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Review

Preventative Measures to Avoid Complications Related to Medication Prior to IBD Treatment

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Abstract

This document outlines key preventative measures to minimize complications associated with inflammatory bowel disease (IBD) treatment, emphasizing the importance of infection screening and vaccination protocols. Combination therapies carry a higher risk of infection than anti-TNF monotherapy, particularly for tuberculosis reactivation and viral infections linked to thiopurines. Screening for infections such as hepatitis B and C, HIV, and latent tuberculosis is essential before initiating biological or immunomodulatory therapies. Vaccination against preventable diseases should be completed before starting immunosuppressive treatments, with careful timing for live vaccines. The document also addresses cancer risk management, noting no significant increase in cancer incidence associated with anti-TNF agents, vedolizumab, or ustekinumab, although higher risks are linked to Janus kinase inhibitors.

Keywords: Biologics, immunosuppression, infection, inflammatory bowel disease, malignancy, ulcerative colitis

SCREENING FOR INFECTION

Treatment regimens for inflammatory bowel disease (IBD), including immunosuppressive agents, carry varying risk profiles for serious and opportunistic infections.

More specifically, combination therapy presents a higher risk of serious and opportunistic infections than anti-TNF monotherapy.[1] An increased risk of opportunistic bacterial and mycobacterial infections has been reported with the use of anti-TNFα.[1-3] Anti-TNFα and, to a lesser extent, non-anti-TNFα biological agents may increase the risk of tuberculosis (TB) reactivation in individuals with latent TB infection (LTBI).[4] Therefore, before initiating biological treatment, screening for LTBI is essential, along with appropriate preventive measures to reduce the risk of active TB.

Thiopurines have been associated with viral infections, such as primary cytomegalovirus, varicella-zoster virus, and Epstein-Barr virus (EBV) infections, all of which can be severe and may lead to hemophagocytic lymphohistiocytosis. Hemophagocytic lymphohistiocytosis is typically linked to primary EBV infection, regardless of gender and age.[1,5,6]

The risk of serious and opportunistic infections is higher when thiopurines are used in combination with anti-TNF agents compared to anti-TNF monotherapy or thiopurine monotherapy.[7]

Data from clinical trials do not indicate an increased risk of infection with vedolizumab; however, there may be a higher incidence of *Clostridium difficile* infections. Further real-world data are needed to confirm this hypothesis.[8] A recent meta-analysis found that patients with ulcerative colitis using vedolizumab had a lower risk of serious infections than those using anti-TNFs.[9]

Similarly, no increased risk of opportunistic infection has been observed with ustekinumab. Several high-quality randomized controlled trials conducted for different indications, including IBD, found no significant increase in infection incidence among patients receiving ustekinumab.[10-13] The aforementioned meta-analysis found that patients with Crohn's disease using ustekinumab had a lower risk of serious infections than those using both anti-TNF agents and vedolizumab.[9]

However, Janus kinase inhibitors have been associated with a higher risk of various infections, particularly herpes zoster (HZ), as indicated by phase II and III studies. The OCTAVE study and its open-label extension study revealed a dose-dependent increase in HZ risk with tofacitinib use.[14]

The following infectious disease screening tests should be performed before initiating treatment in patients using biological and/or immunomodulatory agents:

1. HBsAg, anti-HBc IgG, and anti-HBs; HBV DNA if necessary (if HBsAg and/or anti-HBc IgG are positive)
2. Anti-HCV; HCV RNA if necessary (if anti-HCV is positive)*
3. Anti-HIV 1-2; Western blot test if necessary*
4. Tuberculin skin test or QuantiFERON-TB Gold test, and chest X-ray for latent TB*
5. Pap smear test or HPV test*
6. EBV Ig profile (IgM/IgG anti-VCA, IgM/IgG anti-EBNA, IgM/IgG anti-EA)**

*** Required before starting biologics**
**** Required before starting thiopurines**

Vaccination Before Starting Biologics, Small Molecules, or Immunosuppressive Medication

- Ideally, vaccines should be administered at the time of an IBD diagnosis. If not given previously, they should be administered before starting immunomodulatory treatment. Live vaccines, such as MMR, polio, BCG, and VZV-herpes zoster, are contraindicated during the use of immunosuppressive or anti-TNF agents. These vaccines should be administered at least three months before starting these medications or at least three months after discontinuation. There is insufficient data available on the use of live vaccines with vedolizumab, ustekinumab, and Janus kinase inhibitors.[15,16]

Malignancy

- An increased risk of skin cancers and hematological malignancies, in addition to gastrointestinal cancer, has been reported in IBD.
- No significant increase in the risk of hematological malignancies or solid tumors has been observed with anti-TNF monotherapy.[17]
- Long-term follow-up studies (eight years for vedolizumab and five years for ustekinumab) have shown that these therapies do not increase the risk of cancer.[18,19] Two recent retrospective studies also found no association between these drugs and an increased risk of incident cancer development.[20-24]
- A recent network meta-analysis found no difference in malignancy risk between Janus kinase inhibitors and placebo. However, compared with anti-TNF agents, Janus kinase inhibitors were associated with a higher risk for all cancers, except for hematological malignancies, which could not be analyzed.[25]
- Due to the high risk of lymphoma and urinary tract cancer associated with EBV in men over 50 years of age, long-term use of thiopurines should be avoided. For young men seronegative for EBV, alternative treatments should be considered to reduce the risk of lymphoma. In young men with IBD in remission, combination therapy with thiopurines and anti-TNF agents should be limited to a maximum of two years to decrease the risk of developing hepatosplenic T-cell lymphoma.
- To reduce the risk of skin cancer, all IBD patients should take sun protection measures and undergo regular skin examinations before and after treatment.
- Women with IBD should be screened for cervical cancer before starting thiopurines and should undergo regular follow-up screenings. Additionally, the widespread use of HPV vaccines can help reduce the incidence of cervical cancer.[8]

MAIN POINTS

- Before starting biological treatment for IBD, screening for latent tuberculosis and viral infections (HBV, HCV, HIV, and HPV) should be conducted.
- Patients with IBD who are beginning thiopurine treatment should undergo EBV profile screening.
- If live vaccines (MMR, polio, BCG, and VZV) are to be administered, immunosuppressive therapy should be completed at least three months beforehand.
- In men over 65 years of age and young men who are seronegative for EBV, avoiding thiopurine monotherapy should be considered if alternative treatment options are available.
- Detailed skin examinations should be performed in high-risk groups before initiating thiopurine and/or anti-TNF therapy. Additionally, women receiving thiopurine should undergo a Pap smear examination.

CONCLUSION

Comprehensive preventive measures are essential to minimizing complications in IBD treatment. Given the increased risk of serious and opportunistic infections associated with immunosuppressive therapies, thorough screening for infections such as hepatitis, HIV, and latent tuberculosis is crucial before initiating biological agents and immunomodulators. Vaccination against preventable infections should be prioritized, with careful consideration of live vaccines near immunosuppressive therapy. Additionally, due to malignancy risks-particularly in young men and women-regular screening and protective measures are necessary.

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