so have reports of adverse events.[57,86,156] In particular, TNFIs have been linked to an increased risk of infection.[68] The potential association between TNFIs and infection has been studied in adults with IBD, with inconsistent results across studies. Two meta-analyses and a pooled analysis of CD and UC found no difference in the rates of serious infection for TNFIs compared to placebos,[73-75] but post-marketing observational studies have reported both increased risk[81,82,157] and no association.[66,80]

Despite these inconsistent findings, the FDA issued a black box warning for TNFI-related serious infection in 2008.[59] While the warning applies to both adults and children, most IBD studies evaluating the association were conducted in adults. Although adolescents and young adults have the highest incidence of both CD and UC,[23] these patients were under-represented in clinical trials and observational studies. In addition, childhood-onset IBD usually follows a more severe course than adult-onset IBD.[3,24] Thus children with IBD may benefit more than adults from TNFIs. However, children may also be more susceptible than adults to infection.[144] Therefore, more information is needed on the risk of infection associated with TNFIs when used in children with IBD.

The primary aim of this study was to evaluate the risk of serious infection associated with TNFIs compared to non-biologic immunomodulators in children and young adults with IBD. The secondary aim was to compare infection risk among individual TNFIs and by route of administration.

5.3 Methods

5.3.1 Data Sources

We conducted a retrospective cohort study using the Truven Health MarketScan® Commercial Claims and Encounters database for the period January 1, 2009, through December 31, 2013. This de-identified database contained health care claims for people commercially insured through employer-based coverage across the US and included information on health plan enrollment, medical service utilization, and prescription records. Each claim included patient demographic information, type of encounter, date of service, provider, diagnoses, medical procedures, and expenditures.[109]

5.3.2 Study Cohort

We identified patients aged <30 years diagnosed with IBD (ICD-9-CM code 555.xx or 556.xx) between July 1, 2009, and June 30, 2013. Eligible subjects had to have ≥2 claims with an IBD diagnosis within 1 year or one claim with an IBD diagnosis by a pediatrician or gastroenterologist.[131] From this group, individuals with at least one prescription claim for a TNFI or immunomodulator were identified. The date of first prescription was defined as the index date. To ensure that subjects were medication initiators (i.e., naïve to both TNFIs and immunomodulators), we excluded patients with any prescription claims for TNFIs or immunomodulators in the 6 months before the index date. Also excluded were patients with any of the following: <6 months of continuous health plan enrollment or history of tuberculosis or use of tuberculosis medications, cancer, transplantation, HIV infection, or rheumatic conditions or use of etanercept.

5.3.3 Exposures

Using prescription records and outpatient claims, exposure to TNFIs (infliximab, adalimumab, certolizumab, golimumab) or immunomodulators (methotrexate, azathioprine, 6-mercaptopurine) was determined based on their index treatment. Patients were followed from first prescription date (i.e., index date) to first occurrence of serious infection, discontinuation of treatment, switch from index treatment, disenrollment from the health plan, or the end of the study period (December 31, 2013). We defined treatment discontinuation as a gap of >92 days between the end of one prescription's days supply and the next prescription date. Patients who discontinued their index treatment were followed for 90 days beyond the end of the last prescription's days supply.

5.3.4 Outcomes

The outcome of interest was the first occurrence of a non-GI bacterial infection requiring hospitalization, hereafter called a "serious infection." Patients with a diagnosis of non-GI infection in any position on an inpatient claim were identified using a previously validated algorithm.[145] We excluded GI-related infections because these are important effectiveness endpoints for IBD treatment. If a patient had diagnoses for more than one site on a given date, we determined the major site based on the infection severity, concomitant diagnoses, and medical procedures recorded. Of the serious infections observed, only 11.7% involved more than one site.

5.3.5 High-Dimensional Propensity Score Models

hdPS models were used to control for potential confounding of the relationship between TNFIs and infection. Covariates to be included in the propensity score calculation were categorized into "dimensions." These included inpatient diagnoses, inpatient procedures, outpatient diagnoses, outpatient procedures, and outpatient medications during the 6 months before the index date. The hdPS algorithm ranked variables from each dimension based on the degree of confounding or bias calculated in the association between TNFI use and infection. The algorithm then selected the 500 top-ranked variables for inclusion in the logistic model to calculate the propensity score. The model also included covariates not considered in the algorithm but deemed important, including demographic variables (age, gender, geographic location, calendar year of medication use, and type of health plan on the index date) and healthcare utilization variables (numbers of visits to outpatient, inpatient, and emergency departments during the 6 months before the index date). The propensity score for each patient was a summary measure of the probability of receiving a TNFI.

In our secondary analysis, where risk of serious infection was compared within TNFI agents, patients in the immunomodulator group were excluded. We then applied the process described above to build a second logistic model in order to recalculate the hdPS as the probability of receiving infliximab for each TNFI user.

5.3.6 Statistical Analysis

Demographic variables, IBD-related treatment, healthcare utilization, and comorbidities were compared between the TNFI and immunomodulator groups. A t-test was used for continuous variables, and a chi-square test or Fisher's exact test was used for categorical variables. We computed crude rates of serious infections as the number of events per 100 person-years and 95% CI using the Poisson exact method. We then plotted 1-year rates of serious infections for the TNFI and immunomodulator groups and used a log-rank test to examine whether these rates differed.

Cox proportional hazard models were used to compute HR for serious infection of TNFIs compared to immunomodulators. In the final Cox models, we adjusted for potential confounding effect using the hdPS tertiles and two time-varying covariates during follow-up: corticosteroid use and all-cause hospitalization. Use of corticosteroids is linked to increased risk of infection.[158] Also, because patients have higher risk of hospital-acquired infection after hospital discharge,[159,160] we defined the post-hospitalization window as within 30 days of discharge and adjusted for this in the model.

In the secondary analysis, we restricted the cohort to TNFI users and examined the risk of serious infection for individual TNFIs (adalimumab, certolizumab, and golimumab) compared to infliximab. We added a censor criterion for patients who switched from one TNFI to another and recalculated the hdPS based on the probability of receiving infliximab. In addition, we

examined the risk of infection for TNFIs administered subcutaneously compared to infliximab administered intravenously.

We conducted sensitivity analyses to test the robustness of our findings. First, we restricted our analytical cohort to individuals ≥6 years of age because TNFIs are indicated for pediatric patients aged ≥6 years with CD or UC. Second, in the main analysis, we assumed a duration effect of 92 days in defining treatment discontinuation and observation time after discontinuation; this value was based on half-lives of TNFIs ranging from 1 to 3 months. Then we tested the duration of effect by varying the time window from 92 to 60 or 30 days. Third, instead of adjusting for hdPS tertiles, we conducted sensitivity analyses that adjusted the models using hdPS as deciles and as a continuous variable.

All analyses were performed using SAS statistical software version 9.4 (Cary, North Carolina, USA) and STATA 12 (College Station, Texas, USA). The Institutional Review Board of the University of Illinois at Chicago determined this study to be non-human subject research.

5.4 Results

Numbers of patients who met inclusion and exclusion criteria are displayed in **FIGURE 8**. We identified 10,838 individuals with IBD; 4,502 new TNFI users and 6,336 new immunomodulator users had a median follow-up time of 260 (IQR 146-497) days and 208 (IQR 120-415) days, respectively.

TNFI users had a higher proportion of young adults aged 18-29 years (67.8% vs 56.4%); had more outpatient, inpatient, and emergency room visits; and had a higher proportion of hospitalizations for infection in the previous 6 months than the immunomodulator group (**TABLE XX**). However, the TNFI group used less corticosteroids (42.4% vs 64.2%), 5-ASA (34.7% vs 56.8%), and antibiotics (23.1% vs 29.8%) compared to immunomodulator users.

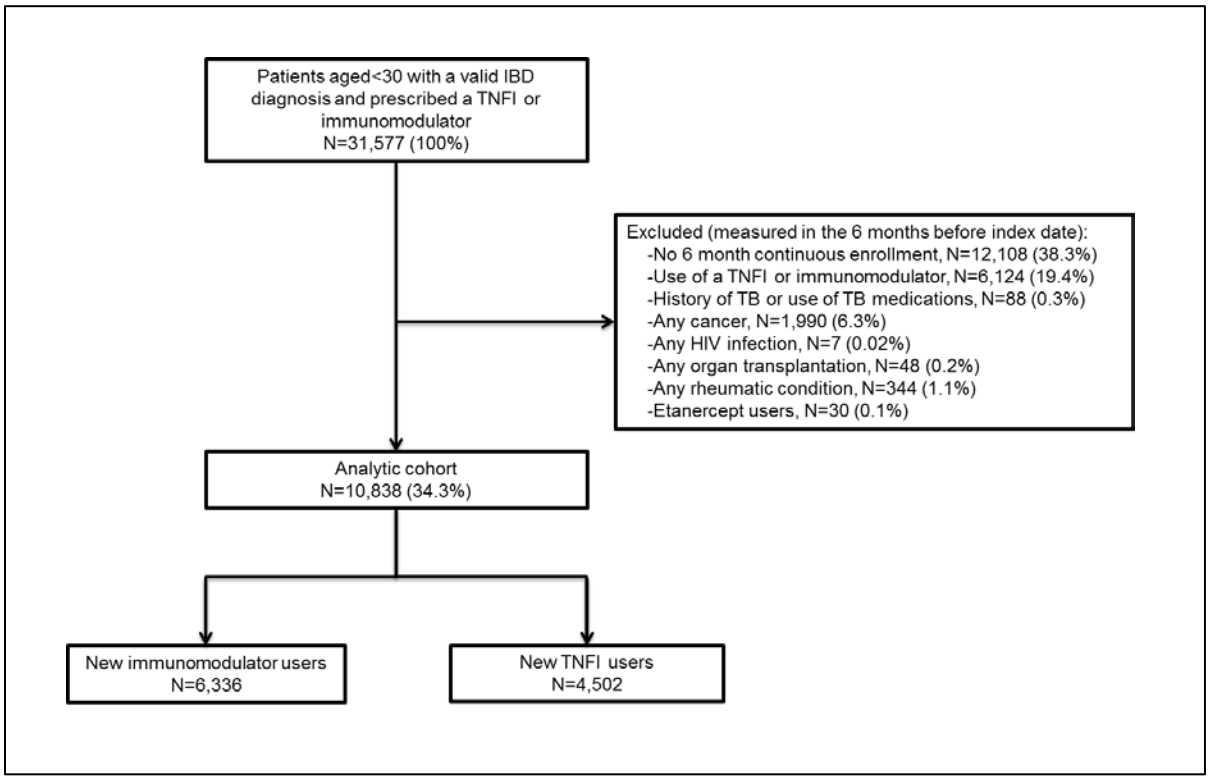

FIGURE 8. Selection criteria for analytic study cohort in children and young adults with IBD

TABLE XX
PATIENT CHARACTERISTICS IN CHILDREN AND YOUNG ADULTS WITH IBD

	Immunomodulators[a] (N=6,336)		TNFIs (N=4,502)		p value
	n	(%)	n	(%)	
Age group					
<18 years	2,762	(43.6)	1,451	(32.2)	<0.0001
18-29 years	3,574	(56.4)	3,051	(67.8)	
Gender					
Male	3,320	(52.4)	2,358	(52.4)	0.9818
Female	3,016	(47.6)	2,144	(47.6)	
Region					
Northeast	1,344	(21.2)	1,079	(24.0)	<0.0001
Midwest	1,734	(27.4)	1,063	(23.6)	
South	2,129	(33.6)	1,585	(35.2)	
West	1,033	(16.3)	643	(14.3)	
Unknown	96	(1.5)	132	(2.9)	
Capitated health plan type					
Non capitated plan	5,065	(79.9)	3,716	(82.5)	<0.0001
Capitatated plan	826	(13.0)	457	(10.2)	
Unknown	445	(7.0)	329	(7.3)	
Year of medication use					
2009	881	(13.9)	517	(11.5)	<0.0001
2010	1,498	(23.6)	911	(20.2)	
2011	1,618	(25.5)	1,213	(26.9)	
2012	1,674	(26.4)	1,345	(29.9)	
2013	665	(10.5)	516	(11.5)	
Number of outpatient visits[b]					
0-2	2,215	(35.0)	1,403	(31.2)	<0.0001
3-4	1,998	(31.5)	1,347	(29.9)	
≥5	2,123	(33.5)	1,752	(38.9)	
Number of inpatient visits[b]					
0	4,748	(74.9)	3,136	(69.7)	<0.0001
≥1	1,588	(25.1)	1,366	(30.3)	
Number of ED visits[b]					
0	4,157	(65.6)	2,750	(61.1)	<0.0001
≥1	2,179	(34.4)	1,752	(38.9)	
IBD related treatment[b]					
Corticosteroids	4,068	(64.2)	1,910	(42.4)	<0.0001
5-ASA	3,599	(56.8)	1,561	(34.7)	<0.0001
Antibiotics	1,888	(29.8)	1,041	(23.1)	<0.0001
GI examination procedures[bc]	3,741	(57.8)	2,577	(54.7)	0.0067
IBD surgical intervention[b]	50	(0.8)	69	(1.5)	0.0001
Charlson Comorbidity Index[b]					
0	5,548	(87.6)	3,948	(87.7)	0.8380
≥1	788	(12.4)	554	(12.3)	

TABLE XX (continued)
PATIENT CHARACTERISTICS IN CHILDREN AND YOUNG ADULTS WITH IBD

	Immunomodulators[a] (N=6,336)		TNFIs (N=4,502)		p value
Comorbidities[b]					
Asthma	377	(6.0)	259	(5.8)	0.6670
Diabetes	51	(0.8)	37	(0.8)	0.9229
Systemic lupus erythematosus	18	(0.3)	6	(0.1)	0.0998
Outpatient visit for infections	1,552	(24.5)	1,142	(25.4)	0.3009
Hospitalizations for infections	171	(2.7)	190	(4.2)	<0.0001

[a] Immunomodulator group included new use of methotrexate, azathioprine, and 6-mercaptopurine.
[b] The covariates were measured in the 6 months prior to the index date.
[c] GI examination procedures included esophagoscopy, endoscopic retrograde cholangiopancreatography, proctosigmoidoscopy, sigmoidoscopy, colonoscopy, small intestinal endoscopy, ileoscopy, anoscopy, and biliary endoscopy.

There were 236 patients in the TNFI group and 192 in the immunomodulator group that experienced a serious infection during the follow-up (**TABLE XXI**). The crude rates of serious infections were 5.25 (95%CI 4.60-5.97) and 3.59 (95%CI 3.10-4.13) events per 100 person-years for the TNFI and immunomodulator groups, respectively. The TNFI group had an additional 1.67 serious infections per 100 person-years compared to the immunomodulator group. The median time (IQR) from drug initiation to serious infection was 95 (35-187) days for TNFIs and 80 (25-176) days for immunomodulators. The Kaplan-Meier plot also showed different cumulative rates of serious infection for TNFIs and immunomodulators (p<0.0001) (**FIGURE 9**). Following adjustment, TNFIs were associated with a higher risk of a non-GI bacterial infection requiring hospitalization (HR 1.36, 95%CI 1.08-1.72) compared to immunomodulators. This risk appeared to be higher among young adults aged 18-29 years (HR 1.49, 95%CI 1.12-1.98) than in children (HR 1.12, 95%CI 0.75-1.68).

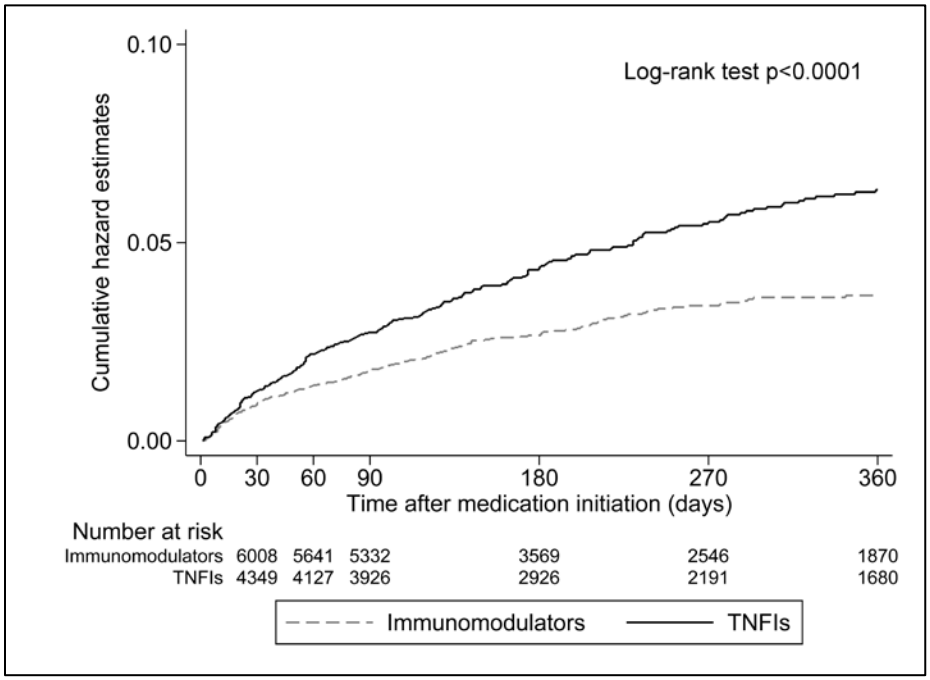

FIGURE 9. One-year cumulative hazard estimates of serious infections in children and young adults wtih IBD

TABLE XXI

RISK OF SERIOUS INFECTIONS ASSOCIATED WITH TNFIS COMPARED TO IMMUNOMODULATORS

	N	Total person-years	Number of serious infections[a]	Crude rate of infection[a], event/100 person-years (95% CI)	Crude HR (95% CI)	Adjusted HR (95% CI)[b]
Main analysis						
Immunomodulators	6,336	5,355	192	3.59 (3.10-4.13)	1.00 (reference)	1.00 (reference)
TNFIs	4,502	4,494	236	5.25 (4.60-5.97)	1.58 (1.30-1.91)	1.36 (1.08-1.72)
Stratified analyses						
Age <18 years						
Immunomodulators	2,762	2,697	85	3.15 (2.52-3.90)	1.00 (reference)	1.00 (reference)
TNFIs	1,451	1,574	68	4.32 (3.36-5.48)	1.45 (1.06-2.00)	1.12 (0.75-1.68)
Age 18-29 years						
Immunomodulators	3,574	2,658	107	4.03 (3.30-4.86)	1.00 (reference)	1.00 (reference)
TNFIs	3,051	2,920	168	5.75 (4.92-6.69)	1.59 (1.25-2.03)	1.49 (1.12-1.98)

[a] Serious infection was defined as a non-GI bacterial infection requiring hospitalization.

[b] Adjusted for high-dimensional propensity score (tertile), time-varying use of systemic corticosteroids, and time-varying post-hospitalization windows in the model.

Among patients who developed a serious infection, infections of the skin and skin structure, especially cellulitis, were the most common for both TNFI (33.1%) and immunomodulator (33.3%) users (**TABLE XXII**). Other infections observed in TNFI and immunomodulator users included bacteremia (19.5% vs 22.4%), urinary tract infection (13.6% vs 14.6%), upper respiratory tract infection (10.6% vs 9.4%), and pneumonia (9.7% vs 7.8%).

The crude rates of serious infection were 4.64, 5.94, and 7.92 events per 100 person-years for infliximab, adalimumab, and certolizumab, respectively (**TABLE XXIII**). Compared to infliximab, the risk of serious infection from adalimumab was elevated (HR 1.33, 95%CI 0.95-1.84) but non-significant, whereas certolizumab was associated with a significant 3.38-fold (95%CI 2.25-5.09) increased risk of serious infection. Among the 18 cases of infection in the certolizumab group, 9 (50%) and 5 (28%) involved cellulitis and urinary tract infection, respectively. Subcutaneous TNFIs were associated with a higher risk of infection (HR 1.34, 95%CI 1.18-1.53) than intravenous infliximab (**TABLE XXIII**).

Results from our sensitivity analyses were similar to those from our main analyses and did not change the direction of our findings. When restricted to patients aged ≥6 years, the risk of serious infection remained elevated (HR 1.39, 95%CI 1.10-1.76). Likewise, findings were similar when we reduced the gap defining treatment discontinuation from 90 days to 60 days (HR 1.34, 1.05-1.70) but were attenuated when we reduced the gap to 30 days (HR 1.29, 1.00-1.66). The results were again similar when adjusted for hdPS deciles (HR 1.37, 1.08-1.73) and as a continuous variable (HR 1.35, 1.06-1.71).

TABLE XXII
SITE OF INFECTION IN CHILDREN AND YOUNG ADULTS WITH IBD

	Immunomodulators		TNFIs	
	N	**(%)**	**N**	**(%)**
Number of patients with serious infection[ab]	192	(100.0)	236	(100.0)
Skin and skin structure	82	(42.7)	103	(43.6)
Cellulitis	64	(33.3)	78	(33.1)
Postoperative wound infection	14	(7.3)	15	(6.4)
Local infections of skin and subcutaneous tissue	1	(0.5)	5	(2.1)
Septic arthritis	2	(1.0)	3	(1.3)
Breast abscess	0	(0.0)	1	(0.4)
Necrotizing fasciitis	0	(0.0)	1	(0.4)
Gangrene	1	(0.5)	0	(0.0)
Others	46	(24.0)	48	(20.3)
Bacteremia/septicemia	43	(22.4)	45	(19.5)
Device-associated infection	3	(1.6)	3	(1.3)
Respiratory tract system	34	(17.7)	50	(21.2)
Upper respiratory tract infection	18	(9.4)	25	(10.6)
Pneumonia	15	(7.8)	23	(9.7)
Retropharyngeal abscess	1	(0.5)	2	(0.8)
Genitourinary system	28	(14.6)	32	(13.6)
Pyelonephritis/urinary tract infection	28	(14.6)	32	(13.6)
Central nerve system	2	(1.0)	2	(0.8)
Encephalitis	0	(0.0)	1	(0.4)
Meningitis	1	(0.5)	1	(0.4)
Brain abscess	1	(0.5)	0	(0.0)
Cardiovascular system	0	(0.0)	1	(0.4)
Endocarditis	0	(0.0)	1	(0.4)

[a] Patients could have diagnoses of infections at more than one site at their event hospitalization, and the major site of infection was used based on clinical expert opinion.
[b] Serious infection was defined as a non-GI bacterial infection requiring hospitalization.

TABLE XXIII

RISK OF SERIOUS INFECTION AMONG TNFI USERS IN CHILDREN AND YOUNG ADULTS WITH IBD

	N	Total person-years	Number of serious infection[a]	Crude rate of infection[a], event/100 person-years (95% CI)	Crude HR (95% CI)	Adjusted HR (95% CI)[b]
Infliximab (IV)	3,012	2,977	138	4.64 (3.89-5.48)	1.00 (reference)	1.00 (reference)
Adalimumab (SC)	1,218	1,096	65	5.94 (4.58-7.56)	1.07 (0.82-1.41)	1.33 (0.95-1.84)
Certolizumab (SC)	271	227	18	7.92 (4.69-12.51)	2.73 (1.90-3.93)	3.38 (2.25-5.09)
Golimumab (SC)	1	0.6	0	NA	NA	NA
All SC TNFIs	1,490	1,324	83	6.27 (4.99-7.77)	1.20 (1.08-1.34)	1.34 (1.18-1.53)

[a] Serious infection was defined as a non-GI bacterial infection requiring hospitalization.

[b] Adjusted for high-dimensional propensity score (tertile), time-varying use of systemic corticosteroids, and time-varying post-hospitalization windows in the model.

5.5 Discussion

In children and young adults with IBD, initiation of TNFIs was associated with a higher risk of serious infection compared to non-biologic immunomodulators. The crude rate of serious infection was 5.3/100 person-years for TNFIs, and skin infections were the most frequently observed. Among individual TNFI agents, adalimumab presented a non-significantly elevated risk, while certolizumab posed a higher risk of serious infection compared to infliximab. Moreover, subcutaneous TNFIs were associated with a higher risk of serious infection than intravenous infliximab.

To our knowledge, this is the first study to evaluate the risk of serious infection associated with TNFIs in children and young adults with IBD. Previous studies examining the safety of TNFIs were mostly small clinical trials,[42,89] registry studies,[161,162] or retrospective reviews of medical charts[163-165] involving <250 children and limited statistical power.[94] Valid comparison of the risk of serious infection between TNFIs and immunomodulators was therefore difficult. However, in using a large health claims database, our study exploited a sizable cohort of children and young adults with IBD. Consequently, our analysis had sufficient statistical power to assess the incremental increase in the risk of serious infections associated with TNFIs versus immunomodulators as well as the comparative safety among TNFI agents.

Our findings for children and young adults were consistent with those of some studies that evaluated the TNFI-infection association in adults with IBD.[81,82] For example, Lichtenstein and colleagues followed 6,273 adults for 5 years in a Crohn's registry and reported a 1.43-fold (95%CI 1.11-1.84) increased risk of serious infection for infliximab compared to immunomodulators and corticosteroids.[81] Also, analysis of data from a Danish registry revealed an increased risk of serious infection (HR 1.63, 95%CI 1.01-2.63) for TNFIs among IBD patients aged 15-75 years (mean age 44.6 years).[82] However, in both studies, the comparator group had lower disease severity than the group using TNFIs. Thus the risk of serious infection associated

with TNFIs may be overestimated because of confounding by indication. Although not completely free from this bias, our comparator group consisted of users of thiopurines and methotrexate–drugs for which there is more equipoise with TNFIs in treatment selection. Nevertheless, we observed a significant risk of serious infection for TNFIs in children and young adults.

Our large cohort enabled us to compare the risk of serious infection among specific TNFI agents. We found that certolizumab posed a higher risk of infection than infliximab. However, this finding should be interpreted cautiously. Although the risk estimate for certolizumab was high, the sample size for this analysis and the number of patients with infection were small. Our results are inconsistent with those from clinical trials of certolizumab, which reported low (2-3%) rates of serious infection similar to those of other TNFIs.[166,167] However, a network meta-analysis by Singh et al. that included results from 160 randomized trials and 48 extension studies found that certolizumab was associated with higher odds of serious infection than adalimumab and golimumab.[168] They also reported higher but not statistically significant odds of serious infection for certolizumab than infliximab.[168] However, their study combined data from clinical trials of TNFIs used for any indication, and no specific analysis for IBD patients was conducted.

Reasons for the higher risk of serious infection observed for certolizumab were not discussed by Singh et al. Certolizumab, an antibody Fab fragment conjugated with polyethylene glycol, is the only TNFI with pegylation. The unique structure of certolizumab results in different pharmacodynamic and pharmacokinetic properties, and certolizumab has higher affinity to TNF and greater potency than adalimumab and infliximab.[169] These differences could translate into greater risk of adverse effects.

We found that subcutaneously administered TNFIs showed a higher risk of serious infection than intravenous TNFIs. This finding conflicts with that of Liu et al., who reported no difference in infection rates between subcutaneous (adalimumab and certolizumab) and

intravenous (infliximab) TNFIs in an observational study of 1,030 adults with CD.[170] The discrepancy may result from dissimilar definitions of infection. We defined serious infections as infection-related hospitalizations, while Liu appeared to identify infections in either inpatient or outpatient settings. The higher risk of infection associated with subcutaneously administered TNFIs might stem from more frequent injections, resulting in skin infections. However, when restricting the analysis to skin infections, we found no difference between subcutaneous and intravenous TNFIs.

Several potential study limitations should be acknowledged. First, insurance claims data pose various inherent issues when used for research.[171] One is potential misclassification of outcomes and exposures. To minimize potential misclassification of the outcome, we used a previously validated algorithm with high sensitivity.[145] In addition, we used prescription records and outpatient claims to define exposure status. These claims indicated that a prescription was dispensed but not that the patient actually administered the medication. However, use of such claims has been validated for exposure identification.[127] Because infliximab is administered in clinics, we had greater confidence that exposure occurred. Finally, because the database we used was primarily comprised of claims from commercially-insured individuals, our findings may not be generalizable to those with other forms of insurance, including Medicaid.

Unmeasured confounding is also common in studies using administrative claims data. Specifically, lack of clinical or laboratory information about patients limited our ability to adjust for severity of illness. IBD severity may be linked to high risk of infection.[172] Additionally, physicians may consider TNFIs more effective and prescribe them preferentially to patients with more severe disease, thus inducing a selection bias, or confounding by indication. As a result, the observed higher risk of serious infection may be attributable to IBD rather than TNFIs. Conversely, because of the FDA warning and other information on the potential association between TNFIs and infection, physicians may have avoided prescribing TNFIs and recommended immunomodulators for patients susceptible to infections. Thus, our results may

have underestimated the relationship between TNFIs and infection. In either case, to minimize this bias, we employed hdPS models to control for a large number of proxy indicators that directly or indirectly reflected disease severity.[38,39] We also used a new-user design to ensure greater homogeneity between the treatment groups in terms of severity of IBD.

5.6 Conclusion

In conclusion, compared to thiopurines and methotrexate, initiation of TNFIs was associated with a higher risk of non-GI bacterial infection requiring hospitalization among children and young adults with IBD. Our study findings support the FDA black box warning for children and young adults. In addition, individual TNFIs may pose different risks of serious infection, as may different routes of administration. Future studies should confirm our findings, especially the comparison among TNFIs, to provide a more definite comparative safety profile for clinicians and patients selecting a TNFI agent.

6. OVERALL CONCLUSIONS

In 2008, the FDA required TNFI manufacturers to include a black box warning in the product label for serious infections leading to hospitalization or death.[66] While the warning applied to both adults and children, most studies evaluating the TNFI-infection association were conducted for adults, and the findings conflicted. It is important for the FDA to identify potential drug safety issues and to warn prescribers and patients. Warnings such as that for TNFIs may make physicians more cautious and may even reduce the use of the drugs. Consequently, there is a possibility that patients who need TNFIs will not receive them. This type of situation is particularly problematic when the warning is based on limited evidence or when it is extended to groups for whom it has not been proven to apply. This was clearly the case for TNFIs.

More objective evidence was needed both to evaluate the utilization of TNFIs after the FDA warning and to assess the risk of serious infection associated with TNFIs—especially in children and young adults, for whom the evidence was most lacking. The research described in this dissertation provided the evidence needed. Specifically, this study examined the prescribing patterns and risk of serious infection associated with TNFIs in children and young adults with JIA/RA and IBD. Four retrospective cohort studies were conducted using the Truven MarketScan Commercial Claims and Encounters database to address the gaps in the literature and to provide evidence to better inform prescribers and patients considering the risk-benefit profile of TNFIs.

The first two aims of this dissertation were to examine the utilization of TNFIs in children and young adults with JIA/RA and IBD, respectively. We conducted separate studies in these two populations. In a cohort of children and young adults newly diagnosed with JIA/RA, we found that 18.6% started treatment with TNFIs versus DMARDs and that etanercept was the most commonly used TNFI. The time from JIA/RA diagnosis to receipt of the first TNFI therapy

appeared to be shorter for patients diagnosed in more recent years. In addition, among TNFI users, the rate of earlier initiation of TNFIs (i.e., initiation of TNFIs before traditional DMARDs, or the top-down approach) was 39.1%. However, the use of the more aggressive top-down approach was not aligned with the recommendations in current clinical guidelines and literature for using a combination of TNFIs and DMARDs.[16,47-49,119,120] Moreover, among the early TNFI users, we found a higher proportion of monotherapy than of combination therapy. The earlier use of TNFIs and the frequency of monotherapy with TNFIs suggest that physicians were not made excessively cautious by the FDA warning.

In children and young adults with newly diagnosed IBD, 27.6% were TNFI initiators, and infliximab was the most commonly used TNFI. Similar to the findings for the JIA/RA cohort, time to TNFI initiation was shorter for patients diagnosed in more recent years. In addition, among patients taking TNFIs, the rate of use of the top-down approach increased from 31.4% in 2009 to 49.8% in 2013 ($p<0.0001$). Moreover, in these top-down patients, 74% received monotherapy without any augmentation or concomitant use of 5-ASA or thiopurines. Again, we found that TNFIs were used more aggressively in children and young adults with IBD over the study period; more patients were treated with TNFIs early in the disease course. Interestingly, the FDA warning did not seem to slow the use of this aggressive treatment strategy, which was supported by recent literature. However, prescribing of a TNFI alone as opposed to a TNFI in combination with other immunomodulators remains controversial. Further studies are needed to evaluate the effectiveness of TNFI monotherapy as opposed to combined therapy as well as the associated clinical consequences in children and young adults with IBD.

The third and fourth aims of this dissertation were to evaluate the risk of serious infection associated with TNFIs in children and young adults with JIA and IBD, respectively. Again we conducted separate studies in these two populations. We followed 2,495 children with JIA for a total of 1,810 person-years and found that the rate of serious infection was 2.7 per 100 person-years for TNFIs and 1.28 per 100 person-years for DMARDs. Employing a new-user design, we

found that TNFI monotherapy was associated with a 2.7-fold increase in the risk of serious bacterial infection compared to DMARDs alone. Notably, the FDA black box warning for TNFIs stated that most infections developed when the drugs were used in combination with other immunosuppressants, such as DMARDs or corticosteroids.[7,148] However, our study provided evidence that TNFI monotherapy is also associated with an increased risk of infection compared to DMARDs while controlling for corticosteroid use and other confounders. In addition, our study confirmed the risk of infection associated with TNFI use in children with JIA.

In another study, we followed 10,838 children and young adults with IBD for 9,849 person-years and observed 5.25 infections per 100 person-years for TNFIs and 3.59 per 100 person-years for immunomodulators (methotrexate and thiopurines). In addition, new use of TNFI monotherapy was associated with a higher risk of non-GI bacterial infection requiring hospitalization (HR 1.36, 95%CI 1.08-1.72) compared to immunomodulator initiation. Again, our findings supported the applicability of the FDA warning to children and young adults with IBD.

Moreover, we found that the risk of serious infection differed by individual TNFIs and route of administration. Compared to infliximab, certolizumab was associated with a significant 3.38-fold (95%CI 2.25-5.09) increase in the risk of serious infection. Subcutaneous TNFIs were associated with a higher risk of infection (HR 1.34, 95%CI 1.18-1.53) versus intravenous infliximab. However, our study findings should be interpreted with caution. Although the risk estimate for certolizumab was high, the sample size for this analysis and the number of patients with infection were small. The unique structure of certolizumab may explain the observed higher risk, as it has different pharmacodynamics and pharmacokinetic properties and greater potency than other TNFIs.[169] However, future studies may be useful to confirm our findings about comparative safety among individual TNFI agents.

While our results suggest increased risk for infection associated with TNFIs compared to DMARDs or immunomodulators, clinicians and patients should consider this risk in light of the benefits of TNFIs. Specifically, TNFIs are highly effective drugs that have been shown to

improve symptoms and quality of life, to induce remission, and to be associated with less use of corticosteroids in both JIA/RA and IBD patients.[39,40,106] In order to balance the risks and benefits associated with TNFIs, both the US FDA and European Medicines Agency have developed risk mitigation strategies for these biologics based primarily on adult studies. However, similar risk management guidance for children is lacking.[91,92] Our findings provide evidence that these agencies could adapt their risk management plans for application to children under TNFI treatment. Such plans could incorporate appropriate screening, monitoring, and even withholding of treatment to mitigate the potential harm posed by TNFIs to children with JIA and IBD.

In summary, among children and young adults with JIA/RA and IBD, this study revealed that TNFIs were used earlier in the disease course and that the rate of monotherapy was high among early TNFI users. In addition, the study found that TNFI initiation was associated with a higher risk of serious infection in both JIA and IBD patients. Moreover, for children and young adults with IBD, comparative safety analyses indicated that the risk of serious infection differed among individual TNFIs and by route of administration.

The study analyses characterized the utilization of TNFIs and indicated that despite the FDA warning, a more aggressive treatment approach has emerged for children and young adults with JIA/RA and IBD. However, study findings support the FDA warning about TNFI-associated serious infection in children with JIA and IBD. This dissertation provides insights into how TNFIs are being used and informs decision-making about use of these drugs–particularly with respect to the balance between the benefits and risks of TNFIs. Nevertheless, further studies might be helpful to confirm the findings for this vulnerable, under-represented population, especially the comparative analysis results for serious infection among individual TNFIs, in order to provide a more definitive comparative safety profile for clinicians and patients selecting a TNFI agent.

APPENDIX

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Wolters Kluwer

Title: Top-down Versus Step-up Prescribing Strategies for Tumor Necrosis Factor Alpha Inhibitors in Children and Young Adults with Inflammatory Bowel Disease.

Author: Wan-Ju Lee, Leslie Briars, Todd Lee, et al

Publication: Inflammatory Bowel Disease

Publisher: Wolters Kluwer Health, Inc.

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ABSTRACTS: Lee WJ, Briars LA, Lee TA, Calip GS, Suda KJ, Schumock GT. Top-down versus step-up prescribing strategies for tumor necrosis factor alpha inhibitors in children and young adults with inflammatory bowel disease. International Conference on Pharmacoepidemiology & Therapeutic Risk Management (ICPE) 32nd Annual Meeting, Dublin, Ireland, 2016.

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