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Guide to Escalation and De-Escalation of IBD Therapy

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Escalation and De-escalation of Medications

- Therapies for treating inflammatory bowel disease (IBD) involve complex decision-making that weighs the risks and benefits of therapy.
- Stopping IBD therapy should be considered among carefully selected patients in biologic remission that have been informed of the risks and who are willing to do appropriate follow-up monitoring.
- De-escalation of therapy may save patients money, time and offer a psychological benefit without causing a flare.
- Often disease activity requires escalation of therapy – what is the roadmap for success?

Why De-escalate Therapy? Is This the Same as Stopping Therapy?

- In order to offer patient-centered care, there may be a reason to stop therapy, especially when deep remission has been documented, and the patient has a strong preference for stopping therapy.
- From a financial standpoint, patients may have additional incentives to de-escalate. High deductibles, existing copays, and challenges with insurance coverage often prompt discussions of de-escalation.

Stopping Biologics – STORI Trial

- The Study of Infliximab (IFX) Discontinuation in Crohn Disease Patients in Stable Remission on Combined Therapy with Immunosuppressors (STORI) 115 patients with CD who were treated for at least 1 year with IFX and an antimetabolite and were in corticosteroid-free remission for at least 6 months.
  - 43% of patients experienced a flare within 1 year, however, 88% of those patients were able to return successfully to combination therapy with IFX.
- Predictors of a flare after IFX discontinuation included a C-reactive protein (CRP) > 5 mg/L or a fecal calprotectin (FCP) > 300 mg/g in the 3-6 months prior to the flare.
- At 7 years of STORI, 21% had not restarted IFX, 30% had treatment failure even after restart of combination therapy, and 18.5% had major complications.

Louis E, Mary JY, Vernier-Massouille G et al. Maintenance of remission among patients with Crohn's disease on antimetabolite therapy after infliximab therapy is stopped. *Gastroenterology*. 2012; 142: 63-70. e5; quiz e31.

De-Escalating Biologics – TAXIT Study

- Trough Concentrations of Infliximab (IFX) Guide Dosing for Patients with Inflammatory Bowel Disease (TAXIT) 263 adults (178 CD and 85 UC). IFX doses escalated or reduced to reach target trough levels of 3-7 ug/mL. Patients IFX dose based on symptoms vs trough levels.
- 43% had therapeutic IFX levels
- 76 patients had low level (< 3) and 91% patients achieved therapeutic level. This resulted in higher proportion of CD patients in remission. 88 % vs 65% compared with before the dose increase.
- 72 patients had high trough levels(> 7) and 93% patients achieved therapeutic level. This did not increase clinical flares at one year.
- This saved patients 28% overall drug cost
- Disease relapse occurred 17% of patients who received symptom-based dosing vs 9% of concentration-based dosing.
- Patients with undetectable levels of a biologic are unlikely to be receiving benefit from that therapy and are likely to be able to stop the biologic but may need a different maintenance therapy when inflammation return.

Vande Casteele N, Ferrante M, Van Assche G et al. Trough concentrations of infliximab guide dosing for patients with inflammatory bowel disease. *Gastroenterology.* 2015; 148: 1320-9. e3.

Stopping Immunomodulators

- Clear risk factors for future flares have been defined using data from a randomized controlled medication withdrawal trial in patients with Crohn's disease on azathioprine. When these patients de-escalated from azathioprine, 53% had a clinical flare within 3 years. The significant baseline risk factors for a flare after withdrawal were CRP ≥ 20 mg/L, Hgb < 12 g/dL, and absolute neutrophil count (ANC) 4 × 109/mm3.
- If a patient is on combination (AZA + biologic) then obtain a drug level of the biologic. If therapeutic, may stop AZA and remeasure drug level in 3 months to ensure that drug levels are still therapeutic.
- Caveat – The biologic dose may need to be increased.

Cassinotti A, Actis GC, Duca P et al. Maintenance treatment with azathioprine in ulcerative colitis: outcome and predictive factors after drug withdrawal. *Am J Gastroenterol.* 2009; 104: 2760-2767.

Stopping 5-ASA Therapy – ECCO Review

- From the 2018 ECCO topical review, it suggests that withdrawal of 5-ASA could be considered in UC patients who have limited disease extension, sustained remission over several years, no recent use of systemic corticosteroid, and those having only a single flare.40
- It is not beneficial to continue using concomitant 5-ASA in patients having moderate to severe UC who escalated to anti-TNF treatment, based on a recent pooled analysis and population-based studies.
- There is no chemoprevention in low dose 5-ASA

Doherty G, Katsanos KH, Burisch J et al. European Crohn's and colitis organisation topical review on treatment withdrawal ['exit strategies'] in inflammatory bowel disease. *J Crohns Colitis.* 2018; 12: 17–31

IBD – Stopping Therapy Considerations

YES

- Patients with a history of well-controlled disease who have had a low rate of accumulation of complications of bowel damage and surgery.
- Patients with solid evidence of control of symptoms and absence of inflammation by endoscopy and biopsy can consider this option. For Crohn's - Small bowel should also be evaluated for inflammation with cross-sectional imaging, capsule endoscopy, or balloon endoscopy.
- Patients must demonstrate that they can reliably obtain monitoring of inflammation every 12 weeks with CRP and FCP to monitor for return of inflammation. Repeat endoscopy in 6 months.

NO

- Based on the data from STORI: patients with upper GI Crohn's disease, repeated penetrating complications or surgeries, or escalated dosing of anti-TNFs should not be considered for de-escalation.

Doherty G, Katsanos KH, Burisch J et al. European Crohn's and colitis organisation topical review on treatment withdrawal ['exit strategies'] in inflammatory bowel disease. *J Crohns Colitis.* 2018; 12: 17-31.

Bottom Line – Stopping Therapy

- 4 possible scenarios to stop therapy. If a patient is on a biologic, stop that. If they're on an immunomodulator, stop that. If they're on combination therapy with a biologic and an immunomodulator, stopping the immunomodulator, or if they're on combination therapy, stopping the TNF agent.
- The most successful patients are those on combination therapy. They may be able to stop either the immunomodulator or the TNF inhibitor if the patient is in a deep remission with no evidence of inflammatory symptoms, elevations of biomarkers, or a normalized colonoscopy with absence of ulcerations.

Case Study

- 38-year-old female with mild left side UC who initially presented with intermittent rectal bleeding 20+ years ago. She has never required steroids, has never been hospitalized, and has no evidence of active disease since she started using 5-ASA 2.4 gm and 5ASA suppositories on an intermittent basis after an initial induction of oral and rectal combination 5-ASA.
- (G1P0)16 weeks pregnant developed rectal bleeding and 8+ loose stools/day. Unsedated flex sig showed severe UC as far as scoped. Infliximab 5 mg/kg monotherapy initiated without steroid taper. Pt responded clinically after first infusion. Continued Infliximab loading dose and maintenance q 8 weeks. Discontinued 5-ASA
- Healthy boy delivered at term (39 weeks). Pt received Infliximab 5 mg/kg prior to discharge and continued q 8 weeks. Colonoscopy and biopsies 6 months later show deep remission.
- After 2 years – patient requests to stop Infliximab.
- What would you do?

Check List Prior to Stopping Therapy

- Are you (and your family) prepared for a major flare of IBD?
  - It could cost you time from work/home
  - You would be in the hospital, unable to support your family
- Are you willing to take high-dose corticosteroids when you flare?
- Do you understand it could take months to return to remission?
- Are you prepared for the risk that we may not be able to get you back in remission, and you may need surgery?
- Will you agree to more frequent testing in place of medications?
  - Do you know the costs of this testing for you?
  - Are you willing to bring stool samples to the lab for testing?
- If you flare, are you willing to go back on your effective medication?
  - Do you understand that 80% will need to go back on their meds by 7 years?
  - Do you understand that 19% will have major complications by 7 years?

Check List Prior to De-Escalation Therapy

- Discuss with the patient the risks and benefits of this approach, as well as the backup plan if de-escalation fails.
- Confirm deep remission with endoscopic evidence of mucosal healing. This should be present for > 1 year on the current regimen at the current dosage.
- Confirm optimization of therapy. It is crucial to make sure that this regimen is achieving its goal and that the patient’s drug levels, or metabolites are adequate.
- De-escalate the chosen therapy in dose or stop altogether.
- Monitor for subclinical relapse. Serial monitoring for early signs of activity is necessary to prevent significant relapse. This should consist of serial clinical assessments and may involve scoping, C-reactive protein, and/or fecal calprotectin.
- Know the rescue plan. If the patient does require re-escalation of therapy, the prior therapy may or may not be the best agent for him or her at that time. Medication decisions must be made based on the current presentation

Case Study

- 21-year-old male with Crohn’s disease diagnosed at age 12. He has ileal strictures and perianal abscesses and was initially on several years of 5-ASA therapy and required two resections. He is now in deep remission on adalimumab and methotrexate. He decides to stop his medications and use marijuana instead. He feels “fine” for 6 months and misses his clinical appointment.
- He turns up in the ER in month 7 with a perianal abscess, active inflammation, and a new small bowel stricture. In addition, he now has antibodies to adalimumab.
- He starts IFX + MTX. 6 Months later MRE shows resolution of stricture and abscess.

Follow Up – High Risk Patient

- History of noncompliance
- Trough IFX level < 3 ng/mL
  - Disease relapse with anti-TNF agents is common; up to 40% of patients initially responding to anti-TNF therapy will lose response in the first treatment year
- Increase IFX from 5 mg/kg to 7.5 mg/kg – 10 mg/kg
- If trough level is 3-7 ng/mL may consider stopping MTX
- Repeat trough IFX 3 months after stopping MTX
- Repeat labs (crp, cbc with dif, cmp q 12 weeks)

Tips for Drug Escalation – High Risk Patients

- If no response after the loading dose – have a low threshold to monitor a trough level and dose escalate if necessary.
  - Determine if there is enough drug, presence of anti drug antibodies or if the patients is a primary non responder
- Understand that most published therapeutic trough levels are 6-12 month maintenance levels.
- If a patient has high inflammation after the loading dose, you will need much higher levels than the published therapeutic trough levels.
- Use the same lab for subsequent monitoring.

Conclusions

- A majority of IBD patients will need to be on long term therapy, however, a subset of patients may be eligible to stop therapy, if they meet criteria
- Communicate expectations for frequent monitoring and risk for relapse for IBD patients.
- De-escalation is not the same as stopping therapy or taking a drug holiday and may be cost effective and provide a psychological benefit to the patient.
- Understanding dose escalation for high-risk patients may increase their chance for remission.