Review of: "Predictive factors of relapse after dose reduction of oral 5-aminosalicylic acid in patients with ulcerative colitis in the remission phase"

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Potential competing interests: The author(s) declared that no potential competing interests exist.

This is a single-center, retrospective cohort study to evaluate predictors of relapse in patients with ulcerative colitis who underwent de-escalation of 5-ASA therapy. The outcome of interest was clinical relapse within 52 weeks, as defined by a partial Mayo score of 3 or greater. The predictors of interest included clinical history, medication usage, and bloodwork. 70 patients were included, of whom 26% experienced relapse during the study period. On univariate analysis, only a history of corticosteroid usage and prior acute severe ulcerative colitis (ASUC) were associated with relapse with $p<0.05$. Multivariable analysis included only those two variables that were significant and did not adjust for other variables. After adjustment for corticosteroid usage, only a history of ASUC was predictive of relapse. The authors conclude that physicians should exercise caution when de-escalating 5-ASA therapy in patients with a history of ASUC.

While the study aims to address an interesting question in the field (the appropriate de-escalation of therapy), there are several design and methodology issues that limit the ability to draw meaningful conclusions from the study.

From the design perspective, by restricting the cohort only to patients who had a de-escalation of 5-ASA therapy, the authors are unable to compare their outcomes to a cohort that continued 5-ASA therapy. Having a 5-ASA control group would have led to more compelling comparisons and would have been simple to analyze with time-to-event techniques. For instance, if the authors found that among patients with a history of ASUC, those with de-escalation of 5-ASA therapy had a greater risk of relapse than those who continued 5-ASA therapy, that would have been compelling evidence demonstrating that de-escalation is probably dangerous in patients with prior ASUC. As the study is designed, the authors could only reasonably conclude that patients with prior ASUC just relapse more than patients without prior ASUC, which simply demonstrates that ASUC is a predictor of a more aggressive disease phenotype.

From the methodology perspective, there were a few minor issues. First, it is unclear why the authors chose to use the binary outcome of relapse by week 52 as the primary outcome as opposed to the time-to-

event outcome of time-to-relapse, for which they had sufficient data to measure based on their Kaplan-Meier curves. Time-to-event data has numerous advantages to simple binary outcomes; one simple reason is that patients who don't have a complete observation period (52 weeks) don't need to be excluded, and instead can just contribute data for their period of observation. For a study with only 70 patients such as this, they lost 10% of their cohort simply because the observation period was less than 52 weeks. Second (and more minor) issue was in the selection variables for the multivariable model. Typically, these models use less stringent criteria for entry (such as $p<0.1$) and adjust for common nuisance variables such as age and gender even if they are not significant. The overall model only used 2 predictors, both of which likely are just downstream variables of the underlying disease severity (although it is interesting and logical that the effect of prior corticosteroid usage disappears once we account for history of ASUC.

Overall, this is an interesting study that could have gone a bit farther toward answering interesting questions about de-escalating 5-ASA therapy in patients with UC if they had included a control group of patients who continued 5-ASA therapy and used a time-to-event outcome. As it is, the primary conclusion of the study is that patients with history of ASUC are more likely to relapse, which isn't novel or contested. Furthermore, since a history of ASUC portends an aggressive phenotype, 5-ASA mono-therapy is probably insufficient for maintenance of remission for most of these patients anyway as the authors allude to in their discussion. I would encourage the authors to consider repeating the study with the above suggestions and re-analyzing it.