

MEDICAL TREATMENT OF CROHN'S DISEASE.

Careful use of medical therapy, combined with surgery, provides the best therapy for Crohn's disease.

Antibiotics: Metronidazole, ciprofloxacin, ornidazole.

- Metronidazole (10 mg/kg/d) or ciprofloxacin (500 mg BID)
- Ciprofloxacin may be better for ileitis and metronidazole for ileocolitis or colitis.
- Anal Crohn's disease without stenosis is easier to treat medically.
- Long-term oral metronidazole therapy is often helpful;
 - other medications (e.g., anti-tumor necrosis factor antibody) may be useful as well.
- Ornidazole, a nitroimidazole antibiotic active against anaerobes, has proven to be effective in decreasing postoperative clinical and endoscopic recurrence.

Anti-inflammatory drugs: Sulfasalazine, 5-ASA products

- Sulfasalazine: marginally superior to placebo for induction of remission, and also not superior to placebo for prevention of postoperative recurrence.
- 5-Aminosalicylic acid agents: Mesalamine (Asacol 2.4–4.8 g/d; Pentasa 4 g/d) is used for the treatment of mild to moderately active ileocolonic and colonic Crohn's disease.
 - Benefits: Remission >40%. Reduction in rate of relapse 10-20%.
 - Modest efficacy for maintenance of remission and reducing postoperative recurrences when initiated soon after ileal or colonic resection.

Immunosuppressive drugs: Conventional steroids, Budesonide, Antimetabolites
Methotrexate, Cyclosporine, 6-mercaptopurine and Azathioprine

- Corticosteroids: induction of remission in patients with active inflammatory disease.
 - Prednisone: 40–60 mg/d
 - active flare-up
 - After improvement at 2 weeks, tapering proceeds at 5 mg/wk until a dosage of 20 mg/d is being given.
 - Thereafter, slow tapering by 2.5 mg/wk is recommended.
 - Side effects:
 - steroid intolerant patients: present adverse effects.
 - steroid-resistant patients: experience little or no improvement in disease activity
 - steroid-dependent patients: experience a flare in disease activity during or after corticosteroid dose reduction 20%.
 - relapse within 1 year after initial remission: 75%
- Budesonide (Entocort):
 - Controlled ileal release.
 - Preferable to conventional corticosteroids in patients with ileal and right colon disease.
 - 9 mg once daily for 8 weeks, induces remission in 50–70% of patients.
- Azathioprine and 6- mercaptopurine:
 - effective in the long-term treatment of Crohn's disease.

- Elimination or reduction of corticosteroids in over 75% and fistula closure in 30% of patients.
- The mean time to symptomatic response is 4 months (not useful for acute exacerbations).
- After remission, these drugs reduce the 3-year relapse rate from over 60% to less than 25%.
- Treatment is initiated with either agent at 50 mg/d and is increased by 25 mg increments at 2-week intervals to a maximum of 1–1.5 mg/kg/d for mercaptopurine or 2–2.5 mg/kg/d for azathioprine,.
- Methotrexate (
 - 5 mg intramuscularly or subcutaneously weekly for 12 weeks
 - followed by 12.5–15 mg once weekly
 - for those unresponsive to or intolerant to mercaptopurine or azathioprine.
 - Side effects of antimetabolite therapy include:
 - Pancreatitis
 - Neutropenia
 - opportunistic infections
 - risk of severe bone marrow suppression
 - blood counts should be monitored every 1–2 weeks until a stable dosage is achieved, then every 3 months

Novel immunomodulators: leflunomide, tacrolimus and mycophenolate mofetil .

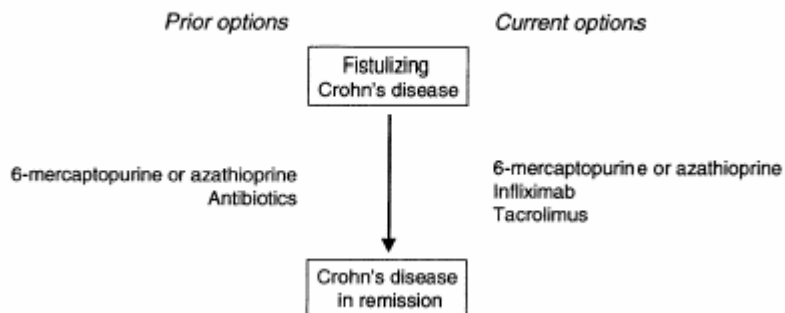
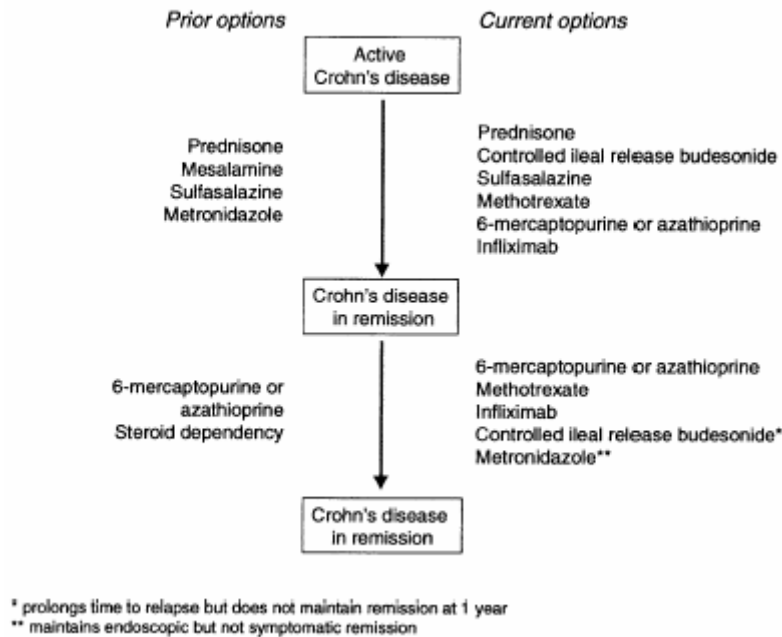
- Tacrolimus
 - inhibits the production of IL-2 by T-helper cells
 - effective for fistula improvement, but not fistula remission, in patients with perianal Crohn’s disease.

Biologic agents: TNF α -blocking agents and investigational agents.

- TNF- α blocking strategies:
 - Infliximab (Remicade):
 - chimeric monoclonal antibody that binds to TNF- α and neutralizes its interaction with cellular receptors.
 - It appears that it acts not only by blocking TNF- α activity but also by modulating apoptosis of specific T cell subsets.
 - A three-dose regimen of 5 mg/kg administered at 0, 2, and 6 weeks is recommended for acute induction.
 - Improvement occurs in two-thirds of patients and remission in one-third.
 - Patients who respond initially to infliximab therapy can receive maintenance therapy with dosing every eight weeks for both inflammatory and fistulizing indications
 - Useful in active CD refractory to glucocorticoids or antimetabolite therapy and as first-line therapy for moderate to severe fistulizing disease.
 - Concomitant therapy with other immunomodulating agents (mercaptopurine, azathioprine, or methotrexate) is recommended to reduce the development of antibodies to infliximab, (ATIs).

- CDP-870 (Cimzia)
 - is a completely humanized anti-TNF- α Fab fragment.
 - Given q/ 4 weeks subcutaneous was effective in inducing remission in patients with elevated C-reactive protein (CRP) at baseline (>10 mg/L).
 - Elevated C-reactive protein may be a biomarker of potentially reversible inflammation or a biomarker of lower rate of placebo response.
- Adalimumab (Humira):
 - recombinant fully human IgG1 monoclonal antibody directed against TNF- α .
 - Induction of clinical remission and response: 80 mg subcutaneously every other week.
- Other TNF-blocking strategies:
 - CDP-571 - recombinant humanized IgG4 monoclonal antibody
 - entanercept - p75 fusion protein
 - monomeroncept = recombinant TNF p55 receptor
 - have failed to show significant benefit in CD and are no longer in development.
- Inhibitors of lymphocyte trafficking:
 - Natalizumab (Tysabri):
 - inhibits the interaction of $\alpha 4$ integrin with its endothelial ligands
 - Statistically significant clinical response and remission rates observed after 12 weeks.
 - Patients who responded to natalizumab continued to respond to ongoing therapy, (300 mg q/4 weeks) with steroid-sparing effects.
 - Retired from the market after three cases of progressive multi-focal leukoencephalopathy were identified.
 - MLN-02:
 - is a recombinant IgG1 humanized monoclonal antibody.
 - Given 2 mg/kg at 1 and 29 days showed statistical difference in remission rates.
- Miscellaneous biologicals:
 - Anti-IL-12:
 - effective at inducing clinical response in patients with CD.
 - Patients who received anti-IL-12 (3 mg subcutaneously) weekly for seven weeks had higher response rates than did patients receiving placebo (75% versus 25%, $P=0.03$).
 - Anti-interferon: Fontolizumab
 - is a humanized IgG1 monoclonal antibody against interferon-g.
 - A Phase II study in patients with moderate-to-severely active CD of intravenous fontolizumab
 - at doses of 4 mg/kg and 10 mg/kg at week 0 failed to achieve the primary endpoint of a response at week 4.

- Granulocyte–macrophage colony-stimulating factor:
 - treatment directed at augmenting the intestinal innate immune defense rather than suppressing a secondary inflammatory response.
 - 6 mg/kg of GM-CSF subcutaneously every day for 56 days , showed that there was a statistically significant difference in clinical response and clinical remission.



1. For the future: the study of genetic predictors of responses to drugs has the greatest potential to permit the individualization of drug choice.
2. The next advances in Crohn's disease therapy may come through the field of pharmacogenomics.

References

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