5 Ways to Advance IBD Care: Dr. K Recaps IBD Innovate, AIBD and CCC

The late fall and winter are typically the time for the three main IBD meetings: IBD Innovate, Advances in IBD (AIBD) and the Crohn's Colitis Congress (CCC). I virtually attended all three meetings and would like to share some of my "takeaways".

The CCC opening keynote speaker, Jean-Frédéric Colombel, MD, PhD, professor of gastroenterology and co-director of the IBD Clinical Center at Icahn School of Medicine at Mount Sinai, provided a framework to review the common themes of this year's meetings in his fabulous presentation, "Breaking the Ceiling on IBD".

Dr. Frédéric presented the cold hard facts: Our treatments for IBD are plateauing. We only maintain control of the disease in about 40%-50% of the patients, and surgeries are unfortunately still necessary in almost 1 in 5 patients. Despite advancements in the field, 18% of patients with Crohn's require surgery within five years of disease onset.

How do we break this therapeutic ceiling? Dr. Frédéric framed the solution in the following categories:

1) Make the most of what we have
2) Personalize our therapy
3) Consider combination therapy
4) Explore new pathophysiology
5) Enhance prevention

I'd like to use these five categories and pull from the three meetings to update all of you on what I learned:

1. Make the most of what we have

To improve the success of treatment, we must begin to decrease the delay to diagnosis. Diagnostic delay is common in the U.S. Fifty-two percent of Crohn's disease patients and 37% of ulcerative colitis patients report at least a 2-year delay in diagnosis. This is not likely a gastroenterology issue, but a primary care one. We need to get more education to our primary care providers on the symptoms and signs of IBD.

Early diagnosis will enable us to start therapy earlier. As the Lehman Index indicates, the sooner inflammation is controlled, the less tissue is permanently damaged. This requires early assessment of disease severity and activity. Jami Kinnucan, MD, senior associate consultant in gastroenterology and hepatology at the Mayo Clinic in Jacksonville, Fla., presented a session where disease activity assessment was discussed for both Crohn's disease and ulcerative colitis.

    - Disease Severity in Crohn's disease involves:
        - Age at diagnosis, with age 30 being the pivotal year
        - Extent of disease
        - Presence of absence of perirectal disease
        - Stricturing or penetrating disease
        - Deep ulcers
        - History of previous surgery

A specific note was made by multiple presenters about a new tool to assess Crohn's disease severity called the CDPath. This is a validated prognostic tool developed by Prometheus Labs that uses a blood test to evaluate an adult Crohn's disease patient's potential risk for developing serious complications within 3 years. It is free to the patient, courtesy of a grant from Takeda.

    - Disease severity in ulcerative colitis involves:
        - Age at diagnosis, with age 40 being the pivotal year
        - Extent of disease
        - Deep ulcers
        - Steroid dependence
        - Previous hospitalizations

    - Disease activity in both Crohn's and ulcerative colitis involves:
        - C-reactive protein (CRP)/erythrocyte sedimentation rate (ESR)
        - Fecal calprotectin (FCP)
        - Indexes: CDAI, Mayo Score, etc.

- Treat to Target (T2T) and therapeutic drug monitoring (TDM) can help maintain tight control. The target for T2T continues to be refined. Patient-reported outcome measures using symptom indexes can be used as a first line of defense to bring patients in for therapy, but they should not be the end goal alone. Biochemical targets like CRP and FCP are next level, more objective measures, with endoscopic healing being the preferred ultimate target. Recognize that this is currently attainable in only a minority of our patients.

- Therapeutic Drug Monitoring (TDM) remains a challenge and the studies are producing equivocal results. William Sanborn, MD, co-founder and chief medical officer of Shoreline Biosciences, stated in his presentation that he reserves the use of TDM for patients with significant inflammatory load. Marla Dubinsky, MD, division chief of pediatric gastroenterology at Mount Sinai Kravis Children's Hospital and co-director of the IBD Clinical Center at the Icahn School of Medicine at Mount Sinai, presented very impressive data on early TDM during induction which can predict long-term dosing. Several other presenters referenced her work, but this needs to be replicated.

2. Personalize our therapy

The era of “one drug fits all” is over and we have entered a personalized phase of drug therapy. Multiple biomarkers have been proposed as tools to assist us in selecting the right drug for the right patient. Several have been studied to assess for anti-TNF sensitivity:

- Genes and RNA biomarkers
- Microbiome biomarkers
- Serologic biomarkers
- Mucosal biomarkers

These are not being used as yet in clinical practice due to problems with reproducibility and practicality. One biomarker is of note, HLADQA1*05. This marker is associated with the development of antibodies to infliximab. If patients don’t have this marker, their chance of developing antibodies to infliximab is quite low.

3. Consider combination therapy

As has been already done in the rheumatology space, combination therapy is coming for IBD. There are studies in progress evaluating the use of multiple biologics from different classes, e.g.,: anti-TNF with anti-integrin or anti-integrin with JAK inhibitor. Currently the available date shows that combination therapy appears safe. These studies have been largely retrospective, and we need prospective studies. The key to having effective combination therapy is to combine drugs that are complementary rather than focused on the same target.

4. Explore new pathophysiology-driven therapeutic targeting

Multiple speakers mentioned the new category of drugs, sphingosine-1-phosphate receptor agonists. The first approved drug of this class is ozanimod, which has been approved for ulcerative colitis. Unlike anti-TNFs and anti-integrins, S1P agonists sequester lymphocytes to peripheral lymphoid nodes, keeping them away from their sites of chronic inflammation.

Currently our therapies are focused on control of inflammation. Maybe it is time to target other parts of the response. The most fascinating alternative target is the fecal microbiome. Fecal Microbial Transplants have been the launching pad for this, but the science has been moving toward complex microbial fractions using defined consortia of bacteria and viruses.

The most ubiquitous organisms in nature are bacteriophages. These are viruses that attack bacteria, and they play a key role in maintaining balanced bacterial populations. They are being studied as tools to control the bacterial populations in our fecal microbiome.

Another area of research is concerned with improving the intestinal barrier. GLP1/GLP2 agonists are being studied in their effect on improving the gut barrier function.

5. Enhance prevention

Since a preclinical phase of IBD has been identified, we may be able to use this to decrease or postpone the incidence of IBD. There is an international collaborative effort to collect information on the preclinical phase of IBD. These complementary studies are attempting to build high-dimensional disease prediction algorithms that will identify new pathophysiologic targets. This information could usher in a new era of IBD treatment, one in which we can break the therapeutic glass ceiling and

prevent or proactively address symptoms of gastrointestinal disease. That's exactly what we're doing for patients at the clinical phase of IBD at SonarMD — we detect and proactively address deterioration before it becomes a health emergency. Applying these same methods to the preclinical phase of IBD could significantly improve quality of life for our patients by reducing complications and the need for aggressive treatments.

Conclusion

After the latest round of IBD meetings, it is clear that therapies for IBD have plateaued — but that doesn't mean we can't continue to drive improvements in health outcomes for patients with IBD. We can start by using current drugs sooner in disease progression. This will require working more closely with primary care providers to speed diagnoses, alongside continued refinement of diagnostic tools. Meanwhile, personalized therapy and combination therapy are two areas to watch. As research continues in these two areas, they present major opportunities to advance the efficacy of treatment. Lastly, we must continue to embrace prevention and early detection as the optimal pathway for IBD. Prevention will always be better than treatment.