ADVANCES IN IBD

Current Developments in the Treatment of Inflammatory Bowel Disease

Section Editor: Stephen B. Hanauer, MD

Inflammatory Bowel Disease and Cardiovascular Disease

Remo Panaccione, MD
Professor of Medicine
University of Calgary CCC Chair in IBD Research
Director, Inflammatory Bowel Disease Unit
Director, Gastrointestinal Research
Cumming School of Medicine
University of Calgary
Calgary, Alberta, Canada

G&H What studies have shown a link between inflammatory bowel disease and cardiovascular disease?

RP Several epidemiologic studies have shown that inflammatory bowel disease (IBD) is associated with an increased risk of a variety of cardiovascular diseases, including ischemic heart disease, heart failure, atrial fibrillation, as well as pericarditis and myocarditis. For example, a study from Denmark that included almost 21,000 patients and almost 200,000 matched controls showed that patients with ulcerative colitis were 3 times more likely to develop acute myocardial infarction and 2 times more likely to develop heart failure than the general population. Studies from France have also shown an increased risk of heart failure and cardiovascular disease in patients with ulcerative colitis, which appears to be highest in females and higher in younger compared with older patients with extensive colitis. Other studies have shown that there is also an increased risk of cardiovascular disease, heart failure, and atrial fibrillation in patients with Crohn's disease.

G&H Has there been any conflicting research disputing this association?

RP Whether looking at epidemiologic studies from western Europe or Scandinavia, the signal has been fairly consistent. The one area where there may be some inconsistency is whether there is an increase in cardiovascular mortality associated with patients with IBD above and beyond the general population.

G&H What are the risk factors associated with cardiovascular disease in the general population and specifically in patients with IBD?

RP In the general population, there are cardiovascular disease risk factors associated with lifestyle, such as smoking and obesity. It is known that males are also at increased risk for cardiovascular disease compared with females. Age is an independent risk factor more so in females; as individuals age, they have an increased risk for developing cardiovascular disease. There are also certain comorbidities that may increase the risk of cardiovascular disease, such as chronic kidney disease, hypertension, diabetes, and hyperlipidemia.

When it comes to IBD, the additional prevailing risk factor is the presence of persistent inflammation. We know that chronic inflammation, not only in IBD but in other immune-mediated diseases, is associated with an increased cardiovascular disease risk. Some of this may be related to certain cytokine profiles such as increased levels of interleukin (IL)-6 (which drives C-reactive protein production), tumor necrosis factor (TNF)-α, or IL-1β, all of which have been linked to the development of atherosclerotic plaque.

G&H What are the possible mechanisms underlying the relationship between IBD and cardiovascular disease?

RP A number of potential mechanisms have been explored to explain the relationship between IBD and increased risk of atherosclerotic or ischemic cardiovascular

disease. One, as I mentioned, involves local and systemic inflammation and an increase in pro-inflammatory cytokines, such as IL-1β, IL-6, or TNF-α. This is thought to be associated with atherosclerotic cardiovascular disease by promoting plaque. It has also been proposed that there might be abnormalities within the gut microbiome in patients with IBD that lead to dysbiosis in the metabolome. This has been linked to atherosclerosis in animal models. We also know from a series of studies that patients with IBD have endothelial dysfunction, which results in lower levels of nitric oxide and higher levels of vascular endothelial growth factor and can be associated with differences in vascular remodeling. Additionally, patients with inflammation are known to have dyslipidemia with increased low-density lipoprotein (LDL) and triglycerides while having decreased high-density lipoprotein (HDL), which have been associated independently with a risk of atherosclerotic cardiovascular disease.

Even in patients as young as age 30 years, it would be reasonable to obtain a quick risk score to see if they have a high risk of cardiovascular disease.

G&H How can cardiovascular disease risk be assessed in patients with IBD?

RP There are no IBD-specific tools, so gastroenterologists can use the same tools as their colleagues in primary care and cardiology. One of the better tools currently available is the atherosclerotic cardiovascular disease risk estimator from the American College of Cardiology. Physicians can go online to https://tools.acc.org/ASCVD-Risk-Estimator-Plus/#!/calculate/estimate/ and enter information regarding a patient's risk factors, such as their age, family history, personal history, sex, and comorbidities. The tool then calculates a score for the patient.

It is important to keep in mind the additional concept that systemic inflammation is linked to atherosclerotic cardiovascular disease. Even in patients as young as age 30 years, it would be reasonable to obtain a quick risk score to see if they have a high risk of cardiovascular disease. If so, providers should consider whether there are any modifiable risk factors that can be addressed in primary care to decrease the risk of cardiovascular disease.

G&H What is the impact of different IBD medications on cardiovascular disease risk?

RP There is specific interest in cardiovascular disease risk associated with certain newer IBD medications such as Janus kinase (JAK) inhibitors or sphingosine-1 phosphate (S1P) receptor modulators. However, I would like to highlight that there are medications that have been used for years that are associated with cardiovascular diseases. For example, mesalamine (5-ASA) is considered a very safe medication but is associated with pericarditis and myopericarditis. Additionally, corticosteroids have been associated with an increased risk of heart failure, likely because of their link to salt and water balance and the fact that they lead to hypertension, dyslipidemia, diabetes, and thromboembolism. Prolonged corticosteroid use is bad for a host of reasons, but it should also be recognized that corticosteroids are associated with an increased cardiovascular disease risk.

Most gastroenterologists know that anti–TNF-α agents, particularly at higher doses, have been associated with worsening congestive heart failure, especially in patients who have preexisting heart failure of New York Heart Association class 3 or 4. On the other hand, anti–TNF-α agents have been shown to have a protective effect in immune-mediated diseases because of a link to decreasing inflammation and/or TNF-α levels.

One class of drugs that has garnered attention recently is JAK inhibitors. Concerns were raised because JAK inhibitors have been associated with an increase in LDL and triglycerides and, in some studies, hypertension. In patients with rheumatoid arthritis, there was a signal that there may be an increase in major adverse cardiac events (MACE). As a result, a large postmarketing safety study mandated by the US Food and Drug Administration examined whether there was an increase in MACE in a high-risk population of rheumatoid arthritis patients (ie, patients over the age of 50 years who had at least 1 cardiovascular disease risk factor) taking tofacitinib (Xeljanz, Pfizer) compared with those taking anti–TNF-α therapy. The study found an increased rate of MACE with tofacitinib (hazard ratio of approximately 1.33) compared with anti–TNF-α therapy. However, that risk was particularly driven by patients over the age of 65 years who had a previous MACE. Taking those patients away, there was no increased risk. That is one of the important takeaways from these data. Usually, in my own practice, I am cautious with patients who are over the age of 65 years, those who had previous MACE, and patients who are active smokers. These are the patients with IBD who

may have an increased risk of MACE. Interestingly, in the IBD literature of newer selective JAK inhibitors such as upadacitinib (Rinvoq, AbbVie), an increased MACE signal has not been seen.

Finally, another class of IBD drugs, S1P receptor modulators, has been associated with bradycardia and cardiac conduction abnormalities. There are S1P receptors on cardiomyocytes, so when those receptors become internalized, they change the way potassium flows across membranes. This is seen only in the first few days of treatment. Bradycardia can be seen, especially early on with S1P receptor modulator treatment, but then resolves after the first few doses. Therefore, with ozanimod (Zeposia, Bristol Myers Squibb) treatment, the dose is escalated slowly over the first week. Additionally, it is recommended that an electrocardiogram (ECG) be done to screen for preexisting conduction abnormalities, and providers should review that patients are not taking other therapies that can cause rhythm disturbances. Therefore, patients who have preexisting bradycardia or first- or second-degree heart block (Mobitz type 1) require first-dose monitoring, which includes an ECG before the dose, a 6-hour monitoring period, and a repeat ECG at the end of the monitoring period.

We should be using therapies that control inflammation, not only in the short term but also in the long term, because much of this increased risk is directly linked to patients who have ongoing inflammation.

G&H What strategies can be followed to help reduce cardiovascular disease risk in IBD patients?

RP One of the things gastroenterologists should be doing, aside from assessing risk, is promoting a healthy diet, physical activity, and a healthy weight. Additionally, we know that there is a negative relationship between smoking and Crohn's disease, as well as that smoking is a risk factor for ischemic cardiovascular disease, so we should be promoting smoking cessation. Most importantly, we should also keep a close eye on managing and controlling inflammation. We should be using therapies that control inflammation, not only in the short term but also in the long term, because much of this increased risk is directly linked to patients who have ongoing inflammation.

G&H Are there any common misconceptions involving this topic?

RP One is that young age precludes individuals from developing cardiovascular disease. Just because patients are young does not mean they are not at risk for cardiovascular disease. As health care providers who treat IBD, we need to have a high level of suspicion for cardiovascular disease in patients, especially when they start to complain of fatigue, shortness of breath, and any type of chest pain.

Additionally, some providers may not prescribe JAK inhibitors because they think these agents are associated with global increase in MACE. That is a misconception because the risk is only in a very specific patient population—patients over the age of 65 years who have already had a cardiovascular event or stroke and possibly who are long-term smokers. JAK inhibitors are safe and do not increase risk of cardiovascular disease aside from these specific patients.

G&H What are the next steps in research in this area?

RP Further research is needed on the overall mortality and morbidity associated with cardiovascular disease. Some of the studies I mentioned were performed before the advent of some of the more effective IBD therapies. Time-trend analysis is needed to determine whether cardiovascular disease risks are decreasing over time and whether they can be decreased by using highly effective therapies to control inflammation.

It is also important to develop a disease-specific lens on the risk factors associated with some of the newer medications, particularly the JAK inhibitors, over the long term. Many patients need to be followed for many years to establish whether this link exists in IBD therapies, and these data will likely come over the next 3 to 5 years.

Disclosures

Dr Panaccione has served as a consultant for Abbott, AbbVie, Abivax, Alimentiv (formerly Robarts), Amgen, AnaptysBio, Arena Pharmaceuticals, AstraZeneca, Biogen, Boehringer Ingelheim, Bristol Myers Squibb, Celgene, Celltrion, Cosmos Pharmaceuticals, Eisai, Elan, Eli Lilly, Ferring, Fresenius Kabi, Galapagos, Genentech, Gilead Sciences, GlaxoSmithKline, JAMPBio, Janssen, Merck, Mylan, Novartis, Oppilan Pharma, Organon, Pandion Pharma, Pendopharm, Pfizer,

Progenity, Prometheus Biosciences, Protagonist Therapeutics, Roche, Sandoz, Satisfai Health, Shire, Spyre Therapeutics, Sublimity Therapeutics, Takeda Pharmaceuticals, Theravance Biopharma, Trellus, Union Biopharma, Ventyx, Viatris, and UCB; has received speaker's fees from AbbVie, Amgen, Arena Pharmaceuticals, Bristol Myers Squibb, Celgene, Eli Lilly, Ferring, Fresenius Kabi, Gilead Sciences, Janssen, Merck, Organon, Pfizer, Roche, Sandoz, Shire, and Takeda Pharmaceuticals; and has served on advisory boards for AbbVie, Alimentiv (formerly Robarts), Amgen, Arena Pharmaceuticals, AstraZeneca, Biogen, Boehringer Ingelheim, Bristol Myers Squibb, Celgene, Eli Lilly, Ferring, Fresenius Kabi, Genentech, Gilead Sciences, GlaxoSmithKline, JAMPBio, Janssen, Merck, Mylan, Novartis, Oppilan Pharma, Organon, Pandion Pharma, Pfizer, Progenity, Protagonist Therapeutics, Roche, Sandoz, Shire, Sublimity Therapeutics, Takeda Pharmaceuticals, and Ventyx.

Suggested Reading

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