CONTEMPORARY TREATMENT OF INFLAMMATORY BOWEL DISEASE

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• Inflammatory bowel disease (IBD) is a chronic inflammatory disease of the GI tract
• Two most common types of IBD
  – Crohn’s disease (CD)
  – Ulcerative colitis (UC)
• Indeterminate colitis - colitis that cannot be diagnosed as CD or UC at presentation. Over time, most patients with indeterminate colitis evolve into a definitive diagnosis of either CD or UC.
Spectrum of inflammatory bowel disease

Crohn’s disease (CD)  

Ulcerative colitis (UC)  

Indeterminate Colitis

• Crohn’s disease
  • Chronic
  • Any portion of GI tract
  • Idiopathic
  • Remitting-relapsing
  • Discontinuous patchy pathology
  • Full-thickness of gut wall involved (transmural)

• Ulcerative colitis
  • Chronic
  • Large bowel (colon) only
  • Idiopathic
  • Remitting-relapsing
  • Continuous pathology
  • Only mucosa involved (not deeper portions of gut wall)
Ulcerative colitis

Crohn’s disease
Normal colon

uc

cd
Ulcerative colitis

(a) proctitis
(b) rectosigmoiditis
(c) Left-sided colitis
(d) pancolitis
Crohn’s disease

- Any part of GI tract can be involved
• Pathogenesis of IBD

- Genetic susceptibility
- Immune response
- Environmental factors eg. Microbiota
IBSEN study: Patients choosing 1 of 4 theoretical, predefined disease courses (n=197)

- n=85 (43%) Decrease in symptom severity
- n=37 (19%) Chronic continuous symptoms
- n=6 (3%) Increase in symptom severity
- n=63 (32%) Chronic relapsing symptoms

Goals of UC medical treatment

• Induce and maintain remission of symptoms and mucosal inflammation to provide improved quality of life

• Reduce the risk of complications

• Avoid the need for surgery

• Improve survival

Treatment goals

Symptom improvement
Treatment goals

- Clinical remission
- Symptom improvement
Treatment goals

Symptom improvement
Clinical remission
Corticosteroid free remission
Treatment goals

- Symptom improvement
- Clinical remission
- Corticosteroid free remission
- Mucosal healing
- Symptom improvement
Treatment goals

- Symptom improvement
- Clinical remission
- Corticosteroid free remission
- Mucosal healing
- Histological remission
- Symptom improvement
Evolving goals of therapy for IBD

From clinical remission ...
... to sustained clinical remission ...
... to mucosal healing ...
... to deep remission ...

... to sustained deep remission?
Treatment options

Conventional treatment options:
• Anti-inflammatory agents (aminosalicylates, corticosteroids)
  — 5-ASA much more efficacious in UC vs CD
• Immunosuppressants (azathioprine / 6-MP, cyclosporine)

Other options:
• Enteral nutrition/TPN
• Probiotics
• Surgery

Biologic treatment option:
• Infliximab and adalimumab
TRADITIONAL STEP-UP THERAPY IN UC

- Surgery
- CyS or IFX
- steroids iv
- IFX
- AZA/6-MP
- Oral steroids
- 5-ASA
TRADITIONAL STEP-UP THERAPY

Aminosalicylates

Aminosalicylates Steroids AZA/6-MP

INFLIXIMAB OR ADA LIMUMAB OR SURGERY

UC=ulcerative colitis; AZA=azathioprine; 6-MP=6-mercaptopurine; CsA=ciclosporin A; IV=intravenous.

Nanna Svartz (1890-1986)

- 1938: The discovery of Salazopyrin (Sulphasalazine) together with chemist Philip Willsted. They combine via an azo-bond Sulphapyridine and 5-aminosalicylic acid (5-ASA)
- 1942: First publication
- 1948: 124 patients with ulcerative colitis
Salazopyrin, a new sulfanilamide preparation.

A. Therapeutic Results in Rheumatic Polyarthritis. B. Therapeutic Results in Ulcerative Colitis. C. Toxic Manifestations in Treatment with Sulfanilamide Preparations.

By

Nanna Svartz.

(Submitted for publication March 23rd, 1942.)

A. Therapeutic Results in Rheumatic Polyarthritis.

For about four years I have been engaged in experiments on the treatment of rheumatic polyarthritis with combinations of sulfanilamide and salicyl preparations. As I have several times pointed out, the earlier known sulfanilamide preparations are active in the so-called septic forms of arthritis, but not in the common rheumatic forms.

At first my experiments concerned the question of whether medication with both salicyl and sulfanilamide preparations at the same time affects rheumatic polyarthritis. These experiments yielded no tangible results, however.

The next phase in the series of investigations consisted of attempts to produce chemical compounds between salicyl preparations on the one hand and sulfanilamide or sulfapyridine on the other. These experiments were first conducted by the writer alone, but later in collaboration with A. B. Pharmacists, where the chemists, Civil Engineer A. Asköld and Dr. Phil. H. Willametz produced different combinations of salicyl and sulfanilamide preparations...
Salazopyrin (Sulphasalazine)

- **Recommended dose:** two 500 mg tablets 4 – 6 times daily

- **Side effects in up to 20% of patients (due to sulphapyridine and not to 5-ASA):** headache, nausea, vomiting, fever, abdominal pain, skin rash, cyanosis (methemoglobin), neutropenia, agranulocytosis, thrombocytopenia, folate deficiency, neuropathy, male infertility etc.

- **Effective in acute attacks of mild-moderate UC and as maintenance treatment (1965)** – lower dose → less adverse events
New 5-ASA agents

• How to deliver 5-ASA (not to be absorbed and not to be metabolized) to colonic mucosa?
• Different delivery systems were developed: azo-compounds, controlled release – pH dependent (pH 6 or pH 7, Eudragit coated) and pH dependent with controlled release (ethyl-cellulose)
• Not superior to sulphasalazine for inducing response or remission, but are better tolerated (cave pancreatitis and interstitial nephritis!)

Sutherland L et al. Cochrane Database Syst Rev 2006
Corticosteroids:

- Used for induction of remission in active disease
- Generally not used in the maintenance of remission due to side effects
- Powerful anti-inflammatory action
- Rapid onset of effects
- Two main types of side effects associated with corticosteroids:
  - Result of long-term steroid use
    - Increased susceptibility to infection
    - Osteoporosis (bone loss)
    - Cataracts, stretch marks, weight gain, diabetes, hypertension, behavioral changes
    - Additionally, growth and/or developmental issues may be seen in children
  - Result of steroid withdrawal (weakness, steroid dependency, steroid resistancy)
Immunomodulators

- Purine analogs (azathioprine and 6-mercaptopurine)
- Methotrexate
- Tacrolimus
- Cyclosporine (limited efficacy for Crohn’s)
- Cause depression of bone marrow activity, which can result in significant hematologic side effects (thrombocytopenia, anemia, leukopenia)
- GI side effects (nausea, vomiting)
- Hepatotoxicity, pancreatitis
Inclusion criteria for biological therapy (anti TNF - α)

• moderately to severely active disease not adequately responding to prior conventional treatment with 5-aminosalicylates, antibiotics, 6-methyl-prednisolone and azathioprine (2.5mg/kg/day) or serious side effects of these medications
Biological therapy

Adalimumab (Humira – 100% human)
Infliksimab (himeric antibody, 75% human in 25% mouse)
Certolizumab (Swiss and USA, only for UC)
Ustekinumab (CB)
Vedolizumab (UC in CB)
Tofacitinib (UC)
Proctocolectomy with permanent ileostomy

• Cures the disease of the GI tract

• Entire colon and rectum are removed

• Anus is also removed

• Surgeon then creates a stoma (the small intestine is sewn to an opening in the abdominal wall to let waste leave the body)
Protocolectomy with IPAA

- ‘Cures’ the disease of the GI tract
- Colon and rectum are removed
- Anus is left in place
- Part of the small intestine is reshaped to form a pouch within the body (pouch works like a rectum); stores waste until the bowel movement occurs
- A temporary ileostomy may be needed as the intestine heals (requiring 2 separate surgeries)