

Perspective

Infectious and Other Complications of Immunobiologic Agents Used by Individuals with HIV Infection

Individuals with HIV infection are living longer, and are at risk of autoimmune disorders and cancers associated with aging. Many of these conditions are treated with immunobiologic agents that affect immune function and may increase risk of opportunistic infections (OIs) and other immune disorders in individuals with HIV infection. For example, tumor necrosis factor-alpha inhibitors, used to treat such disorders as Crohn's disease, are associated with risk of tuberculosis and histoplasmosis. Rituximab, used to treat lymphoma, has been associated with progressive multifocal leukoencephalopathy due to JC virus and reactivation of other viral infections. Idealisib, used to treat chronic lymphocytic leukemia, has been associated with Pneumocystis pneumonia, and immune checkpoint inhibitors used to treat a variety of cancers have been associated with a wide range of immune-related adverse effects. Practitioners must maintain high vigilance for OIs and other immune-related disorders in patients with HIV infection who are receiving biologic therapies. This article summarizes a presentation by Peter Chin-Hong, MD, at the IAS-USA continuing education program held in Chicago in May 2018.

Keywords: HIV, immunobiologics, biologics, opportunistic infections, immune-related disorders

Individuals with HIV infection are living longer, and they are at increased risk of the autoimmune disorders and malignancies that occur with aging in the general population. Treatment for many of these diseases includes use of immunobiologic agents that may pose risk of immune-related complications in individuals with HIV infection, including opportunistic infections (OIs).

Immunobiologic Agents

Immunobiologic agents are biologically derived products that bind or interfere with a specific molecular target. These agents include monoclonal antibodies (mAbs), receptor analogues, and chimeric small molecules. The types of agents can be distinguished by the suffixes in drug names that allude to their structure and activity; for example: "-cept" refers to fusion of a receptor to the fragment crystallizable part of human immunoglobulin gamma 1; "-mab" indicates a mAb; "-ximab" indicates a chimeric mAb; and "-zumab" indicates a humanized mAb.

Dr Chin-Hong is Professor of Medicine at University of California San Francisco.

Examples of biologic agents include: tumor necrosis factor (TNF)-alpha inhibitors such as infliximab, adalimumab, and etanercept, which are used to treat autoimmune and connective tissue diseases such as rheumatoid arthritis, vasculitis, Crohn's disease, ulcerative colitis, and psoriasis; anti-CD20 agents such as rituximab, used in treatment of lymphomas; and immune checkpoint inhibitors, such as ipilimumab and pembrolizumab, and chimeric antigen receptor (CAR)-T cells used in treatment of such malignancies as melanoma, leukemia, lung cancer, and prostate cancer.

Biologic treatments for autoimmune diseases and cancers are associated with direct effects on immune function. For example, rituximab affects humoral immunity, and TNF-alpha inhibitors and a variety of other biologic agents affect cell-mediated immunity. Conventional cytotoxic cancer chemotherapy affects innate immunity. HIV infection presents another dimension of immunosuppression that needs to be considered in the context of the immune effects of such treatments. During HIV

infection, the immune defect is death of CD4+ cells; the CD4+ cell count allows for stratification of risk for OIs or other immune-related conditions. In the case of non-HIV-related immunosuppression, such as that which can be caused by biologic agents, the immune defects are heterogeneous and there are no reliable methods for determining risk for OIs or other immune-related conditions. Thus, little information on risk of OIs exists for individuals with HIV infection receiving biologic agents, and no current guidance is available on providing prophylaxis against such diseases. Practitioners need to maintain vigilance for OIs in individuals with HIV infection receiving biologic agents beyond that warranted by the patient's immune status with regard to HIV infection alone.

Treatment with Biologic Agents and OIs in HIV Infection

Some of the difficulties encountered in use of biologic agents in individuals with HIV infection can be appreciated by consideration of several cases.

Case 1: A 56-year-old woman with HIV infection (CD4+ cell count 360/ μ L, plasma HIV-1 RNA level <50 copies/mL) was on antiretroviral therapy (ART) and had Crohn's disease managed with the TNF-alpha inhibitor infliximab and 6-mercaptopurine. She presented to an emergency department complaining of shortness of breath for 3 weeks. She lived in Boston, and returned 4 weeks before from a trip to Puerto Rico, where she visited family and helped with property cleanup from a recent hurricane. Chest computed tomography (CT)

Table. Identifying Suffixes in Biologic Agents

Suffix	Type of Biologic Agent
-cept	Receptor, fuses to Fc of human IgG1
-mab	Monoclonal antibody (mAb)
-ximab	Chimeric mAb
-zumab	Humanized mAb

Abbreviations: Fc indicates fragment crystallizable; IgG1, immunoglobulin gamma 1



Figure 1. Chest computerized tomography scan showing bilateral nodules in a patient with pulmonary endemic mycosis (pulmonary coccidioidomycosis). Image courtesy of Brett Elicker, MD; University of California San Francisco.

showed symmetric nodules consistent with mycobacterial or fungal disease (Figure 1). Workup included negative respiratory smears and cultures for *Mycobacterium tuberculosis*, but the patient was positive for urinary *Histoplasma* antigen, resulting in a diagnosis of acute histoplasmosis.

Histoplasma capsulatum is a fungus that lies in the soil and is endemic to the Ohio and Mississippi river valleys in the United States but also the Caribbean. Thus, the patient's recent travel and exposure to soil in cleanup work was an important clue in identifying her opportunistic disease, particularly because her residence in Boston would not have normally put her at risk.

Tuberculosis (TB) has been considered the classic OI associated with TNF-alpha inhibitor use. However, the patient was evaluated for active TB and found to be negative. Suspicion for TB in patients receiving TNF-alpha inhibitors was supported by post-marketing data from 1998 to 2001 following release of infliximab that showed 70 reported cases of TB.¹ Median time to diagnosis in these cases was 12 weeks (range, 1-52 weeks). Most cases were not pulmonary, with extrapulmonary disease accounting for 57% of cases and disseminated disease being found in 24% of cases. Such findings underscore the importance of TNF-alpha receptors in immune response to mycobacterial infection, because inhibition appears to be

associated with rapid spread and disease outside the lungs, including miliary TB.

Subsequent investigation showed that non-TB mycobacterial infections were more common than TB, and surprisingly, that histoplasmosis was more common than mycobacterial infections in patients receiving TNF-alpha inhibitors. A survey of serious infections among individuals on TNF-alpha inhibitors in the United States reported in 2008 showed 32 cases of non-TB mycobacterial infection, 17 cases of TB, and 56 cases of histoplasmosis.² Further, a US

Food and Drug Administration alert in 2008 reported 256 cases of histoplasmosis in patients on TNF-alpha inhibitors. Figure 2 shows the distribution of endemic mycoses in the United States.

Case 2: A 42-year-old man living in Hong Kong with Crohn's disease for 3 years was started on infliximab after persistent diarrhea 5 months prior. He was admitted to hospital with 3 weeks of shortness of breath, low-grade fever, and dry cough. He was treated for presumed community acquired pneumonia with amoxicillin for 1 week, with no improvement. Testing of sputum was negative for acid fast bacilli on smears and culture and negative on respiratory virus polymerase chain reaction (PCR). After a chest x-ray was performed, showing a military pattern of infiltrates, chest CT showed ground glass opacities (Figure 3), and bronchoalveolar lavage direct fluorescent antibody testing was positive for *Pneumocystis jiroveci*. The patient was then found to be HIV antibody-positive and was diagnosed with *Pneumocystis* pneumonia. The patient had an allergy to trimethoprim-sulfamethoxazole, and

so received treatment with clindamycin and primaquine. ART was initiated. The patient's CD4+ cell count was above 240/ μ L, not normally considered the threshold for *Pneumocystis* pneumonia risk. There may have been a synergy between the HIV infection and use of a TNF-alpha antagonist in causing immunosuppression that permitted *Pneumocystis* infection at a higher CD4+ cell count.

Case 3: A 74-year-old HIV-seronegative man with interstitial lung disease and chronic lymphocytic leukemia (CLL), for which he was receiving the biologic agent idelalisib (a PI3K δ inhibitor), was admitted with progressive shortness of breath on exertion and dry cough for 1 month. The diagnosis was *Pneumocystis* pneumonia, again characterized by a subacute presentation, unlike what is seen with community acquired pneumonia or influenza.

Thus, there is risk of *Pneumocystis* pneumonia in patients receiving biologic agents even in the absence of HIV infection. A retrospective analysis of 2198 patients with relapsed CLL or non-Hodgkin lymphoma across 8 studies showed that treatment with idelalisib with or without rituximab or rituximab/bendamustine had a relative risk of *Pneumocystis* pneumonia of 12.5. Median time to diagnosis was 141 days.^{3,4} Yet there remains no standard *Pneumocystis* pneumonia prophylaxis guidance to address such risk.

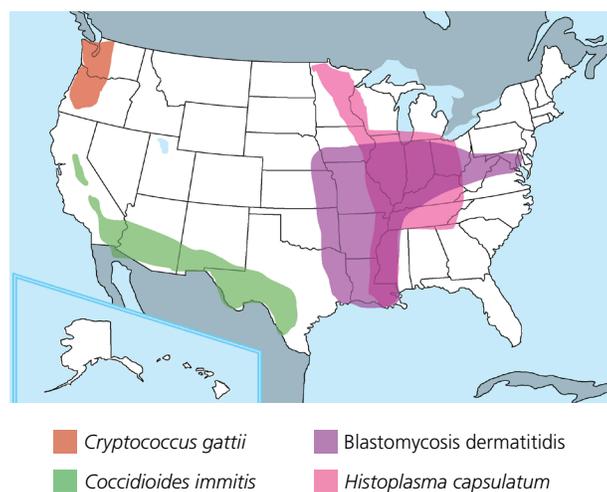


Figure 2. Distribution of endemic mycoses in the United States. Adapted from Winthrop et al.²

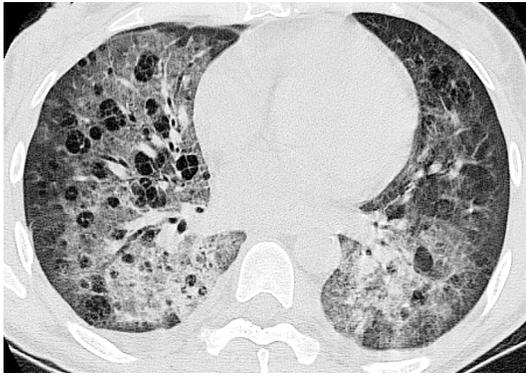


Figure 3. Chest computerized tomography scan showing diffuse ground glass opacities in a patient with *pneumocystis pneumonia*. Image courtesy of Brett Elicker, MD; University of California San Francisco.

Case 4: A 69-year-old HIV-seronegative woman with low-grade lymphoma treated with rituximab developed slowly progressive mental status changes months after starting treatment. A cerebrospinal fluid PCR was positive for JC virus and magnetic resonance imaging findings were consistent with progressive multifocal leukoencephalopathy (PML), and a diagnosis of PML was made (Figure 4).

Such cases illustrate not that specific OIs are necessarily associated with specific biologic agents—although the linkage between TNF-alpha inhibitors and TB is robust—but that OIs occur even in circumstances in which they are unexpected. Again, the primary point to be gleaned from these scenarios and available data is that practitioners must be vigilant for OIs in their patients with HIV infection who are taking biologic agents.

With regard to viral infections associated with biologic treatment, hepatitis B virus (HBV) reactivation is a well-known risk with TNF-alpha inhibitors, requiring screening for HBV infection before starting treatment, and is also common with rituximab treatment.⁵ JC virus infection resulting in PML is associated with use of natalizumab (used in Crohn's disease and multiple sclerosis). JC virus IgG must be assessed before starting treatment, with the drug not being used in those with positive results. As noted, PML has also been found in patients receiving rituximab, although

there currently is no guidance on screening for JC virus in this setting. Rituximab has also been associated with varicella zoster virus reactivation.

Immune checkpoint inhibitors have had a dramatic impact on treatment of numerous cancers, including such agents as the anti-CTLA-4 antibody ipilimumab and the anti-PD1 antibodies pembrolizumab and nivolumab.⁶ These agents act to block inhibitory immune system signaling, resulting in increased immune activation and anti-tumor activity. Due to their mechanism of action, the agents are associated with a wide variety of immune-related adverse effects including increased risk of infection.

Case 5: A 52-year-old man with HIV infection (CD4+ cell count, 450/ μ L; plasma HIV-1 RNA level, <50 copies/mL) on abacavir/dolutegravir/lamivudine with skin squamous cell cancer was enrolled in a trial of the PD-1 inhibitor nivolumab for 1 year. He presented with fecal incontinence and diarrhea. The diagnosis was checkpoint inhibitor-associated colitis (Figure 5). The patient was treated with high-dose prednisone and the TNF-alpha inhibitor infliximab; the nivolumab was stopped. His skin cancer remained in partial remission. As indicated by this case, a common treatment for immune-related adverse events with immune checkpoint inhibitors is TNF-alpha inhibitor therapy, which suppresses the immune activation produced by the checkpoint inhibitors; and, this agent itself poses risk for OIs.

Another immune therapy that has shown activity in treatment of cancers is CAR-T cell therapy. Treatment involves collection of autologous T cells from an individual patient with cancer. The T cells are then genetically modified to respond to tumor cell surface antigens. The population of these T cells is expanded and then infused into the patient with cancer. The treatment is



Figure 4. T2-weighted magnetic resonance imaging scan showing progressive multifocal leukoencephalopathy. Taken from radswiki.net under the Creative Commons License.⁷

associated with substantial immune-related adverse events, including cytokine release syndrome.⁸ Patients receiving this treatment are also at risk of OIs due to the immunosuppressive therapy used to treat the immune effects of CAR-T cell therapy.

Conclusion

The main points in managing individuals with HIV infection who are receiving biologic agents are understanding what the agent is being used for, the mechanism of action of its

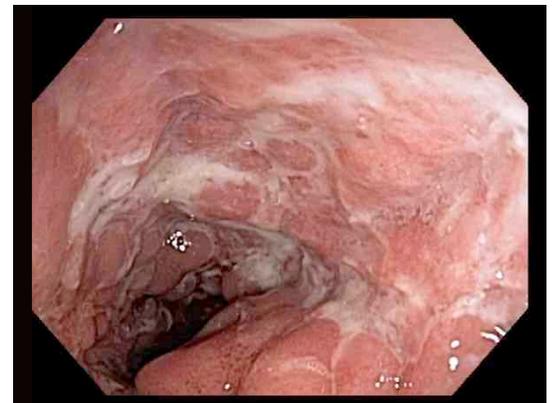


Figure 5. Colonoscopy showing diffuse colitis. Image courtesy of Justin Sewell, MD, MPH; University of California San Francisco.

therapeutic effect, and the immune-related adverse effects associated with the agent. Maintaining vigilance for OIs that may occur given immunosuppressive effects in patients who are already immunosuppressed due to HIV infection is crucial. This includes vigilance for OIs that could be considered to be 'unexpected' given the patient's clinical status with regard to HIV infection alone. For evaluation of patients with HIV infection who are using biologic agents, it is important to know whether the patient has adequate immune reconstitution (eg, CD4+ cell count >200/ μ L), and whether there are drug interactions between ART and biologic agents. Patient status with regard to TB history and risk must be ascertained, and patient HBV status should be known. It is also prudent to stay apprised of patient travel history and to be aware of endemic mycoses. It is important to recognize that individuals with HIV infection receiving treatment with a biologic agent may present with a new complication that has not been previously reported. 

Presented by Dr Chin-Hong in May 2018. First draft prepared from transcripts by Matthew Stenger. Reviewed and edited by Dr Chin-Hong in September 2018.

Acknowledgements: The author would like to thank Michelle Hermiston and Brian Schwartz (University of California San Francisco [UCSF]) for conceptual framework of presentation; Ivan Hung (University of Hong Kong), Camille Kotton (Harvard University), and Jackie Wang and Jen Mulliken (UCSF) for providing clinical cases for discussion; Brett Elicker and Justin Sewell (UCSF) for images; and Paul A. Volberding (UCSF) for mentorship.

Financial affiliations the past 12 months: Dr Chin-Hong has received research support from Karius.

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Top Antivir Med. 2019;26(4):100-103.

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