Shifts in Crohn's Disease Treatment Models

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Has there been a shift in the treatment paradigm for Crohn’s disease, should be using infliximab-based therapy be given serious consideration even early, or is it too risky for many patients. Joining us to discuss new Crohn’s disease developments is Dr. William Sandborn, Professor of Medicine in Dorothy A. Adair Professor of Gastrointestinal Research at Mayo Clinic, College of Medicine, Dr. Sandborn is also Vice Chairman of the Division of Gastroenterology and Hepatology at Mayo Clinic.
DR. MARK DELEGGE:
Welcome Bill?

DR. WILLIAM SANDBORN:
Thank you very much.

DR. MARK DELEGGE:
Bill, I have heard a lot recently in the literature I read a lot about these paradigms for treatment of Crohn’s disease. What I hear either step-up or step-down? Can you explain that and tell us what the current treatment paradigm is for Crohn’s disease?

DR. WILLIAM SANDBORN:
Well, the historic treatment paradigm is to begin with the drugs that we think are the safest and perhaps the least effective and move up through different courses of therapy, so historically patients have received mesalamine drugs, then steroids, then azathioprine, or 6-mercaptopurine, and finally biologic agents such as infliximab and this would be the so-called step-up for pyramid treatment paradigm. In the last few years, the idea has been proposed to reverse that pyramid or take it topdown approach for use of the most effective drugs first or very early in the course and we have had some preliminary studies and more recently a more definitive study looking at this so-called topdown strategy.

DR. MARK DELEGGE:
So that you will be moving more so towards the biologic agents first perhaps and then moving back
down from there.

DR. WILLIAM SANDBORN:

That was the hypothesis and you know I think most of us like to change our practice based on new data and so many practitioners I think have been anxiously waiting more substantive data about what the ideal toptdown strategy might be and just how good would it be. So, it wasn’t fair to complete that it would be a biologic and actually the study that we will talk about today was comparing the idea of using azathioprine as a toptdown agent versus biologic therapy with infliximab versus the combination and the outcome of that trial kind of would dictate what the ideal toptdown strategy would be.

DR. MARK DELEGGE:

Now, from my own perspective I know that I have a small number of patients with Crohn’s disease and therefore I may not even have a good idea about what the actual progression of Crohn’s disease is meaning in a large group of patients followed for years, what is the progression of Crohn’s disease?

DR. WILLIAM SANDBORN:

There is 2 separate dynamics going on in patients with Crohn’s disease. One dynamic is the acute kind of flare or relapse and then going back in to a symptomatic remission and then there is the long-term progression of the disease. So, in the short term, which is where many practitioners are in terms of seeing a patient in the office that are either well or not and you know you are looking at just at that snapshot in time and so at any given time about half of the patient’s will be in symptomatic remission and about half of patients will be flared up. In the longer term if you look at things, the patients typically start with what we would called inflammatory disease, so if you do colonoscopy or CT or MRI, enterography, you will see evidence of active inflammation without the complications of stricture fistula and abscess that occur later and then is that chronic inflammation persist about 80% of patients will have progression to the development of strictures, fistulas, or abscesses overtime and its post
complications that account for most of the surgery that occurs in patients with Crohn’s disease. So, 15 or 20 years out from diagnosis cumulatively about 80% of patients will have progressed from inflammatory disease to having the complication of stricture, fistula, or abscess and the majority of those patients then will require surgery and we know that the majority of patients, who require for surgery will have recurrent Crohn's disease and many will require second surgery and so on.

DR. MARK DELEGGE:

Knowing that majority I guess here patients are going to have some difficulties. My knee-jerk response when I see Crohn’s patient who is perhaps flaring or having problems with steroids and we will give him some prednisone or IV steroids or other pros and cons to using steroids?

DR. WILLIAM SANDBORN:

The steroids are highly effective in the short-term for resolving the symptoms of Crohn’s disease. When it has been looked at, they don’t lead to very high rates of bowel healing with the subsequent followup colonoscopy and the biggest problem with steroids is they are not effective for the long term in maintaining remission of symptoms or bowel healing and so as many as 70% or 80% of patients will respond in the short term to a course of steroids, but then if you withdraw the steroids, a large percentage of those patients will relapse and several studies have now demonstrated that once you start the patient on steroid the chances that they will be in clinical remission of steroids at the end of the year is somewhere in the range of 25% to 30%. So, the majority of patients will respond to steroids in the short-term, but failed in the intermediate to long term. The other issue with steroids is that the toxicity has been under appreciated. So, we all know that steroids can cause moon face and weight gain and hypertension and diabetes and osteoporosis and osteonecrosis, but the really serious problem that we see is infection and there are now a number of studies that have shown about a 2-fold increase in the risk of mortality with steroid use and this doesn’t mean the patients are necessarily on steroids for many months or years that can be even shorter periods of time, so although we see infections with azathioprine and we see infections with the anti-TNF agents and there is no question about that the most clear link between fatal outcomes and medical therapy is with steroid therapy.
DR. MARK DELEGGE:

If you are just tuning and you are listening to GI Insights on ReachMD, The Channel for Medical Professionals. I am your host Dr. Mark DeLegge and joining me to discuss new Crohn’s disease development is with Dr. William Sandborn, Professor of Medicine and the Dorothy A. Adair professor of Gastrointestinal Research at Mayo Clinic, College of Medicine.

Bill, how about the antimetabolites that we call them such as azathioprine, are they effective?

DR. WILLIAM SANDBORN:

I think they are effective. These were first reported in control trials going back to about 1980. There is 2 drugs in this class, azathioprine and 6-mercaptopurine. Neither drug is FDA approved for the treatment of Crohn’s disease, but there is good scientific evidence that they are effective for maintaining remission and for steroid sparing. Because the large trials that would lead FDA approval have never been performed, the exact magnitude of the fact has been somewhat uncertain. The clinical trials that have studied these drugs and Crohn’s disease have been quite small and it has also been a bit hard to be certain about the level of side effects that you see with the medicines for exactly the same reasons and there has been very little information about whether these drugs will lead to bowel healing or mucosal healing at colonoscopy, so I think most of us believe that the drugs are effective. They have a role in clinical practice and we used them, but exactly how effective they are and what the relative efficacy is to alternative therapies, no one has been quite sure.

DR. MARK DELEGGE:

What about the anti-TNF therapies, their effectiveness prior to this we were reserving this for those patients who failed other therapies. What about its effectiveness?
DR. WILLIAM SANDBORN:

Well, I think you’ve stated it very well. These drugs were initially developed for patients that had failed other therapies and recurrent FDA approval is from moderate-to-severe Crohn’s disease unresponsive to conventional therapy and conventional therapies are little bit loosely defined, but I think many of us have interpreted that in general to mesalamine steroids and immunosuppressive drugs like azathioprine. When you used the biologic last after feeling all of those therapies you will see about 60% to 70% of patients, who will have meaningful clinical response in the short term and about 30% to 35% of patients will enter a clinical remission in the short-term and then if you continue the drug in patients who respond he will have about two-thirds of those patients maintaining response or remission out through the course of the subsequent year. So, you know if you think about 60% to 70% of patients respond initially and 60% to 70% of those patients will continue to respond overtime, you get down to as little as 30% or 40% of patients that will really stay well over the course of the year having started with moderate-to-severe Crohn’s disease. But you know in that setting you are treating patients who’ve often had surgery, who may have already had some progression of complications from the disease like a partially obstructing stricture and so you know it has left many of us wondering what would happen if you used these therapies earlier in the course before you’ve had this much surgery and its much irreversible valve damage from the progression of the disease.

DR. MARK DELEGGE:

I know that a number of gastrologists have been concerned with side effects from anti-TNF therapies. What you take on that?

DR. WILLIAM SANDBORN:

I think it is a very reasonable on legitimate concern, but it is very important to put the issue of side effects under perspective. So, the first thing is to think about Crohn’s disease itself. Crohn’s disease itself has a clear association with the reduction in life expectancy, so an increased mortality, a high cumulative rate of surgery, and as we discussed earlier high cumulative rate of requiring multiple surgeries. So, the Crohn’s disease itself is associated with increased mortality and morbidity. The
mesalamine drugs are not FDA approved for Crohn’s disease and the preponderance of the data is that the reader minimally effective or perhaps not effective at all, so although they are safe in terms of drug side effects, they are not safe in terms of progression of Crohn’s disease because of their low efficacy of the Crohn’s disease will often progress and you have a risk associated with progression of Crohn’s.

DR. MARK DELEGGE:

Well, Bill, it certainly sounds like we are going to have to keep an eye on this topdown therapy paradigm, and I would like to thank my guest from the Mayo Clinic, College of Medicine Dr. William Sandborn.

Dr. Sandborn, thank you very much for being our guest this week on GI Insight.

DR. WILLIAM SANDBORN:

Thank you so much for the invitation.

DR. MARK DELEGGE:

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