

The *Warnings and Precautions* section of the package insert cautions against fungal infections:

WARNINGS AND PRECAUTIONS. Do not start Enbrel during an active infection. If an infection develops, monitor carefully and stop Enbrel if infection becomes serious. Consider empiric anti-fungal therapy for patients at risk for invasive fungal infections who develop a severe systemic illness on Enbrel (those who reside or travel to regions where mycoses are endemic).

The mechanism of TNF-alpha, in combating infections, has been reviewed (314). In short, bacteria, which possess molecules that stimulate toll-like receptors (TLRs), contact macrophages during the course of infection, and stimulate the TLRs of the macrophage, with the consequent expression of TNF-alpha.

#### c. Drugs That Inhibit Migration of T Cells to the Central Nervous System

*Natalizumab* (Tysabri®) is another immunosuppressive drug that is used to treat an autoimmune disease, that is, multiple sclerosis. The drug impairs the passage of T cells into the central nervous system, thus preventing pathological inflammation of the central nervous system. Unfortunately, a rare consequence is infections by JC virus in the central nervous system, resulting in a disorder called progressive

multifocal leukoencephalopathy (315,316). The package label for natalizumab includes a black box warning regarding this disorder (317):

WARNING: PROGRESSIVE MULTIFOCAL LEUKOENCEPHALOPATHY. TYSABRI increases the risk of progressive multifocal leukoencephalopathy (PML), an opportunistic viral infection of the brain that usually leads to death or severe disability.

#### d. Antibody Drugs That Inhibit Epidermal Growth Factor Receptor

Recombinant antibodies that bind to epidermal growth factor receptor (EGFR) are used for treating solid tumors. These antibodies include *cetuximab* and *panitumumab*, which are used for treating colorectal cancer. However, clinical trials using these drugs for treating colorectal cancer demonstrated an increased risk for infections.

Altan and Burtness documented the fact that the association between the anticancer drug and infections was not suspected, writing that, “[u]ntil recently, the infections observed during treatment with EGFR ... directed antibodies have not been attributed to ... the antibodies themselves ... [t]he mechanism of action for this effect has not been established” (318). Please note that, it was eventually discovered that EGF (ligand)

<sup>314</sup>Parameswaran N, Patial S. Tumor necrosis factor-alpha signaling in macrophages. *Crit. Rev. Eukaryot. Gene Expr.* 2010;20:87–103.

<sup>315</sup>van Rossum JA, et al. Safety, anxiety and natalizumab continuation in JC virus-seropositive MS patients. *Multiple Sclerosis J.* 2014;20:108–11.

<sup>316</sup>Tavazzi E, et al. Progressive multifocal leukoencephalopathy: an unexpected complication of modern therapeutic monoclonal antibody therapies. *Clin. Microbiol. Infect.* 2011;17:1776–80.

<sup>317</sup>Package insert for TYSABRI (natalizumab) injection for intravenous use; December 2013 (29 pp.).

<sup>318</sup>Altan M, Burtness B. EGFR-directed antibodies increase the risk of severe infection in cancer patients. *BMC Med.* 2015;13:37 (3 pp.).