

## **New Therapies and IBD**

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### **BRIEF OVERVIEW**

- Identify the problems and/or limitations of our current therapies.
- Can we improve on what we already have prior to reaching for a new medication?
- If that is not good enough, we need to take another look at the pathophysiology of IBD to see how new drugs can fit into our repertoire of medications.
- Need to be aware that as medications get more sophisticated, the possible risks/side effects should remain small.
- Look to possible alternative ways to augment the immune system (and therefore the disease) outside of medications i.e. Nutrition, Parasites therapy, leukocytapheresis

### **RESEARCH**

#### **I. Current Therapies with modifications:**

Aminosalicylates (5'ASA)

- First line therapy for patients with mild to moderate disease
- Examples include: Asacol®, Pentasa®, Sulfasalazine, Colazal®
- The compound known as 5-aminosalicylate (5'ASA), has anti-inflammatory properties.
- Each of these medications delivers the active compound to different parts of the GI tract where it works as an anti-inflammatory agent
- Mesalamine (Asacol®) is usually prescribed as 3.6 grams per day in divided doses -3 pills, 3 times/day
- Recently, higher doses or oral Mesalamine was confirmed to be beneficial in 2 trials, the ASCEND I and ASCEND II

ASCEND I and ASCEND II

- 2 multicenter, randomized, double-blind, controlled trials
- 423 patients with moderately active disease (the 2 studies combined)
- The patients were randomized into one of two groups:
- One group received 2.4g/day of Mesalamine
- The second group received 4.8g/d of Mesalamine

Results:

- After six weeks, 72% of patients receiving 4.8g/d of Mesalamine had overall improvement compared with 58% of patients receiving 2.4 g/d of Mesalamine
- In addition, there was greater mucosal healing (seen via colonoscopy) with Mesalamine 4.8g/d (80%) compared with 2.4g/d (68%)

- This benefit was demonstrated regardless of the extent of disease (Proctitis vs. left sided colitis vs. pancolitis)
- Both doses of Mesalamine were well tolerated by the patients
- Similar frequency of adverse effects occurred
- As a result of this study, many physicians are now starting to prescribe higher doses of 5'ASA medications
- This is resulting in an improvement of symptoms without having to add and/or change the medication(s) the patient is taking

#### Rectal 5'ASA

- Although we hesitate to prescribe rectal medications, they can be very effective
- A meta-analysis was recently conducted
- They based their analysis on 7 comparative trials

#### Results:

- Rectal Mesalamine was found to be more effective than rectal corticosteroids in the management of UC
- There was symptomatic, endoscopic and histologic improvement
- This is different than what was previously thought and practiced
- Patients were often prescribed rectal steroids over rectal Mesalamine especially when the patient was felt to have more aggressive disease

#### Aminosalicylates Combination Therapy

- Multicenter study
- 60 patients with mild-moderate disease
- Randomized to 3 groups: Mesalamine enema, Mesalamine oral and combination of both oral and enema

#### Results:

- Treatments were given for 6 weeks
- Combination therapy produced earlier and more complete relief
- Combination therapy was well tolerated and there were no adverse events
- These results prompted another study that demonstrated the benefit of combination therapy even in patients with extensive disease

#### LIALDA® (Mesalamine delayed release tablets)

- Until recently, currently available Mesalamine require three to four times daily dosing and 6 to 16 pills a day.
- According to a Crohn's and Colitis Foundation of American (CCFA) survey, 65 percent of patients with UC reported being poorly compliant with their current therapy due to pill burden and inconvenience
- LIALDA® utilizes a novel MMX technology.
- LIALDA® with MMX technology combines a pH dependent gastro-

resistant coating, which delays the release of Mesalamine to the colon with a tablet core containing Mesalamine with hydrophilic and lipophilic excipients that allow for a slow release.

- Phase III clinical trials included two studies that were designed to examine the efficacy of LIALDA® versus placebo in patients with active, mild to moderate UC.

Results:

- Both studies were randomized, multi-center, double-blind, placebo-controlled studies
- Both studies demonstrated the induction of remission in patients with active, mild to moderate UC
- LIALDA® is generally well tolerated and has a similar safety profile to other currently available mesalamines
- This new information will hopefully improve compliance and quality of life for many patients

## **II. Biologic Therapies**

- A new class of drugs
- Genetically engineered medications made from living organisms and their products, such as proteins, genes, and antibodies
- They interfere with the body's inflammatory response by targeting specific components in the inflammatory cascade

Infliximab/Remicade® anti-TNF

- First FDA- approved biologic therapy for Crohn's Disease
- Targets TNF – tumor necrosis factor
- A cytokine (specialized protein) that promotes inflammation in the intestine and other organs
- People with active Crohn's Disease have an increased production of TNF-alpha in their intestinal lining and in their stool
- Remicade® is a chimeric, monoclonal antibody
- It is 75% human and 25% mouse
- It is given intravenously
- Can produce infusion reactions

Headache, fever, chills, difficulty breathing, low blood pressure, hives.

Therefore, must be given with medical supervision

- Because Remicade® is partially from a mouse, one can develop antibodies against the mouse component rendering the drug less effective

Adalimumab/Humira®

- Also an anti-TNF molecule
- Used for patients who no longer respond to Remicade®

- Well tolerated by patients who experience infusion reactions with Remicade®
- Given subcutaneously on a weekly basis
- First with a loading dose, 80 mg
- Followed by a maintenance dose, 40 mg
- Some local discomfort at injection site
- Given at home
- Convenient
- Less scheduling, waiting, etc.

Like Remicade®, anti-TNF drugs have side effects:

- Reactivation of tuberculosis
- Infections
- Demyelinating process (neurologic)
- Lymphoma

CIMZIATM certolizumab pegol, CDP870

- PEGylated Fab' fragment of a humanized anti-TNF-alpha antibody
- High affinity for human TNF-alpha
- Selectively neutralizing the pathophysiological effects of TNF-alpha
- First biologic administered by monthly subcutaneous injection

### III. What about diet?

The Specific Carbohydrate Diet

- The carbohydrates that are allowed are monosaccharides
- Monosaccharides have a single molecule structure
- Monosaccharides are easily absorbed by the intestine wall
- Complex carbohydrates (disaccharides and polysaccharides) are not allowed
- The creators of the diet believe that "complex carbohydrates are not easily digested and they therefore feed harmful bacteria in our intestines causing them to overgrow and produce by-products that inflame the intestine wall"
- The creators of the diet believe, "the diet works by "starving these bad bacteria and restoring the balance of good bacteria in our intestine"
- Based on the premise that, "early man ate a diet of meat, fish, eggs, vegetables, nuts, and low-sugar fruits"
- "Our modern diet including starches, grains, pasta, legumes, breads and complex sugars has only been consumed in recent times during which there has been an increase in bowel disorders"
- Although some say it helps, it is a very rigid, strict diet to follow, especially long term
- Even when a patient strictly adheres to the diet, it rarely allows the

patient to remain in remission over time  
- It is not effective in all patients

#### **IV. Other Approaches**

Trichuris suis - whipworm

- In 2005, Summers, et.al. published a paper introducing the concept that natural exposure to helminths affords protection from immunological diseases, like Crohn's disease
- Crohn's disease is common in highly industrialized Western countries where helminths are rare
- Crohn's disease is uncommon in less developed areas of the world where most people carry worms
- Helminths diminish immune responsiveness in naturally colonized humans (downregulated the host immune response)
- Helminths diminish inflammation in experimental colitis
- 29 patients with active Crohn's disease were enrolled
- All patients ingested 2500 live Trichuris suis ova every 3 weeks for 24 weeks
- Disease activity was monitored using the CDAI (Crohn's disease activity index)
- At week 24, 23 patients (79.3%) responded and 21(72.4%) were in remission
- No adverse events
- This was a small study
- Must be repeated before this could be thought of as a therapy

Leukocytapheresis

- Novel "non-drug" approach
- The technique involves the passage of peripheral blood through a column of cellulose diacetate beads
- Some of the patient's white blood cells are extracted
- The body replaces these white blood cells with new naïve white blood cells
- These naïve white blood cells have a decreased expression of adhesion molecules and reactive oxygen species
- This alters how the white blood cell responds to proinflammatory cytokines and endotoxins
- Although the process appears safe and effective, blinded placebo-controlled trials are lacking
- Until these can be completed, this therapy awaits in the pipeline