Biologic Therapy in Crohn’s Disease: The Tricky Tincture of Timing

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February 28, 2014

Learning Objectives

1. Describe the pathophysiology and traditional treatment approach for Crohn’s disease
2. Identify proposed alternative treatment strategies for Crohn’s disease
3. Discuss outcomes in Crohn’s disease patients treated with an early biologic strategy
4. Summarize a plan for the timing of biologic use in Crohn’s disease patients
CROHN’S DISEASE OVERVIEW

I. Definition and epidemiology
   A. Crohn’s disease (CD) and ulcerative colitis (UC) are chronic inflammatory disorders primarily of the gastrointestinal tract which are classified as inflammatory bowel disease (IBD)
   B. Incidence and prevalence of CD worldwide have risen over the last several decades

<table>
<thead>
<tr>
<th>Table 1. Epidemiology of Crohn’s Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incidence (per 100,000/year)¹ ²</td>
</tr>
<tr>
<td>0.03 – 15.5</td>
</tr>
<tr>
<td>Prevalence (per 100,000)³⁴⁵</td>
</tr>
<tr>
<td>3.6 – 214</td>
</tr>
<tr>
<td>Female : Male³⁶⁷</td>
</tr>
<tr>
<td>0.82 : 1 (pediatrics)</td>
</tr>
<tr>
<td>1.18 : 1 (adults)</td>
</tr>
<tr>
<td>Age of Onset²</td>
</tr>
<tr>
<td>Most common between 10 – 30 or 60 – 80 years of age, but can be any age</td>
</tr>
<tr>
<td>Ethnicity²</td>
</tr>
<tr>
<td>Jewish &gt; Non-Jewish Caucasian &gt; Black &gt; Asian</td>
</tr>
</tbody>
</table>

II. Etiology and pathogenesis
   A. Exact etiology is unknown, but is believed to arise from genetic, immunologic, and environmental contributions
      i. Genetics⁵
         a. Familial aggregation – 35% of monozygotic pairs but only 3% of dizygotic pairs were concordant for IBD in a German nationwide study
         b. Genome wide association studies link inflammatory extraintestinal symptoms and associated autoimmune diseases with susceptibility loci
         c. First-degree relatives of patients with IBD may have a 20-fold increase in risk²
      ii. Immunobiology²⁵ – the immune theory hypothesizes an inappropriate response of the immune system in CD
         a. Autoimmune mechanisms
            1. Abnormal adaptive immune response leads to chronic inflammation
            2. Autoantibodies to abnormal structures on colon epithelial cells
         b. Non-autoimmune mechanisms
            1. Intestinal immune system reacts to external antigens but is usually tolerant of the normal commensal microbiota (intestinal homeostasis)
               a. Hypothesis – inappropriate inflammation and changes in microbiome (dysbiosis) develop due to a disruption of the intestinal homeostasis
            2. The protective mucus biofilm may become insufficient in CD due to a reduced expression of the mucin gene MUC1 in the terminal ileum
            3. Changes in tight-junctions between intestinal epithelial cells may make the intestine “leaky”, increasing access of intestinal antigens to immune cells
            4. Dysregulation of cytokines – an imbalance between helper T cells (Tₕ) and tolerance-inducing regulatory T cells (Tₕₑₑₑ) promotes the secretion of interferon γ, tumor necrosis factor α (TNF-α) and interleukin 12, leading to intestinal inflammation and damage
               a. Tₕ₁ cell activity is upregulated in CD
               b. Dendritic cell function of activating Tₑₑₑ cells may be impaired in CD
      iii. Environmental factors⁵
         a. Infections
            1. Gastroenteritis – CD has been shown to occur after gastric infections
               a. Bacterial chemotactic factors can attract inflammatory immune cells
               b. Some bacteria produce toxins that can cause direct mucosal damage
2. *Clostridium difficile* infections can lead to more frequent relapses and an increased severity of IBD
3. Increased numbers of intramucosal bacteria are present in CD patients
4. Animal studies have shown that viral infections can potentially convert a genetic predisposition to IBD into a disease outbreak

b. Smoking
   1. Early exposure to tobacco smoke (first and second hand) has been shown to increase the risk of developing CD
   2. Patients who quit smoking have decreased disease severity

c. Other environmental factors – associations noted but evidence is conflicting
   1. Stress – many patients endorse increased flares/severity with stress
   2. Drugs – NSAIDs may trigger flares; oral contraceptives
   3. Diet – Cow’s milk, refined sugar, dietary fat

III. Clinical and pathological characteristics

A. Common Features of CD

<table>
<thead>
<tr>
<th>Table 2. Common Features of Crohn’s Disease</th>
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<tbody>
<tr>
<td>Presenting symptoms</td>
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<tr>
<td>Location</td>
</tr>
<tr>
<td>Pattern of GI involvement</td>
</tr>
<tr>
<td>Rectal involvement</td>
</tr>
<tr>
<td>Ileal involvement</td>
</tr>
<tr>
<td>Strictures or fistulas</td>
</tr>
<tr>
<td>Depth of inflammation</td>
</tr>
<tr>
<td>Recurrence post-surgery</td>
</tr>
</tbody>
</table>

*N/V/D = nausea/vomiting/diarrhea, GI = gastrointestinal*

B. Extraintestinal manifestations of CD
   1. Ocular (2% – 29% occurrence) – inflammation of the iris, uvea, episclera, and conjunctiva
   2. Oral (4% - 20% occurrence) – aphthous stomatitis, pyostomatitis vegetans
   3. Hepatobiliary – primary sclerosing cholangitis (PSC), cholelithiasis, hepatic steatosis
   4. Anemia (up to 74%) – chronic blood loss, malnutrition, hemolysis, myelosuppression
   5. Coagulopathies – increased risk for venous thromboembolism (VTE)
   6. Osteoporosis/metabolic bone disease – increased risk in IBD patients due to corticosteroid use, chronic inflammation, and calcium & vitamin D deficiencies
   7. Joints – typically asymmetric, large joints, and severity fluctuates with IBD activity
   8. Dermatologic Complications – Erythema nodosum, pyoderma gangrenosum

C. Activity and course of disease
   1. Classifying activity of disease – there is no classification system universally utilized for all types of CD; the following classifications are most commonly used:
      a. Crohn’s Disease Activity Index (CDAI) – used for luminal, non-fistulizing CD to determine response to therapy and onset of remission
      b. Practice guidelines classify CD activity based on signs and symptoms, disease activity and location, and phenotype (penetrating, stricturing, or inflammatory).

The following are general categories:
1. **Mild-Moderate** (CDAI 150 – 220) – ambulatory patients with no dehydration, weight loss, abdominal tenderness, mass, or obstruction

2. **Moderate-Severe** (CDAI 220 – 450) – fever, weight loss, dehydration, abdominal tenderness, N/V, obstruction, anemia; includes mild-moderate presentations that fail to respond to initial treatment

3. **Severe-Fulminant** (CDAI > 450) – persistent symptoms or toxicity despite steroid or biologic treatment or intractable symptoms plus cachexia, rebound tenderness, obstruction, or abscess

ii. **Disease course**
   a. Periods of disease exacerbation alternating with periods of remission
   b. A large percentage of patients will have a favorable course with only approximately 50% requiring initiation of corticosteroid therapy
   c. Depending on severity, presentations can range from intractable symptoms to those with longer periods of remission

### IV. Diagnosis of IBD

A. Based on a combination of clinical presentation, imaging, and laboratory findings

B. Intestinal imaging
   i. Endoscopy is the gold standard for all patients with suspected IBD – cannot detect IBD located only in the small intestines
      a. Ileocolonoscopy – identifies disease in the terminal ileum and colon; CD lesions appear thickened, fatty, edematous with “cobblestone” or “fried egg” appearance
      b. Esophagastroduodenoscopy (EGD) – can identify more proximal lesions in CD in the esophagus, stomach, and the first part of the duodenum
      c. Biopsies are taken and examined for mucosal inflammation and damage
   ii. Small bowel follow through
      a. Used to identify small bowel disease if EGD and ileocolonoscopy are negative
      b. Barium contrast is ingested and X-rays are taken to visualize small intestines

C. Laboratory findings
   i. No laboratory tests can specifically establish a diagnosis of IBD
   ii. Biomarkers are used as indicators of inflammation but are nonspecific
      a. Erythrocyte Sedimentation Rate (ESR)
      b. C-Reactive Protein (CRP)
      c. Fecal granulocyte proteins lactoferrin and calprotectin

### V. Non-pharmacologic treatments

A. Nutritional support
   i. Patients are often malnourished due to impaired absorption of nutrients, impaired digestion, and anorexia secondary to nausea and pain
   ii. Exclusion diets to eliminate certain foods thought to exacerbate disease are not routinely recommended; may result in unnecessarily excluding nutritious foods
   iii. Enteral nutrition can aid in reducing intestinal inflammation and cytokine production which promotes healing and induction of remission

B. Surgery
   i. May be necessary due to severe inflammation, when medical management is unsuccessful, or with complications including perforation, strictureing, uncontrolled hemorrhaging, and toxic megacolon
   ii. Recurrence after surgical resection is common
VI. Pharmacologic therapies by class
   A. Aminosalicylates (AS)—commonly used but no longer recommended by CD guidelines
      Several dosage formulations of 4 drugs with different brand names:
      Sulfasalazine (Azulfidine®) – [sulfonamide antibiotic + mesalamine]
      Mesalamine (Canasa®, Rowasa®, Pentasa®, Lialda®, Asacol®, Asacol HD®)
      Balsalazide (Colazal®)
      Olsalazine (Dipentum®, Apriso®)
      MOA: acts topically in the gut; mechanism not fully understood but has anti-inflammatory
effects related to inhibition of cyclooxygenase and lipoxygenase enzymes (decreases
prostaglandin and leukotriene production), interference with TNF-α, and suppression
of IL-1 production
   B. Antibiotics – some evidence for inducing remission and decreasing relapses in CD
      Antibiotics, Ciprofloxacin, Rifamycin derivatives
      MOA: unknown, but have anti-inflammatory and immunosuppressive properties
      Adverse Effects: antibiotic resistance and increased risk of C. difficile, especially with long-
term use
   C. Corticosteroids (CS) – induction treatment in IBD (70% – 80% response)
      Prednisone, prednisolone, methylprednisolone, budesonide, hydrocortisone
      MOA: exact mechanism unknown but corticosteroids suppress the immune system and
inhibit cytokines and prostaglandins
      i. Do not work for maintenance of remission and systemic use has significant long-term
side effects and complications (e.g. increased risk of infection)
      ii. Budesonide enteric-coated – reduced toxicity due to high first pass effect; useful for
distal ileal involvement in CD or right-sided colon disease
      iii. Hydrocortisone rectal suspension – useful in proctitis, proctosigmoiditis, and left-sided
colon disease
      Adverse Effects: adrenal suppression, glucose intolerance, hypertension, sodium/water
retention, osteoporosis, cataracts, impaired wound healing
   D. Immunomodulators – used to maintain remission and reduce steroid use
      Azathioprine, mercaptopurine, methotrexate, cyclosporine, tacrolimus
      MOA: Suppression of the immune system by different mechanisms
      i. Traditionally reserved for patients that fail aminosalicylate therapy, are refractory to
steroids, or have become steroid-dependent
      ii. May induce remission but are not preferred due to their slow onset of action (weeks to
months) – must be used with another agent with faster onset
      iii. Cyclosporine and tacrolimus are reserved for severe or refractory cases
      Adverse Effects
      i. Azathioprine and Mercaptopurine: pancreatitis, bone marrow suppression, nausea,
diarrhea, rash, hepatotoxicity; Risk of hepatosplenic T-cell lymphoma (especially in
young male patients) with increased risk if combined with anti-TNF biologics
      ii. Methotrexate: bone marrow suppression, nausea, diarrhea, rash, pneumonitis,
pulmonary fibrosis, hepatotoxicity, neurotoxicity
### Table 3. Biologic Agents Used in Crohn’s Disease

<table>
<thead>
<tr>
<th>Class</th>
<th>Tumor Necrosis Factor α Inhibitors</th>
<th>α4 Integrin Inhibitor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medication</td>
<td>Infliximab (Remicade®)</td>
<td>Adalimumab (Humira®)</td>
</tr>
<tr>
<td>FDA Approved Indications*</td>
<td>CD, UC</td>
<td>CD, UC</td>
</tr>
<tr>
<td>Antibody Type</td>
<td>Chimeric (Mouse) Human 75%</td>
<td>Human 100%</td>
</tr>
<tr>
<td>Mechanism of Action</td>
<td>Binds TNF-α, inhibiting its effects: Normal TNF-α Functions Inhibited - Induces inflammatory cytokines → ↓ Inflammation - Increases VEGF → ↓ Angiogenesis - Increases adhesion molecules → ↓ Immune cell infiltration</td>
<td>Effect of Inhibition Blocks integrin binding to vascular receptors inhibiting the adhesion and transmigration of leukocytes into tissues (not specific for gut tissue)</td>
</tr>
<tr>
<td>Administration</td>
<td>IV infusion</td>
<td>Subcutaneous</td>
</tr>
<tr>
<td>Dosing</td>
<td>I: 5 mg/kg on weeks 0, 2, 6</td>
<td>I: 160 mg on week 0, 80 mg on week 2</td>
</tr>
<tr>
<td></td>
<td>M: Every 8 weeks</td>
<td>M: 40 mg every other week</td>
</tr>
<tr>
<td>Black Box Warnings</td>
<td>Infection: ↑ risk of serious and opportunistic bacterial, viral, and fungal infections</td>
<td>Cancer: ↑ in children/teenagers; hepatosplenic T-cell lymphoma in young males taking AZA or 6-MP</td>
</tr>
</tbody>
</table>

*All are approved for moderately to severely active forms of the corresponding disease with inadequate response to conventional therapy (a full and adequate course of CS and/or immunomodulator therapy)
6-MP=mercaptopurine, AZA=azathioprine, CD=Crohn’s disease, I=Induction, M=maintenance, TNF-α=tumor necrosis factor alpha, UC=ulcerative colitis, VEGF=vascular endothelial growth factor

### Adverse effects

1. Infusion reactions (infliximab & natalizumab): hypotension, fever, chills, urticaria, pruritus; can pretreat with acetaminophen and diphenhydramine
2. Delayed hypersensitivity: fever, rash, myalgia, headache, or sore throat 3 – 10 days after administration
3. Exacerbation of heart failure: relatively contraindicated in New York Heart Association class III/IV
4. Antibody induction: up to 50% of patients can develop antinuclear antibodies
5. Bone marrow suppression (pancytopenia)
6. Hepatitis: can cause reactivation of hepatitis B virus; autoimmune hepatitis
7. Vasculitis with CNS involvement
TREATMENT STRATEGIES AND GUIDELINES

I. Traditional treatment approach (step-up strategy)
   A. Less toxic (but often less effective) medications are used initially and those with higher risk profiles are added as disease severity progresses
      i. Aminosalicylates first-line for mild disease
      ii. Corticosteroids first-line for moderate to severe disease
      iii. Immunomodulators added when patient becomes CS dependent or resistant
      iv. Biologics added when immunomodulators and CS are no longer effective
   B. Problems with the traditional strategy
      i. Focuses on treatment of acute flares and maintenance of clinical remission instead of prevention of disease progression
      ii. CS use is effective short-term but a large percentage of patients become refractory or dependent and the side effects become a major problem with prolonged use
      iii. Reserving biologics until the disease progresses has not been shown to reduce complications or the need for surgery in retrospective studies

II. Proposed alternative treatment strategies
   A. Accelerated step-care – starting treatment in early CD with an immunomodulator plus a CS then adding a biologic upon disease progression
   B. Top-down strategies – use biologics early in hopes of preventing disease progression
      i. Start an immunomodulator plus a biologic as combination therapy initially
      ii. Start biologic monotherapy early for induction and maintenance

III. Guidance from clinical practice guidelines
   A. American College of Gastroenterology
      i. A large percentage of patients will have a mild disease course and can be controlled with occasional treatment using CS, metronidazole, or ciprofloxacin
      ii. Moderate – Severe CD
         a. Anti-TNF biologics have been shown to be effective for induction and maintenance and are generally recommended for use in patients that have not responded to aminosalicylates, antibiotics, CS, or immunomodulators
   B. European Crohn’s and Colitis Organization
      i. Moderate – severe localized CD
         a. Anti-TNF biologics should generally be reserved for CS refractory or dependent patients while CS and immunomodulators are first line treatments
         b. Early use of anti-TNF biologics is not directly recommended but is noted as an approach to minimize CS use
      ii. Extensive small bowel CD
         a. Early anti-TNF biologic use can be considered in extensive (> 100 cm) disease for patients with clinical indicators of poor prognosis

DEFINING THE CLINICAL QUESTION

I. Preventing disease progression
   A. Focus on therapies that will prevent complications and the need for surgery
   B. Comparisons with rheumatoid arthritis (RA)
      i. Earlier use of disease-modifying antirheumatic drugs (immunomodulators and biologics) has been successful in preventing clinical and radiologic progression of RA
      ii. This early use of immunomodulators or biologics has also been shown to prevent erosions and joint-space narrowing in patients who do not have these complications yet
II. Clinical question: Is earlier use of biologics in moderate – severe CD better?

A. Definition of “earlier use”
   i. There is no single definition used uniformly in the literature, but there are two that are seen in several studies:
      a. Early in disease course: time since diagnosis
      b. Early in treatment course: naïve to immunomodulators/biologics or using them earlier than would be done in the conventional step-up treatment approach

B. Measuring the benefit (defining what is “better”)
   i. Short-term outcome measures
      a. Response and remission rates
      b. Corticosteroid use
      c. Relapse rates
   ii. Long-term outcome measures
      a. Complications
      b. Need for surgery
      c. Hospitalizations
   iii. Mucosal healing (MH)
      a. Important treatment goal increasingly studied in clinical trials
      b. Interpretation of studies is difficult due to lack of a standard definition and timing of endoscopic evaluation
      c. Definition of MH used as an outcome measure in several clinical trials: complete absence of all inflammatory and ulcerative lesions
      d. Anti-TNF biologics can induce rapid and sustained MH
         1. MH as a primary outcome measure in the EXTEND trial
            a. After the first 12 weeks, MH was seen in 27.4% of adalimumab patients and 13.1% of placebo patients (p = 0.056)
            b. At 52 weeks in 129 patients, MH was seen in 24.2% adalimumab patients and 0% of placebo patients (P < 0.001)
      e. Complete MH (as compared to no or incomplete healing) in early CD two years after initiation of therapy was associated with significantly higher rates of CS-free clinical remission during years three and four

III. Safety concerns of immunosuppressive therapy

A. Infection
   i. Overall risk of infection may be increased by immunomodulators and biologics
   ii. A meta-analysis of placebo-controlled trials enrolling 5,356 patients concluded that the use of TNF antagonists did not increase the risk of serious infections or death
   iii. Observational case-control study of opportunistic infections from the Mayo Clinic
      a. CS, AZA, and infliximab use were each independently associated with a significantly increased risk of opportunistic infection
      b. Combined treatment with two or three of these medications resulted in an OR of 14.5 (95% CI, 4.9 to 43)
      c. Patients > 50 years old had three times more risk of serious opportunistic infection
   iv. TREAT registry – study of the long-term safety of infliximab and other treatments
      a. Infliximab use was associated with an increased risk of serious infection
      b. Prednisone was the only immunosuppressant associated with increased mortality

B. Cancer
   i. Patients with colonic CD have an increased risk of colon cancer
ii. AZA and 6-MP are associated with an increased risk of non-Hodgkin’s lymphoma\textsuperscript{19}

iii. In all cases of hepatosplenic T-cell lymphoma reported in IBD, patients have had at least 2 years of exposure to thiopurine therapy alone or in combination with TNF antagonists\textsuperscript{19}

iv. TREAT registry\textsuperscript{18}
   a. No overall increase in cancer incidence observed in patients receiving infliximab
   b. No significant increase in the incidence of lymphoma, non-melanoma skin cancer, or solid tumors was seen relative to the general population

### EARLY BIOLOGIC THERAPY FOR CD IN THE LITERATURE

<table>
<thead>
<tr>
<th>Purpose</th>
<th>To analyze the efficacy and safety of certolizumab pegol based on duration of CD at baseline</th>
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</thead>
<tbody>
<tr>
<td>Design</td>
<td>• Post hoc analysis of data from the PRECiSE 2 trial</td>
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<tr>
<td></td>
<td>• A 6 week open-label certolizumab pegol lead-in identified patients with a clinical response</td>
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<tr>
<td></td>
<td>• These patients were randomized to the double-blind, placebo-controlled phase which continued through week 26</td>
</tr>
<tr>
<td>Population</td>
<td>Ages: Adults ≥ 18 years old with CD diagnosis for &gt; 3 months</td>
</tr>
</tbody>
</table>

#### Table 4. PRECiSE 2 Post hoc Schreiber S, Colombel JF, Bloomfield R, et al.
Increased response and remission rates in short-duration CD with subcutaneous certolizumab pegol: an analysis of PRECiSE 2 randomized maintenance trial data. Am J Gastroenterol. 2010;105(7):1574-1582\textsuperscript{26}

<table>
<thead>
<tr>
<th>Duration of CD*</th>
<th>Activity, mean ± SD (Baseline CDAI)**</th>
<th>Prior Treatment History</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 1 year (n = 54)</td>
<td>291.1 ± 48.7</td>
<td>All types of previous treatment histories were allowed</td>
</tr>
<tr>
<td>≥ 1 to &lt; 2 years (n = 42)</td>
<td>295.4 ± 57.0</td>
<td></td>
</tr>
<tr>
<td>≥ 2 to &lt; 5 years (n = 100)</td>
<td>303.9 ± 66.3</td>
<td></td>
</tr>
<tr>
<td>≥ 5 years (n = 229)</td>
<td>307.6 ± 61.6</td>
<td></td>
</tr>
</tbody>
</table>

* Stratified by time since diagnosis at baseline
** All patients had moderate – severe CD based on CDAI between 220 and 450

#### Methods
- Induction with certolizumab pegol 400 mg SC was given at weeks 0, 2, & 4
- Patients with a clinical response at week 6 (reduction in CDAI of ≥ 100 points, CR100) continued into the randomized maintenance phase
- Maintenance was certolizumab pegol or placebo given every 4 weeks from weeks 8 to 24

#### Results
- Response defined as CR100; Remission defined as CDAI ≤ 150
- Independent predictors of week 26 response to certolizumab pegol
  - Shorter duration of CD, < 2 years (p < 0.006)
  - No prior resection, no prior infliximab use, and no corticosteroid use on entry
- Induction of response & remission by open-label treatment at week 6
  - No trends identified across disease duration
  - Duration subgroup rates were similar to the rates in the overall population

<table>
<thead>
<tr>
<th>Response Rates at Week 6 (%)</th>
<th>Remission Rates at Week 6 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall Population</td>
<td>62.5</td>
</tr>
<tr>
<td>&lt; 1 year</td>
<td>61.7</td>
</tr>
<tr>
<td>≥ 1 to &lt; 2 years</td>
<td>58.0</td>
</tr>
<tr>
<td>≥ 2 to &lt; 5 years</td>
<td>65.4</td>
</tr>
<tr>
<td>≥ 5 years</td>
<td>62.3</td>
</tr>
</tbody>
</table>

- Maintenance of response & remission at week 26
  - Response and remission rates were inversely related to disease duration
  - Response rate for the < 1 year subgroup (89.5%) was statistically higher than the response rate for the > 5 year subgroup (57.3%); p < 0.05
Remission rates showed similar trend as response rates but did not achieve significance

<table>
<thead>
<tr>
<th>Response Rates at Week 26 (%)</th>
<th>Remission Rates at Week 26 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Certolizumab</td>
<td>Placebo</td>
</tr>
<tr>
<td>All Patients</td>
<td>62.8</td>
</tr>
<tr>
<td>&lt; 1 year</td>
<td>89.5</td>
</tr>
<tr>
<td>≥ 1 to &lt; 2 years</td>
<td>75.0</td>
</tr>
<tr>
<td>≥ 2 to &lt; 5 years</td>
<td>62.2</td>
</tr>
<tr>
<td>≥ 5 years</td>
<td>57.3</td>
</tr>
</tbody>
</table>

<sup>a</sup>p<0.05, <sup>b</sup>p<0.01, <sup>c</sup>p<0.001

- Safety
  - Overall incidence of any adverse event was not affected by disease duration at baseline
  - A trend toward more serious events in longer CD duration was noted
  - The incidence of serious AEs was lower in certolizumab patients than placebo patients
  - There were no serious AEs in certolizumab treated patients with CD duration < 2 years

** Authors’ Conclusions**
- The efficacy and safety of certolizumab pegol for the treatment of CD over 26 weeks is independent of disease duration
- Treatment outcomes with certolizumab pegol may be better in CD of shorter duration

** Strengths **
- Included all types of prior treatment history and allowed concomitant non-biologic treatments of CD to be continued
- Open-label 6 week lead-in helped identify responders and exclude primary non-responders

** Weaknesses **
- Post hoc analysis
- Relatively short 26 week study does not provide long-term outcome data

** Take Home Points **
- CD duration may be an independent predictor of response to certolizumab pegol
- Patients with early CD (< 1 year) may have higher rates of maintaining response with certolizumab pegol maintenance treatment than those with longer duration (≥ 5 years)

AE=adverse effects, CD=Crohn’s disease, CDAI=Crohn’s disease activity index, CR100= reduction in CDAI of ≥ 100 points, SC=subcutaneous, SD=standard deviation

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**Table 5. CHARM/ADHERE Post hoc Schreiber S, Reinisch W, Colombel JF, et al.**

<table>
<thead>
<tr>
<th>Purpose</th>
<th>Assess the relationship between CD duration and remission rates in moderately to severely active CD patients treated with adalimumab</th>
</tr>
</thead>
<tbody>
<tr>
<td>Design</td>
<td>Post hoc analysis of data from the CHARM trial and the follow-on ADHERE trial</td>
</tr>
<tr>
<td></td>
<td>CHARM trial – a 56 week, randomized, double-blind, placebo-controlled trial of adalimumab treatment for induction and maintenance</td>
</tr>
<tr>
<td></td>
<td>ADHERE trial – patients from the CHARM study could continue in this open-label study of continued adalimumab maintenance for a total of 3 years (from the beginning of CHARM)</td>
</tr>
</tbody>
</table>

**Population**
- Ages: Adults 18 to 75 years old with CD diagnosis for > 4 months

<table>
<thead>
<tr>
<th>Duration of CD*</th>
<th>Activity (Mean Baseline CDAI)**</th>
<th>Prior Treatment History</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 2 year (n = 93)</td>
<td>298.8</td>
<td>All types of previous treatment histories were allowed</td>
</tr>
<tr>
<td>≥ 2 to &lt; 5 years (n = 148)</td>
<td>302.9</td>
<td>All types of previous treatment histories were allowed</td>
</tr>
<tr>
<td>≥ 5 years (n = 536)</td>
<td>315.5</td>
<td>All types of previous treatment histories were allowed</td>
</tr>
</tbody>
</table>

* Stratified by time since diagnosis at baseline
** All patients had moderate – severe CD based on CDAI between 220 and 450
Methods

- Induction with adalimumab 80 mg SC week 0 and 40 mg SC week 2 was given to all patients
- On week 4 patients were randomized to 3 groups: adalimumab 40 mg SC every other week, adalimumab 40 mg SC weekly, and placebo for 52 weeks (total study period = 56 weeks)
- For patients that continued in the ADHERE follow-on study, those still on blinded treatment were changed to adalimumab 40 mg every other week (with the option to increase to weekly if required) and those already on open-label adalimumab continued their current dose
- For the analysis of remission for patients continuing in ADHERE, only patients randomized to adalimumab in CHARM were included (total of 3 years adalimumab maintenance treatment)

Results

- Response defined as CR100; Remission defined as CDAI ≤ 150
- Predictors of remission at week 56 with adalimumab maintenance treatment
  - Baseline CD duration (p = 0.046) and aminosalicylate use (p = 0.033) – not significant predictors at 26 weeks
  - Baseline CRP and CDAI, prior anti-TNF use – all were also significant at week 26
- Maintenance of remission at weeks 26 and 56
  - Remission rates at 56 weeks were significantly greater in adalimumab treated patients than placebo treated patients in all CD duration subgroups
  - At both weeks 26 and 56, the CD duration < 2 years subgroup had numerically higher remission rates than the other CD duration subgroups

<table>
<thead>
<tr>
<th></th>
<th>Remission Rates at Week 26 (%)</th>
<th>Remission Rates at Week 56 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Adalimumab</td>
<td>Placebo</td>
</tr>
<tr>
<td>All Patients</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 2 years</td>
<td>33</td>
<td>14</td>
</tr>
<tr>
<td>≥ 2 to &lt; 5 years</td>
<td>46</td>
<td>19</td>
</tr>
<tr>
<td>≥ 5 years</td>
<td>28</td>
<td>23</td>
</tr>
<tr>
<td></td>
<td>32</td>
<td>10</td>
</tr>
</tbody>
</table>

- Results for response were similar to those for remission
- Long-term remission rates by CD duration subgroup (3 years of adalimumab therapy)
  - The < 2 years CD duration subgroup had consistently higher remission rates

Safety

- Overall rate of any adverse event was highest in the ≥ 5 years subgroup
- Placebo patients tended to have more serious AEs and discontinuations due to AEs
- The incidence of serious infections was low in all groups regardless of treatment
- No serious infections seen in adalimumab treated patients with CD duration < 2 years

Authors’ Conclusions

- Significantly higher remission and response rates were obtained with adalimumab vs. placebo at weeks 26 and 56 in almost all CD duration subgroups (excluding only the week 26, ≥ 2 to < 5 years subgroup)
- Shorter CD duration was associated with a higher likelihood of maintaining clinical remission with adalimumab through 3 years of maintenance treatments
### Methods

#### Population

<table>
<thead>
<tr>
<th>Ages</th>
<th>16 to 75 years old</th>
</tr>
</thead>
</table>

#### Prior Treatment

- All patients had never received CS, immunomodulators, or TNF inhibitors

#### Treatment Group

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>Activity, mean ± SD (Baseline CDAI)*</th>
<th>Weeks from diagnosis, median (IQR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early Combined</td>
<td>330 ± 92</td>
<td>2.0 (1.0 – 5.0)</td>
</tr>
<tr>
<td>Conventional</td>
<td>306 ± 80</td>
<td>2.5 (1.0 – 11.0)</td>
</tr>
</tbody>
</table>

*All patients had active CD defined as a CDAI > 200 for a minimum of 2 weeks

#### Methods

**Response or Worsening Defined by CDAI**

- Initial CDAI of 200 – 250: response = 50 point reduction
- Initial CDAI of 250 – 350: response = 75 point reduction
- Initial CDAI > 350: response = 100 point reduction
- Worsening defined as CDAI increase of ≥ 50 to give a score > 200

**Early Combined Immunosuppression**

- Three infusions of infliximab 5 mg/kg given at weeks 0, 2, and 6 in combination with AZA 2.0 – 2.5 mg/kg daily starting from day 0
  - If patient responded and tolerated this regimen, AZA was continued for the entire trial
  - Patients who did not tolerate AZA were given MTX 25 mg weekly x 12 weeks then 15 mg weekly thereafter
- If a patient worsened, additional infliximab infusions were given
- If symptoms persisted, methylprednisolone was started and AZA or MTX was continued

**Conventional Management**

- Induction treatment of methylprednisolone or budesonide was given (if patient responded, the dose was tapered, for a total CS treatment of 10 weeks for either medication)
  - If symptoms worsened during tapering, the CS was increased back to the initial dose and the CS induction was repeated
  - If symptoms continued to worsen after the second CS attempt, AZA or MTX was added

---

**AE=adverse effects, CD=Crohn’s disease, CDAI=Crohn’s disease activity index, CR100=reduction in CDAI of ≥ 100 points, SC=subcutaneous**

---


**Purpose**

- Compare the effectiveness of early combined immunosuppression (infliximab + AZA or MTX) with conventional step-up therapy in newly diagnosed CD patients naïve to CS, immunomodulators, and TNF inhibitors

**Design**

- Prospective, open-label, multi-center, randomized trial
- Early combined immunosuppression vs. conventional management with a follow-up of 2 years

**Population**

- Ages: 16 to 75 years old
- Prior Treatment: All patients had never received CS, immunomodulators, or TNF inhibitors

**Methods**

**Response or Worsening Defined by CDAI**

- Initial CDAI of 200 – 250: response = 50 point reduction
- Initial CDAI of 250 – 350: response = 75 point reduction
- Initial CDAI > 350: response = 100 point reduction
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---

**AE=adverse effects, CD=Crohn’s disease, CDAI=Crohn’s disease activity index, CR100=reduction in CDAI of ≥ 100 points, SC=subcutaneous**
• Patients who relapsed after a successful CS induction were advanced to CS + AZA or MTX
• Any patient who remained symptomatic after 16 weeks of AZA were advanced to infliximab induction course + AZA or MTX
• Patients who were intolerant to both AZA and MTX were given infliximab monotherapy (induction course + repeat infusions for symptom relapse) – if symptoms persisted after infliximab infusion, CS course was started

Results
• Remission defined as CDAI ≤ 150
• Primary Outcome = remission + no CS treatment + no intestinal resection at weeks 26 and 52

<table>
<thead>
<tr>
<th></th>
<th>Week 26</th>
<th></th>
<th>Week 52</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Early Combined</td>
<td>Conventional</td>
<td>P Value (95% CI of difference)</td>
<td>Early Combined</td>
</tr>
<tr>
<td></td>
<td>60.0%</td>
<td>35.9%</td>
<td>0.0062 (7.3 – 40.8)</td>
<td>61.5%</td>
</tr>
</tbody>
</table>

• Secondary Outcomes
  Median time to relapse after successful induction at week 14, p = 0.031
  • Early Combined: 329.0 days, IQR 91.0 – not reached
  • Conventional: 174.5 days, IQR 78.5 – 274.0
  Daily methylprednisolone dose (95th percentiles)
  • Early Combined: 0 mg
  • Conventional: 35 mg
  Mucosal healing (proportion without ulcers at 104 weeks) - subgroup analysis, p = 0.0028
  • Early Combined: 19/26 (73.1%)
  • Conventional: 7/23 (30.4%)

• Safety
  • No significant differences in any adverse events was found between groups

Authors’ Conclusions
• Combined immunosuppression with infliximab and AZA or MTX initiated early after CD diagnosis in patients naïve to CS, antimetabolites, and TNF inhibitors was more effective than conventional management for inducing remission
• Starting more intensive treatment regimens earlier in the course of CD may lead to better outcomes

Strengths
• Compared an early combined immunosuppression (top-down) strategy directly to conventional management (step-up strategy)
• Assessed subjective measures (CDAI) in addition to objective measures (ulcers on endoscopy)

Weaknesses
• Unblinded study
• Infliximab maintenance therapy every 8 weeks was not used; may provide more benefit

Take Home Points
• Early combined immunosuppression with infliximab + AZA or MTX resulted in higher remission rates than conventional management in newly diagnosed CD patients
• The early combined strategy resulted in less CS use than conventional management, lower rates of relapse, and a higher rate of patients without ulcers at 2 years

AZA=azathioprine, CD=Crohn’s disease, CDAI=Crohn’s disease activity index, CS=corticosteroids, IQR=inter-quartile range, MTX=methotrexate, SD=standard deviation

| Purpose | Compare the efficacy of infliximab, AZA, and the two drugs combined for inducing and maintaining CS-free remission in biologic and immunomodulator naïve patients with active CD
| Design | Prospective, double-blind, placebo-controlled, multi-center, randomized trial
| 30-week trial with a 20-week extension in which blinding was continued
| Ages: ≥ 21 years old and diagnosed with CD for ≥ 6 weeks
| Prior Treatment: All patients had never taken AZA, 6-MP, MTX, or an anti-TNF biologic agent and met one of the following criteria:
| - CS-dependent (having a CDAI of ≥ 220 after reducing the CS dose)
| - Being considered for a second course of CS within 12 months
| - No response to ≥ 4 weeks of either mesalamine or budesonide treatment
| Treatment Group | Activity, mean ± SD (Baseline CDAI)* | Median disease Duration (years)
| All Patients (n = 508) | 287.3 ± 56.7 | 2.3
| Combination (n = 169) | 289.9 ± 55.0 | 2.2
| Infliximab (n = 169) | 284.8 ± 62.1 | 2.2
| AZA (n = 170) | 287.2 ± 52.9 | 2.4
| * All patients had moderate–severe CD based on CDAI between 220 and 450
| No significant differences between any baseline characteristics
| Methods | Patients were randomized to one of three groups:
| - **Infliximab** 5 mg/kg at weeks 0, 2, and 6 then every 8 weeks + AZA 2.5 mg/kg daily
| - **Infliximab** 5 mg/kg at weeks 0, 2, and 6 then every 8 weeks + **placebo capsules** daily
| - **AZA** 2.5 mg/kg daily + **placebo infusions** at weeks 0, 2, and 6 then every 8 weeks
| - At week 30, patients were given the option of continuing blinded therapy for 20 more weeks
| - For patients taking mesalamine at baseline, it was continued at the same dose
| - Systemic CS could be continued or initiated for the first 14 weeks; after week 14 the dose was tapered by at least 5 mg/week
| - Budesonide could be maintained or dose reduced up to week 14 after which it was reduced by 3 mg every 2 weeks to a dose ≤ 6 mg/day
| - Ileocolonoscopy was performed at baseline; the procedure was repeated at week 26 in patients found to have mucosal ulcers at baseline
| Results | Corticosteroid-free clinical remission defined as CDAI < 150 and no budesonide at a dose > 6 mg daily or any systemic CS for ≥ 3 weeks
| Primary Outcome = rate of CS-free clinical remission at week 26
• **Secondary Outcomes**

  Mucosal Healing at week 26 (absence of ulcers in patients with ulcerations at baseline)

  ![Graph showing rates of CS-free remission](image)

  **Rate of CS-free remission at week 50**
  
  (patients not continuing in extension trial were assumed to not be in remission)

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>CS-free Remission, No. (%)</th>
<th>P Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Combination (n = 169)</td>
<td>78 (46.2)</td>
<td>Combination vs. Infliximab 0.04</td>
</tr>
<tr>
<td>Infliximab (n = 169)</td>
<td>59 (34.9)</td>
<td>Combination vs. AZA &lt; 0.001</td>
</tr>
<tr>
<td>AZA (n = 170)</td>
<td>41 (24.1)</td>
<td>Infliximab vs. AZA 0.03</td>
</tr>
</tbody>
</table>

• In patients with normal CRP (< 0.8 mg/dL) or with no baseline ulcerations, there were no differences in rates of CS-free remission between the three groups, however, combination therapy and infliximab monotherapy did have significantly higher rates than AZA monotherapy in patients with elevated CRP or mucosal ulcerations at baseline

• **Safety**
  
  - The incidence of adverse events was similar between the three groups
  - There was a numerically higher incidence of infusion reactions in the infliximab group

**Authors’ Conclusions**

- Treatment with infliximab monotherapy and combination infliximab and AZA compared to AZA monotherapy in patients naïve to immunomodulators and biologics with active moderate – severe CD resulted in significantly higher rates of CS-free clinical remission

**Strengths**

- Prospective, randomized, double-blind, placebo-controlled
- Included data on mucosal healing
- Subgroup analyses provide information regarding which patient subpopulations might benefit

**Weaknesses**

- Mucosal healing analysis was performed for only a subset of the population
- Does not provide any long-term data (only 1 year in length)

**Take Home Points**

- This study is essentially comparing one group treated with the conventional step-up method (AZA monotherapy) to two different types of accelerated top-down strategies (infliximab monotherapy and combination infliximab + AZA)
- The combination of infliximab + AZA resulted in significantly higher rates of CS-free remission than either infliximab or AZA monotherapy in patients naïve to immunomodulators and biologics; infliximab monotherapy was also better than AZA monotherapy
- Mucosal healing of baseline ulcerations occurred at a significantly higher rate in the combination and the infliximab monotherapy groups as compared to the AZA group

6-MP=Mercaptopurine, AZA=azathioprine, CD=Crohn’s disease, CDAI=Crohn’s disease activity index, CRP=C reactive protein, CS=corticosteroids, MTX=methotrexate, SD=standard deviation
RISKS AND BENEFITS OF EARLY BIOLOGIC THERAPY IN CD

I. Risks of early biologic use
   A. General concerns
      i. Infection – possible increased risk of:
         a. Opportunistic infections
         b. Serious Infections
      ii. Corticosteroids are the only immunosuppressant associated with increased mortality
      iii. Cancer risk appears to be similar to the general population in CD patients treated with a biologic
   B. Safety findings
      i. Trend toward higher rate of AEs or more serious AEs with longer CD duration
      ii. More serious AEs seen in placebo treated patients compared to biologic treated patients
      iii. No serious AEs were reported in biologic treated patients with CD duration < 2 years

II. Benefits of early biologic use
   A. Short-term outcome measures
      i. Response and remission rates
         a. Higher rates observed in early CD (< 1 to 2 years) than in late CD (≥ 5 years)
         b. In newly diagnosed patients, combination therapy (biologic + immunomodulator) achieved higher remission rates than conventional step-up treatment
         c. In patients naïve to immunomodulators and biologics, CS-free remission rates from highest to lowest were, Combination Therapy (biologic + immunomodulator) > Biologic Monotherapy > Immunomodulator Monotherapy
      ii. Corticosteroid use & relapse rates
         a. Combination therapy (biologic + immunomodulator) resulted in less CS use and lower rates of relapse than conventional management
   B. Long-term outcome measures – the impact of early biologic treatment strategies on CD complications, hospitalizations, or the need for surgery has not been reported due to the relatively short duration of follow-up in the studies
   C. Mucosal healing
      i. Biologics used in combination and monotherapy strategies in early CD have been associated with higher rates of MH compared to conventional treatment
      ii. In a post hoc analysis of the SONIC trial, MH rates were higher in patients with CD duration ≤ 2 years compared to those with duration > 2 years

III. Cost of biologic therapy
   A. Specific costs for biologic agents are highly dependent on the health care system but the cost is significantly higher than that of corticosteroids or immunomodulators
   B. A cost-effectiveness analysis based on a United Kingdom cohort found that early use of adalimumab or infliximab was cost-effective for a treatment period of up to 4 years compared to conventional treatment; use of these biologics past four years was not cost-effective
I. Is earlier use of biologics in moderate – severe CD better?
   A. Yes, but only in the right patients
   B. Factors to consider for selection of patients for early biologic therapy
      i. Approximately half of patients presenting with CD will have a non-progressing course
         a. Indiscriminant use of biologics in these patients would unnecessarily expose many
            patients to the associated AE and cost burden
      ii. Patients with elevated CRP (≥ 0.8 mg/dL) and/or ulcers prior to initiation of therapy have
           been shown to have higher rates of CS-free clinical remission with early biologic
           treatment strategies compared to conventional treatment
      iii. Predictors of disease progression and disability (poor prognostic factors)
           a. Disease of the terminal ileum is associated with an increased risk of stricturing,
              penetration, and need for surgery
           b. Presentation at diagnosis of young age (< 40 years old), initial need for CS therapy,
              perianal disease, stricturing behavior, and loss of > 5 kg were found to be
              independent risk factors for a severe disease course
           c. Severity of ulceration – presence of deep ulcers was significantly associated with
              an increased risk of bowel resection
           d. The presence of genetic markers and serologic immune responses may help
              identify patients at risk of disease progression in the future

II. Recommendations
   A. Determining risk of severe disease course
      i. Create three risk categories based on:
         a. Guideline classification of CD activity at diagnosis
         b. Presence of poor prognostic factors
   B. Stratifying the strategies
      i. Based on CD risk class at diagnosis (Figure 1, pg. 18)
<table>
<thead>
<tr>
<th>CD Activity Classification</th>
<th>Poor Prognostic Factors</th>
<th>Risk of Severe Disease Course</th>
<th>Initial Treatment Strategy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild - Moderate</td>
<td>None</td>
<td>Low Risk</td>
<td>Conventional Step-Care</td>
</tr>
<tr>
<td></td>
<td>≥ 1</td>
<td>Moderate Risk</td>
<td>Accelerated Step-Care</td>
</tr>
<tr>
<td>Moderate - Severe</td>
<td>None</td>
<td>High Risk</td>
<td>Top-Down Biologic Strategy</td>
</tr>
<tr>
<td>Severe - Fulminant</td>
<td>≥ 1</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Figure 1. Initial treatment strategy for CD based on the risk of having a severe disease course
REFERENCES

Appendix A: Crohn’s Disease Activity Index

<table>
<thead>
<tr>
<th>Variable</th>
<th>Description</th>
<th>Score</th>
<th>Multiplier</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of liquid stools</td>
<td>Sum of 7 days</td>
<td></td>
<td>2</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>Sum of 7 days</td>
<td>0 = none, 1 = mild, 2 = moderate, 3 = severe</td>
<td>5</td>
</tr>
<tr>
<td>General well-being</td>
<td>Sum of 7 days</td>
<td>0 = generally well, 1 = slightly under par, 2 = poor, 3 = very poor, 4 = terrible</td>
<td>7</td>
</tr>
<tr>
<td>Extraintestinal</td>
<td>Number of listed complications</td>
<td>Arthritis, arthralgia, iritis, erythema nodosum, pyodermangrenosum, uveitis, aphthous stomatitis, anal fissure/fistula, abscess, fever &gt; 37.8°C (100°F)</td>
<td>20</td>
</tr>
<tr>
<td>complications</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antidiarrheal drugs</td>
<td>Use in the previous 7 days</td>
<td>0 = no, 1 = yes</td>
<td>30</td>
</tr>
<tr>
<td>Abdominal mass</td>
<td></td>
<td>0 = no, 2 = questionable, 5 = definite</td>
<td>10</td>
</tr>
<tr>
<td>Hematocrit</td>
<td>Expected minus observed level</td>
<td>Male: 47% - observed; Female: 42% - observed</td>
<td>6</td>
</tr>
<tr>
<td>Body weight</td>
<td>From within the previous 7 days</td>
<td>1 – (ideal observed) x 100</td>
<td>1 (not if &lt; 10)</td>
</tr>
</tbody>
</table>

Remission = CDAI < 150, Response: decrease in CDAI of > 70 or > 100 (depending on the trial), Moderate to Severe Crohn’s disease = CDAI of 220 – 450, Severe Crohn’s disease = CDAI > 450