WORLD DIGESTIVE HEALTH DAY
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Inflammatory Bowel Disease (IBD): Navigating Evolving Therapies In An Evolving Disease

Frequently Asked Questions about IBD for Physicians

When prescribing anti-TNF therapy should I use an immunosuppressive drug with it?

- The short answer is yes for infliximab and possibly for adalimumab, certolizumab or golimumab. Combination therapy has clearly been shown to enhance the benefit of infliximab in the SONIC trial without an important increase in adverse events; there have been no equivalent studies with the other anti-TNF agents, but all agents are peptides and potentially immunogenic. Real world studies such as that from Northern France have also shown the benefit of adding azathioprine to infliximab; when a study of similar design was conducted with adalimumab in Oxford and Liege, it was difficult to identify a benefit. Concern about the exceptionally rare hepatosplenic T cell lymphoma after thiopurines (azathioprine or mercaptopurine) has led some specialists to favour methotrexate as a concomitant immunosuppressive, especially in younger males who seem to have greater susceptibility. Immunosuppressive drugs reduce antibody formation and sustain higher drug levels. At this point there is some individualization that is necessary. When starting someone on an anti-TNF it is reasonable to use concomitant immunosuppressives, be it a thiopurine or methotrexate. However, it may also be reasonable to withdraw the immunosuppressive medication after 1-2 years if the patient has clearly responded to the anti-TNF. Withdrawal at that stage should not promote antibody formation and may reduce long term risk. Further, when starting an anti-TNF in the elderly the risk of dual immunosuppression may be outweighed and monotherapy with any of the anti-TNF drugs may be the preferred strategy.

Is one anti-TNF more effective or safer than another?

- There does not seem to be any significant difference in terms of inducing remission or long term response rates between infliximab, adalimumab or certolizumab for Crohn's disease, or adalimumab, golimumab or infliximab for ulcerative colitis. Not all agents are approved for these indications in all healthcare jurisdictions. However, these drugs have never been studied head to head, so we are comparing results of completely different clinical trials with each other. It seems clear that in Crohn's disease when there is secondary loss of response or intolerance to one anti-TNF, one of the other agents can often be used with success, albeit a lesser chance of success than when a patient is prescribed their first anti-TNF.

Are there medications that can reduce recurrence rates after surgery in Crohn's disease?

- The one agent that has consistently been shown to reduce short term (less than 1 year) recurrence rates is metronidazole. Important side effects can limit the long term use of this drug (over 3 months) at the doses used in the studies. Thiopurines (azathioprine or mercaptopurine) also appear to reduce the risk, especially after a second operation or in higher risk patients. Help to stop smoking may also be effective at reducing the risk of relapse in Crohn´s disease. 5-ASA drugs have minimal benefit in reducing recurrence rates. For patients with severe disease an anti-TNF agent or vedolizumab can be considered. While a controlled trial of infliximab suggested no difference in clinical relapse rates after 18 months compared to placebo, the endoscopic recurrence rates were lower in those treated with infliximab. As endoscopic recurrence of sufficient severity usually forebodes a clinical recurrence it is appropriate to do a colonoscopy to examine the ileocolic anastomosis 6-12 months after surgery and either advance therapy or start therapy (often with a biologic) if there are early signs of endoscopic recurrence.

As there are more biologic agents proven to be effective in both Crohn's disease and ulcerative colitis is there an obvious first line or second line choice?

- Other than the anti-TNF drugs, Vedolizumab has been shown to be effective in both Crohn's disease and ulcerative colitis, ustekinemab has been shown to be effective in Crohn's disease and Tofacitinib has been shown to be effective in ulcerative colitis. Furthermore, drugs that have similar effects such as Etrolizumab or novel effects such as mongersen or ozanimod have been studied showing positive results. Hence, where these drugs are available, we are practicing in an era where doctors and patients will be faced with many choices for treatment. Choosing first line drugs is difficult because none of the different classes of drugs has been studied head to head. Anti-TNF drugs have been used for nearly two decades and hence most doctors are quite comfortable with prescribing them, recognizing ill effects from them and knowing how to dose adjust them. Anti-TNF drugs may be the optimal first line choice if the patient has a concomitant disease known to respond to anti-TNF (i.e. ankylosing spondylitis). While anti-TNF drugs are common first line choices in either Crohn's disease or ulcerative colitis, Vedolizumab may be a desirable first line choice in persons where avoidance of systemic immunosuppression is highly desired (i.e the elderly). Ustekinemab may be a preferred first line choice as doctors gain more experience with using it, especially since dosing may be as infrequent as every 8 to 12 weeks. Because of its known efficacy and longstanding use in persons with psoriasis Ustekinemab may be an optimal first line choice for persons with both IBD and psoriasis. Having more than anti-TNF drugs available means that if one fails an anti-TNF as first line therapy or loses response over time then depending on the circumstance (i.e. concomitant illnesses, age, or reason for loss of response) one could choose another anti-TNF, or a drug of a completely different class.

How should I incorporate therapeutic drug monitoring into my practice when using a biologic drug?

- Two clinical trials have been reported that failed to show a benefit of therapeutic drug monitoring of infliximab over clinical judgement. However, measuring a drug level can be very instructive when a patient has failed to respond or has lost

response to the drug. For instance the finding of unmeasurable or low circulating drug levels would encourage boosting the dose or frequency of dosing. Finding high circulating antibodies to the drug could encourage either adding an immunosuppressive to reduce antibody levels to the biologic or alternatively stopping the biologic and switching to another one. Another way to use drug monitoring could be proactively, that is to increase drug dosing until a specific drug level has been met. However, this has not been adequately studied to make this a standard approach. Hence, where available, therapeutic drug monitoring is mostly used when patients have failed to respond or have lost response to the biologic.

Is there a role for altering the gut microbiome with any of antibiotics, probiotics or fecal transplant in managing IBD?

- While there has been a considerable amount of research on the gut microbiome and its role in triggering IBD, there has yet to be found a consistent way to modulate the gut microbiome to induce or maintain disease remission. Antibiotics should be used to treat any infectious complications. In Crohn's disease they are used along with surgical management to treat perianal fistulas based mostly on anecdotal evidence. Patients with stricturing Crohn's disease, bloating and explosive diarrhea may benefit from a trial of antibiotics to treat presumed bacterial overgrowth. They do not have a role as primary therapy in ulcerative colitis, but they do work for pouchitis in patients who have had ileoanal pouch surgery. Probiotics have little role in managing either Crohn's disease or ulcerative colitis. However, one agent made up of 8 microorganisms, *Lactobacillus plantarum, Lactobacillus casei, Lactobacillus acidophilus, Lactobacillus delbrueckii subsp. bulgaricus, Bifidobacterium infantis, Bifidobacterium longum, Bifidobacterium breve* and *Streptococcus salivarius subsp. thermophilius,* has been successful in the management of pouchiits. It is common for persons, worldwide, to use probiotics for a variety of ailments or under the assumption that they maintain good health. Hence, clinicians managing patients with IBD should expect their patients to be using probiotics whether it is for their IBD or not. To date there does not seem to be any harm in their use in IBD. Fecal transplantation has been successful in managing recurrent Clostridium difficile associated colitis. This, together with the notion that persons with IBD have some disruption in their microbiome has led to interest in fecal transplantation in IBD. A number of randomized trials of fecal transplant have been reported in management of ulcerative colitis with varying efficacy, although none with overwhelming benefit. In one Canadian study feces donated from one donor led to a high rate of response while feces donated from a different donor led to a low response rate. This underscores that fecal transplantation requires considerably more study. There are issues regarding how it should be administered to maximize effectiveness (i.e. by pill or enema or colonoscopy or in what form either fresh or frozen) and how to identify optimal donors. While fecal transplantation is relatively easy, in that patients can take it upon themselves to find a donor, and learn how to mix the stool for easy enema use, this should be pursued in clinical trials so that a true understanding of its efficacy and optimal approaches can be rigorously defined.

How often do patients with ulcerative colitis require colonoscopy?

- Patients require colonoscopy when disease diagnosis or activity assessment is warranted. This is warranted obviously at the time of diagnosis, and may be necessary when therapy is changed to determine that there is mucosal healing (that the therapy is working to heal the active inflammation) or when symptoms are persistent despite adjusting therapy. Debate continues about the importance of confirming mucosal healing. It seems sensible to check for mucosal healing before a decision is made to de-escalate (reduce or withdraw) treatment. If a patient has a severe relapse or if independent confirmation of disease activity is needed (for instance before starting biological therapy or to exclude CMV), then a flexible sigmoidoscopy provides the necessary information. Full colonoscopy is usually not necessary in acute severe colitis but may be helpful if the original diagnosis of ulcerative colitis is in some doubt.Colonoscopy is also warranted for colon cancer surveillance. Colon cancer continues to be shown to be increased in persons with ulcerative colitis compared to the general population, however, the absolute risk has been shown to be lower than used to be considered. The frequency of colonoscopy depends on the extent, activity and duration of disease. Colonoscopy should be performed at diagnosis and again after 8 years of disease to reassess the extent and for dysplasia surveillance at that time. Dysplasia surveillance is optimized when disease is inactive and the bowel preparation is excellent. Chromoendoscopy (spraying a dye such as methylene blue to accentuate raised or atypical and potentially dysplastic lesions) has been shown to outperform random biopsying. However, especially if high resolution endoscopy equipment is available use of chromoendoscopy is less important than careful and slow mucosal inspection of a well prepared colon. The optimal surveillance interval after 8 years of disease is not fully known but every 3 years may be reasonable. The frequency of dysplasia surveillance should be increased in patients with primary sclerosing cholangitis who are at a greater increased risk of colon cancer than persons with ulcerative colitis who do not have primary sclerosing cholangitis. Persons with first degree relatives with colorectal cancer should also be more regularly screened, The presence of multiple pseudopolyps poses an increased challenge for dysplasia surveillance and may also be an indication for increased surveillance frequency. Beware of persistently active disease since inflammation drives cancer. So if the mucosa is persistently inflamed, make sure treatment is optimized (and taken!). There has been controversy whether 5-ASA prevents colon cancer. It may be that patients whose mucosa fully heals and stops 5-ASA and remains well may get no further chemoprophylaxis from 5-ASA use. Thiopurines may also reduce cancer risk but again the common denominator may be that the use of any drugs that will reduce if not eliminate inflammation will reduce cancer risk.

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