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ReachMD
www.reachmd.com
info@reachmd.com
(866) 423-7849

Expert Perspectives on Anti-TNF Therapy in the Perioperative Period

Dr. Buch:
Welcome to *GI Insights* on ReachMD. I'm your host, Dr. Peter Buch. Joining us today to discuss the safety of anti-TNF therapy in the perioperative period are Drs. Benjamin Cohen and Stefan Holubar. Dr. Cohen is the Co-Section Head and Clinical Director for Inflammatory Bowel Disease at the Cleveland Clinic, and Dr. Holubar is the Inflammatory Bowel Disease Surgery Section Chief and Director of Research at the Cleveland Clinic.

Dr. Cohen, welcome to the program.

Dr. Cohen:
Thanks for having me.

Dr. Buch:
And Dr. Holubar, excited to have you join us, as well.

Dr. Holubar:
Thank you very much, Peter.

Dr. Buch:
So let's dive right in. Let's start with you, Dr. Cohen. Can you tell us about the PUCCINI trial and why it's important?

Dr. Cohen:
For years, there's been a lot of confusion in literature regarding the safety of anti-TNF therapies in the perioperative period. And a lot of the initial studies done on this topic with retrospective, mostly single-center analyses and at the time we conceived the PUCCINI study, there were no prospective cohorts built to answer the question. And really, it's important to study this particular topic prospectively as there are many potential confounding factors that can contribute to postoperative infections, and not all will be available accurately in the medical record from retrospective review. This is part of the reason why there was conflicting data out there regarding the relative safety of TNF inhibitors in that perioperative period.

So the PUCCINI study was a large prospective cohort study run through the Crohn's & Colitis Foundation Clinical Research Alliance. It included 947 patients over 17 sites from different regions of the country with different levels of IBD expertise, and patients were enrolled preoperatively for up to four days postoperatively so we may include patients who had emergency surgeries as this could be a risk factor for postoperative complications including infection. And the main outcome we were looking at was risk of postoperative surgical site infections and any infection including non-surgical site infections.

About two-thirds of the cohort had Crohn's disease and the rest ulcerative colitis and almost 40 percent of the cohort reported use of TNF inhibitors within 12 weeks of surgery, which was the most common exposure definition for TNF inhibitors in the literature. But one

key aspect of the PUCCINI study, which separates it from the other studies on the topic, is that we also explored TNF inhibitor exposure through measurements of perioperative drug levels. And in recent years, therapeutic drug monitoring has become a key aspect of our use of biologic drugs, and we've learned that exposure may be more accurately assessed through measurements of serum drug concentrations than by timing of the use of the drugs. This is because there can be different degrees of clearance of these drugs in patients, and one patient who receives a TNF inhibitor eight weeks before surgery may have a higher drug level than somebody who receives it four weeks before surgery, so really that drug level concentration is the true indicator of exposure.

The main findings that we had in the study were that preoperative TNF inhibitor exposure, defined either by patient use within 12 weeks of surgery or having detectible serum drug concentrations at the time of the surgery, were not associated with any infection or surgical site infection even after we controlled for multiple known confounding risk factors. And additionally, the preoperative TNF inhibitor exposure was not associated with other key secondary noninfectious outcomes, including postoperative length of stay, readmission, reoperation, or postoperative ileus.

Dr. Buch:
Thank you for that. And moving on to Dr. Holubar, can you comment on doing a diverting stoma if a patient is on biologics?

Dr. Holubar:
Yes. Whether or not the biologics are associated with perioperative complications has been hypothesized since around 2005 and 2006 when two different studies came out, one from Cleveland Clinic and one from Mayo Clinic, and these were suggesting that they were associated with postoperative infectious complications, and this really was an early warning signal.

Now fast forward to 2022 when we have the results of the PUCCINI study, and that study doesn't really suggest that the biologics are a risk factor, so we don't really feel that biologics alone mandate diversion with a stoma. Now the decision to make a stoma depends on the other risk factors, not for infection but for anastomotic leak. So although things have changed, we still hold by the statement in the Crohn's & Colitis Foundation position statement, stating that the decision to divert is best left to surgeon discretion.

I will state furthermore, that there's two other concepts that come to mind, one for ulcerative colitis and one for Crohn's disease. For ulcerative colitis presently, approximately, 90 percent of J-pouches done in the United States are done in a 3-stage manner, and this is because patients are tending to present at a later stage. And we're doing these operations for the most part laparoscopically now, so a patient who's sick, we don't want to make a J-pouch. It's the wrong time to remove the rectum and make a pouch that really needs to last the patient for the rest of their life, and pouches have an approximately five percent anastomotic leak rate. So the majority of pouches are being done in a 3-stage manner, so the question is a little bit irrelevant for ulcerative colitis.

Now for Crohn's disease it's a little bit different because we've looked at a couple of different studies, and at Cleveland Clinic and nationally we know that at IBD centers at least, approximately 20–25 percent of ileocolic Crohn's disease patients are being diverted. And again, that's not necessarily due to biologics. It may be a little bit overinflated due to surgeon fear over biologic but typically, it's done for other risk factors such as malnutrition, anemia, smoking, and most importantly, corticosteroid use.

Dr. Buch:
Thank you for that useful information. Continuing with you, Dr. Holubar, how soon do you restart at-risk postoperative patients on anti-TNFs?

Dr. Holubar:
That's another great common question that comes up very frequently in clinical practice. Again, it's different for ulcerative colitis and for Crohn's disease because for the most part, the ulcerative colitis patients are going laparoscopic total abdominal colectomy with end ileostomy, and then basically biologics are stopped. So it's not an issue for ulcerative colitis, but for Crohn's disease it is an issue because frequently these patients are medically refractory and having bowel damage progression despite the biologic that they're on or already had bowel damage by the time the biologic was started too late, perhaps. Often, we're trying to resume the biologic as soon as possible after surgery or switch them to a new biologic, either immediately after they recovered or after a six month interval colonoscopy, to assess record score for inflammation.

So the bottom line is, if we want to continue the same biologic or standard, practice at IBD centers is to resume the biologic somewhere

between two and four weeks after the operation, and basically, we want to make sure that the patient has made a full recovery in terms of infectious complications before we resume the biologic in the Crohn's disease population.

Dr. Buch:
For those just tuning in, you're listening to *GI Insights* on ReachMD. I'm Dr. Peter Buch, and today I'm speaking with Drs. Benjamin Cohen and Stefan Holubar about the safety of anti-TNF therapy in the perioperative period.

Coming back to you, Dr. Cohen, is it time to extrapolate the anti-TNF data to all classes of biologics?

Dr. Cohen:
With regards to other biologics, we don't really have all of the data in the same way that we do with TNF inhibitors, though in the PUCCINI study, we actually did collect patients who were on vedolizumab because vedolizumab became an approved therapy during the time of the PUCCINI study. We haven't yet published this data, but the theme was the same as with the TNF inhibitors, that there was no signal for postoperative infectious complications associated with preoperative vedolizumab use. And there's been other retrospective multicenter studies that have showed the same thing with vedolizumab. My suspicion is, it will be the same story as we begin to pull together data regarding ustekinumab.

There has already been retrospective data in this regard but I think with each therapy it's important that we build large prospective cohorts so that we can really get high-quality data to guide us in the use of these medications in the perioperative period. And that's really the significance of Dr. Holubar's National Surgery Quality Improvement Program project that is already enrolling a lot of these patients prospectively, and now beginning to collect their biologic use in the perioperative period to help us be able to answer these questions because we're in a period of great drug discovery in IBD. And there's going to be more and more new drugs and new mechanisms and these questions are going to keep coming up, so we have to have a mechanism in place by which we can study the safety of the drugs in the peri-op period.

Dr. Buch:
Dr. Cohen, that was a wonderful segue into Dr. Holubar's next question, and that is if you can discuss the National Surgical Quality Improvement project database, what it collects, and what you expect to obtain after a period of time using it.

Dr. Holubar:
Sure. To summarize, for those who are not aware, NSQIP, the National Surgical Quality Improvement Program, was started in 2005 by a colorectal surgeon named Clifford Ko at UCLA, and he designed this very large data structure, data program, which now has over 900 hospitals throughout the world that subscribe.

And so about 2016, I met with Sonia Ramamoorthy, a colorectal surgeon, as well as Sam Eisenstein, a friend and collaborator of mine, and Sam and I designed the NSQIP-IBD Collaborative. And basically, we added five new variables to NSQIP, which were IBD-specific, and this included more granular data regarding corticosteroids, biologics, immunomodulators, what type of stoma was made, if a pouch was made, and dysplasia, so those were the new variables.

So as of year four data, we had 4,500 patients and about half of those were on biologics, so really big numbers. is study, for the first couple years, included 14 centers from around the country for patients undergoing colectomy or proctectomy, and we made a propensity score and it was the propensity to receive biologics. And then we performed a univariate conditional regression, which basically just answered the question, when you adjust for everything else, were biologics associated with the infectious outcomes? And then we did a traditional multivariable logistic regression in a propensity score-matched group. And out of the 4,500, we came up with 2,700 propensity-matched patients. That was based on the half of the patients who got biologics. We kept all those. The biologic patients were quite different from the nonbiologic patients. They were more likely to be on concomitant steroids, to have Crohn's disease, be getting immunomodulators, to be anemic and malnourished, and they were also more likely to undergo urgent surgery, colectomy, and ileostomy, but the propensity modeling in multivariate really gets rid of those differences.

What we found in both the unmatched and matched cohorts was that, in both conditional regression and multivariate logistic regression, biologics were not associated with any infection, any surgical site infection, or any leak.

We do have some limitations of the study, including lack of IBD extent or severity. There's obviously variation in the different types of

biologics and the timing. There is surgeon variability and there's also a question if this is generalizable to non-IBD centers, as we only included IBD centers. But in summary, biologics within two months of surgery were not independently associated with postoperative infections or anastomotic leaks. And this is a big ongoing collaborative project. The paper is presently under revisions in the journal *Diseases of the Colon & Rectum*.

Dr. Buch:
Looking forward to all of that data. This was an important discussion of anti-TNF therapy in the perioperative period. And I want to thank my guests, Dr. Benjamin Cohen and Dr. Stefan Holubar, for sharing their insights. Dr. Cohen, thanks so very much for joining us today.

Dr. Cohen:
Thanks for having me.

Dr. Buch:
And, Dr. Holubar, it was a pleasure speaking with you, as well.

Dr. Holubar:
The pleasure is all mine. Thank you, Peter, and thank you, Ben.

Dr. Buch:
For ReachMD, I'm Dr. Peter Buch. To access this and other episodes in this series, visit ReachMD.com/GIInsights where you can Be Part of the Knowledge. Thanks for listening, and see you next time.