Inflammatory Bowel Disease Seattle Journal Club

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1. SCENIC is changing the landscape of dysplasia surveillance and management in IBD

Current US guidelines for neoplasia surveillance in IBD recommend obtaining > 32 random biopsies in addition to targeted biopsies of lesions visible with white light colonoscopy. These recommendations are clearly flawed and based on the premise that a significant proportion of neoplasia is invisible according to data accumulated in the ‘80s and ‘90s or before the advent of high-definition video-colonoscopy and image-enhanced endoscopy. Recent studies, instead, have reported that most dysplasia in IBD patients is visible using more advanced technologies and therefore a paradigm change in surveillance is overdue. An international group of experts has developed a consensus statement on the surveillance and management of dysplasia in patients with IBD (SCENIC) based on extensive review, synthesis and grading of the available evidence. The overarching message from this document is that current surveillance guidelines are flawed and a new approach is needed given the advances in technology and knowledge of the natural history of neoplasia. These can be summarized in a few bullet points:

- The terminologies of ALM and DALM should be abandoned. Instead, polypoid, non-polypoid and resectable or non-resectable lesion attributes are recommended.
- Chromoendoscopy (CE) with dye spraying is recommended or suggested over standard-or high-definition white light endoscopy (WLE), respectively. Since the overwhelming majority of endoscopic platforms currently use high-definition imaging, the first part of this statement is relatively superfluous.
- Narrow-band imaging (NBI) is not recommended as a surveillance technique in IBD
- Resectable polypoid and non-polypoid dysplasia can be managed with surveillance rather than colectomy if complete removal is documented.

Noteworthy, the SCENIC panel was unable to reach consensus on one of the most controversial parts of the current surveillance guidelines which is the issue of random biopsies. There was a trend in favor of dropping random biopsies when CE is performed but overall it was concluded that the evidence for a firm recommendation is lacking. However, a systematic review of the data showed that < 1.5% of patients with dysplasia will be missed if random biopsies are not performed. An even more appalling statistic is that only about 1:1,000 random biopsies identify dysplasia.

Comments: This document is the most significant evidence of progress in the field of dysplasia surveillance and management in IBD in the last 30 years. The guidelines that are currently in effect in the US, are flawed both due to poor effectiveness and high cost. Several European societies have already changed their approach to surveillance by a more firm endorsement of CE. While this statement is a huge first step, it is a bit disappointing to see that the lack of high-quality evidence prevents a more drastic revision of current US guidelines. In addition to
providing surveillance recommendations, this document also provides a detailed description of the CE technique as well as extensive references to more in-depth resources for learning the technique including atlases and videos. It is clear that we are witnessing a tidal change in IBD surveillance and this important document should serve as a major springboard for further research and developments in this field.


2. How common is deep remission with combination or monotherapy in Crohn’s disease?

As we have become more aware that clinical response scores are imperfect, clinical trials have started to incorporate more objective markers of disease activity as their endpoints. The concept of deep remission has thus been coined and it means attaining both clinical remission (absence of symptoms) and – at least endoscopic – mucosal healing. In some cases, CRP normalization has also been incorporated in this concept. In this post-hoc analysis, investigators are re-analyzing the data from SONIC (an RCT of Aza, IFX or combo therapy for bio-naïve CD) using a subset of patients in whom both endoscopic activity and CRP were available at baseline and at 26 weeks. A number of composite endpoints permutations were used to define remission. Data was only available for 188 of the 508 patients enrolled in SONIC. Of these, 72% of patients achieved clinical remission (CR) and 48% mucosal healing (MH), both much higher than in the complete SONIC cohort. All composite endpoints (combinations of 2 or 3 of CR, MH and CRP) were significantly higher with combination therapy compared to IFX or Aza monotherapy in this subset of patients. Median serum IFX levels were higher among patients who achieved deep remission compared to those who did not. Patients with “early” CD had better remission rates compared to those with longer disease duration. Although deep remission (clinical remission, normal CRP and MH) was only achieved in 52% of patients on combo therapy the relative difference from IFX and Aza monotherapy was significantly higher than in the original cohort (26% for IFX and 13% for Aza). Interestingly, health-related quality of life scores were associated with clinical remission but not CRP or mucosal healing.

Comments: Although this paper’s strength lies more in combinatorial math than clinical science, the message here is that deep remission can be achieved with combination therapy. However, as expected, the more stringent the criteria we use to define the outcome, the more likely we are to see lower response and remission rates regardless of the treatment used. As both investigators and regulating agencies are now requiring objective markers of response to therapy in clinical trials, this trend is likely to continue. Intuitively this may make comparative effectiveness studies easier to perform (even across trials). On the other hand, the question that remains unanswered is how deep a remission we need to aim for in order to achieve patient-directed goals of treatment. It is remarkable that in this study, the patient’s “QOL remission” did not correlate very well with any objective marker and was only associated with clinical remission. So, from the patient’s perspective, “best” does not appear to be better than “good”.


Studies like SONIC have demonstrated the utility of combination therapy in patients who are naïve to immunosuppressive therapy, but the benefit of continuing IMM when “stepping up” to anti-TNF therapy for CD is unclear. The theoretical reason to continue IMM in this setting would be to achieve higher biologic trough levels and lower levels of antibodies. However the clinical benefit of this strategy is unclear. Investigators have conducted a retrospective study including 2,300 patients with CD from a Medicare database to compare the efficacy and safety of combination vs. monotherapy when stepping up to a biologic. Outcome measures were the rate of surgery, hospitalization and discontinuation of anti-TNF for efficacy and the rate of serious and opportunistic infections for safety. In order to match the two cohorts of patients - mono- vs combo-therapy - a number of covariates were used to build a propensity score.

Overall there was no significant difference in the rates of surgery (HR 1.2), hospitalization (HR 0.82), discontinuation of anti-TNF or surgery (HR 1.09) or serious infections (HR 0.93) between the two groups at a median follow-up of < 2 years, but there was a higher risk of opportunistic infections (HR 2.64) and especially herpes zoster (HR 3.16) in the combo therapy group.

Comments: Although the results of this study are plausible, they are difficult to extrapolate to the general Crohn’s disease population. This study included a very heterogeneous Medicare population in which 52% of patients were over the age of 60 and the majority of those younger than 60 were on disability. Despite this, < 5% of patients had prior bowel surgery indicating either very slowly progressive disease or under-reporting. The study was also underpowered based on pre-specified power calculations and the baseline level of disease activity and smoking status are unknown. The authors have also purposefully excluded malignancy as a safety outcome probably due to the small sample size. It is unclear if by extending the follow-up beyond two years additional differences in efficacy or safety between these two groups would have become apparent. Since the use of IMM in combination with biologics is more important during the first year of dual therapy, this study further supports this paradigm particularly in elder patients who are at higher risk of complications including infections and neoplasms. However, further prospective studies in younger patient populations are needed to confirm these findings.