

MANAGEMENT OF FISTULAS IN CROHN'S DISEASE

- Infliximab and azathioprine (6-MP) to date have the most established roles in the medical treatment of fistulous disease, however the efficacy of other medical therapies such as cyclosporine A, tacrolimus, mycophenolate mofetil (CellCept), and methotrexate are currently under investigation

INFLIXIMAB (Remicade):

- **Indication:** induction and maintenance of remission in patients with moderate to severe disease who have had inadequate response to conventional therapy
 - reduces the number of draining fistulas and maintains fistula closure
 - should be used for setting of actively draining fistula
- **Mechanism of action:** chimeric monoclonal antibody to TNF-alpha that interferes with stimulation of interleukins
 - enhancement of leukocyte migration
 - activation of neutrophils and eosinophils
 - induction of acute phase reactants and tissue degrading enzymes
- **Efficacy:** approved for use based on the results of 2 randomized trials published in The New England Journal of Medicine
 - 1999- randomized, double blind, placebo-controlled study where 94 adults with draining abdominal or perineal fistulas were randomized into 3 groups (placebo, remicade 5mg/kg, remicade 10mg/kg). Two end points were assessed:
 - Decrease of greater than 50% from baseline in the number of draining fistulas. Results: 68% in 5mg/kg; 56% in 10mg/kg vs. 26% in placebo
 - Closure of fistula. Results: 55% in 5mg/kg; 33% in 10mg/kg vs. 13% in placebo (note: median length of time fistulas stayed closed was 3 months)
 - 2004- randomized, double blind, placebo-controlled study designed to assess the efficacy of remicade as maintenance therapy in patients with fistulas.
 - The study included 306 patients with one or more draining abdominal/perineal fistula of at least three months duration
 - the results of this trial showed that patients with fistulous Crohn's disease who respond to induction therapy have increased likelihood of sustained response over a 54 week period

AZATHIOPRINE (IMURAN)/6-MP

- **Indication:** considered in patients with enteroenteric fistula associated with high output diarrhea and enterovesical fistulas presenting with UTI (multiorganism), pneumaturia and fecaluria
- **Mechanism of action:** imidizolyl derivative of mercaptopurine that antagonizes purine metabolism and may inhibit DNA, RNA and protein synthesis
 - may also interfere with cellular metabolism and inhibit mitosis
- **Efficacy:** In 1995 a meta-analysis assessed the efficacy of azathioprine and 6-mercaptopurine in inducing remission of active Crohn's disease and the effectiveness of azathioprine in maintaining remission of quiescent disease.
 - Results: Fistulas improved with therapy but improvement was temporary (~3 mos). Most will eventually become refractory to therapy and require surgery

CYCLOSPORINE A

- **Indication:** was used in treatment of ulcerative colitis now being studied for fistula closure especially in refractory disease
 - used to bridge to maintenance therapies
- **Mechanism of action:** inhibition of production and release of IL-2 which inhibits IL-2 induced activation of resting T cells
- **Efficacy** still under investigation
 - study published in 1998 in The American Journal of Gastroenterology to determine the outcome following treatment of refractory Crohn's disease with intravenous CSA
 - 18 patients in the study (9 with refractive inflammatory Crohn's Disease and 9 with complex fistulizing disease).
 - All were treated with IV CSA 4mg/kg/day and patients who responded were then converted to oral CSA.
 - Outcomes were classified as full, partial or no response.
 - Results: seven of nine patients with fistulizing Crohn's disease had a partial response and 5/7 maintained or improved their response during oral CYA therapy.
 - After discontinuing oral CYA, all five patients in the " fistulizing group relapsed despite 1-17 weeks of concomitant treatment with azathioprine or 6-mercaptopurine.
 - From this it was concluded that CYA appeared to benefit fistulizing Crohn's disease.
 - Most patients who respond to IV CYA will maintain their response during oral CYA therapy. However, the majority of these patients relapse when oral CYA is discontinued, probably because of inadequate duration of overlap with the slow acting maintenance drugs, AZA/6MP.

SURGICAL MANAGEMENT

- Surgical management of fistulas depends on the cause, type, response to medical therapy and complications associated with the fistula.
- **ABDOMINAL**
 - **Enteroenteral:** presence without signs of sepsis is not an indication for surgery, however most patients will require surgical intervention due to progressive disease and worsening abdominal pain
 - management should include excision of involved segments
 - **Enterocutaneous:** rarely spontaneous and are likely to follow resection or drainage of intra-abdominal abscesses, should be managed by excising the fistula tract along with the diseased segment of intestine and performing a primary reanastomosis
 - **Enterocolic:** does not always require surgical treatment,
 - except occasionally patients with ileal-sigmoid fistulas will develop increased diarrhea and require resection of the diseased terminal ileum With minimal inflammation the sigmoid defect can be simply closed, as long as the primary site of the fistula (the ileum) is resected

- **Colo/Enterovesical:** the segment of the diseased small bowel and fistulous tract should be resected and the defect in the bladder closed
- PERINEAL/PERIANAL
 - Definitive fistulotomy (unroofing the tract without excision of all surrounding tissue) is indicated in patients with superficial, low transsphincteric, and low intersphincteric fistulas
 - important to recognize that a degree of anal stenosis may occur as a result of chronic inflammation.
 - Note: studies have demonstrated that removal of the entire fistula tract along with the surrounding scar tissue (fistulectomy) unnecessarily results in a larger wound, prolonged healing time, and higher risks of incontinence.
 - High transsphincteric, suprasphincteric, and extrasphincteric fistulas are usually treated with noncutting setons - to prevent incontinence and in cases where poor wound healing is expected.
 - A Seton is a nonabsorbable nylon or silk suture that is guided through the fistula tract and tied exteriorly to maintain suture placement and cause compression of the tract.
 - The ischemic compression by the Seton and the local inflammatory reaction of adjacent tissues initiates fibrosis which helps maintain the integrity of the sphincter musculature during subsequent fistulotomy.
 - Advancement flap closure of perineal fistulas may be required in certain instances.
 - Fibrin glue

References

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