EDITORIAL

Illuminating the Black Box: The Real Risk of Serious Infection With Inflammatory Bowel Disease Therapies

See "Risk of serious and opportunistic infections associated with treatment of inflammatory bowel diseases," by Kirchgesner J, Lemaitre M, Carrat F, et al, on page 000.

Although combination therapy with anti-tumor necrosis factor (anti-TNF) agents and thiopurines has demonstrated superiority over monotherapy with either agent in the treatment of inflammatory bowel disease (IBD),[1,2] the effect of this combination on the risk of adverse events is unclear. Of the 2 categories of adverse events that garner the most attention, patients and providers tend to worry more about the risk of malignancy than the risk of infection. Likewise, available safety data are often more focused on cancer risk, whereas the infectious risk of competing therapies has been less well-scrutinized.

Most available safety data come from randomized controlled trials or pooled analyses of these trials, which have largely suggested no differences in serious or opportunistic infections between combination and monotherapy with either agent.[3,4] However, owing to inherent limitations of standard trial design, including short-term follow-up, selected patient populations, controlled environments, and low event rates, judgement of long-term safety in randomized controlled trials should be interpreted with caution. Larger observational studies of real-world populations with longer follow-up periods are required.

In this issue of *Gastroenterology*, Kirchgesner et al[5] provide a valuable assessment of the risk of serious and opportunistic infections within a large population-based cohort of patients with IBD treated with thiopurine monotherapy, anti-TNF monotherapy, or combination therapy. Using the French National Health Insurance database (Système National d'Information Inter-Règimes de l'Assurance Maladie [SNIIRAM]) and the French national hospital discharge database, they compiled a cohort of almost 200,000 patients with IBD with about 900,000 person-years of follow-up.

Not surprisingly, patients unexposed to thiopurines or anti-TNF agents had the lowest annual incidence of serious infections, defined as those requiring hospitalization, at 0.8% (1 in 125), compared with 1.1% (1 in 91), 1.9% (1 in 53), and 2.2% (1 in 45) for patients with exposure to thiopurine monotherapy, anti-TNF monotherapy, and combination therapy, respectively. Further highlighting the gravity of serious infection was the 3.9% mortality rate at 3 months in those who developed these infections. Moreover, in a subgroup analysis of patients >65 years of age, the risk of serious infections was further amplified, with an annual incidence of 2.7% (1 in 37) in the thiopurine group, 5.3% (1 in 19) among anti-TNF–exposed patients, and 5.1% (1 in 20) in the combination therapy group. Patients on anti-TNF monotherapy were 71% more likely to develop a serious infection than those on thiopurine monotherapy, whereas patients on combination therapy were 23% more likely than those on anti-TNF monotherapy.

For opportunistic infections, the incidence rates were again lowest in unexposed patients at 0.04% annually (1 in 2500), compared with 0.17% (1 in 588) in the thiopurine-exposed, 0.21% (1 in 476) in the anti-TNF–treated patients, and 0.41% (1 in 244) for the combination therapy group. The 3-month mortality rate within this group was similar, at 3%. Patients on anti-TNF monotherapy and those on thiopurine monotherapy were about equally as likely to develop an opportunistic infection. This finding is likely explained by the fact that, although anti-TNF therapy produced a higher risk of bacterial and mycobacterial infections, this risk was offset by an increased risk of viral infections among the thiopurine-treated group.

Often the results of observational studies are confounded by "bias by severity" or "bias by indication"—sicker patients are typically the ones on more intensive therapy and disease activity itself is an independent risk factor for serious infections.[3,6] One strength of the study by Kirchgesner et al[5] is the adjustment for IBD activity, as measured by corticosteroid use, IBD-related hospitalizations and surgeries, and IBD-related endoscopic and radiologic procedures. Adjustments were also made for sex, age, disease duration, and narcotic use.

Lichtenstein et al[6] recently published updated safety data from the TREAT registry, including 6273 patients with Crohn's disease followed for a combined 35,777 patient-years. Infliximab-treated patients developed serious infections at an annual rate of 2.15% (1 in 46) compared with 0.86% (1 in 116) in those treated with other therapies, including corticosteroids, immunomodulators or methotrexate. Furthermore, of the 577 patients who developed a serious infection in either group, 32 (5.5%) died from complications of their infection.

Although malignancy is often the more feared complication of thiopurine and anti-TNF therapy, the current study by Kirchgesner et al,[5] in conjunction with another recent publication from the same group,[7] highlights the fact that serious infectious complications are exceedingly more common than malignancy in this population. Using the same SNIIRAM database, Lemaitre et al[7] reported 336 cases of

EDI 5.5.0 DTD ■ YGAST61962_proof ■ 4 July 2018 ■ 4:37 pm ■ ce

Table 1. Vaccination Recommendations for Patients with Inflammatory Bowel Disease[9,10]

Vaccine-Preventable Illness	Who Should Be Considered?	Dosing Regimen
Inactive vaccines		
Hepatitis B	All patients (HBsAg, anti-HBc, anti-HBs to determine status before immunosuppression)	If patient nonimmune: 3 doses at 0, 1, and 6 months Check titer 1 month after last dose If no response, consider: revaccination, doubling the dose HBV vaccination or combined HAV/HBV vaccine
Hepatitis A	All patients (anti-HAV IgG if unclear status)	If patient non-immune: 2 doses (6 months apart)
Pneumococcal pneumonia	All patients	PCV13 Administered first PPSV23 Give ≥8 weeks after PCV13 (or ≥1 year if immunocompetent) Booster at 5 years and when age 65
Influenza	All patients	Inactivated intramuscular form Annually Only option when immunosuppressed Ages ≥65 and older: high-dose vaccine
Human papilloma virus	Ages 9-26 (both females/males)	3 doses (0, 2, and 6 months)
Zoster (shingles)	Age ≥50	Shingrix[a] (inactive) 2 doses (2-6 months apart)
Tdap (tetanus, diphtheria, acellular pertussis)	All patients	1 dose Tdap followed by Td booster every 10 years
Meningococcal meningitis	Selected at risk patients[b] if not previously vaccinated	2 doses (2 months apart)
Live vaccines (contraindicated in immunosuppressed patients)[c]		
Varicella (chicken pox)[c]	If no documented immunity (VZV IgG if unknown status)	2 doses (4-8 weeks apart)
Zoster (shingles)[c]	Age ≥50	Zostavax (live vaccine) Single dose
MMR (measles, mumps, rubella)[c]	If no documented immunity (MMR IgG if unknown status)	2 doses (4 weeks apart)
Influenza[c]	All patients	Live-attenuated intranasal: Only for use in non-immunosuppressed, nonpregnant patients

HAV, hepatitis A virus; HBc, hepatitis B core; HBs, hepatitis B surface; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; PCV13, pneumococcal conjugate vaccine; PPSV23, pneumococcal polysaccharide vaccine.
[a]Shingrix was approved in 2017 as an inactive zoster vaccination; although not contraindicated in immunocompromised individuals, the Advisory Committee on Immunization Practices has not recommended its use in this population until further evidence becomes available.
[b]College students or military recruits living in close contact, complement component deficiency, anatomic or functional asplenia, infected with the human immunodeficiency virus.
[c]Contraindicated in immunosuppressed patients: Avoid if patient has been on immunosuppressive therapy in the past 3 months or plan to start immunosuppressive therapy within 4-6 weeks.

lymphoma in 189,298 patients with IBD over a median follow-up of 6.7 years. The annual incidence rate of lymphoma among the unexposed group was 0.026% (1 in 3846), compared with 0.054% (1 in 1852) in the thiopurine-treated patients, 0.041% (1 in 2439) for anti-TNF monotherapy, and 0.095% (1 in 1053) in the combination therapy group. This finding suggests that patients treated with either class of these medications, whether as monotherapy or in combination, are 20 to 50 times more likely to suffer from a serious infection than develop lymphoma. Furthermore, if one assumes that the mortality rate from serious infections was equal across medication groups, the risk of a fatal serious infection approximates that of developing a lymphoma in the 3 medication groups.

What conclusions can be made from the information in this study? Obviously, we cannot assess risk in isolation—the benefits of anti-TNF therapy, either alone or in combination with thiopurines, are significant. However, this study reminds us that the risk of serious infections is real with anti-TNF therapy, and this risk increases further when they are used in combination with thiopurines. Therefore, the decision to use these medications, either in isolation or combination, should be made on an individualized basis, keeping in mind not only efficacy, but also patient and disease characteristics. This caveat is