# Tumor necrosis factor blockade and the risk of viral infection

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**Abstract** | Tumor necrosis factor (TNF) blockers are widely used to treat rheumatoid arthritis and other chronic inflammatory diseases. Many studies have demonstrated an increased risk of opportunistic infections such as tuberculosis and fungal infection in patients treated with TNF blockers, which is thought to be related to the primary role of TNF both in host defense and in the immune response. Little is known, however, about the association between TNF blockade and the development of viral infection. Owing to the critical role of TNF in the control of viral infection, depletion of this cytokine with TNF blockers could facilitate the development or reactivation of viral infection. A number of large observational studies have found an increased risk of herpes zoster in patients receiving TNF blockers for the treatment of rheumatoid arthritis. This Review draws attention to the risk of several viral infections, including HIV, varicella zoster virus, Epstein–Barr virus, cytomegalovirus, and human papillomavirus, in patients receiving TNF-blocking therapy for chronic inflammatory conditions. In addition, implications for clinical practice and possible preventative approaches are discussed.

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## Introduction

Tumor necrosis factor (TNF) plays an essential part in host defense and the immune response.[1] TNF receptors (TNFRs) are found on virtually all cell types, and TNF affects a variety of physiologic processes. TNF blockers are an effective treatment for several chronic inflammatory disorders, including rheumatoid arthritis (RA), and the increasingly widespread use of these agents highlights the importance of understanding their safety. Much attention has been paid to the risks of opportunistic infection (such as tuberculosis and fungal infections) associated with use of TNF blockers.[2,3] Conflicting data exist, however, on the association between the use of these agents and serious infections that lead to hospitalization or mortality.[4–6] A recent meta-analysis by Bongartz *et al.*[7] reported that the number needed to harm for up to 1 year of therapy with infliximab or adalimumab was 59 (95% CI 39–125) for serious infection.

To date, most studies have focused on the risk of bacterial and opportunistic infections, with few assessing a possible association between viral infections and TNF-blocking agents. Since TNF plays a critical role in the control of viral infection—through the recruitment and activation of macrophages, natural killer cells, T cells, and antigen-presenting cells—the depletion of TNF by treatment with TNF blockers might facilitate the development or reactivation of viral infection.[8,9] This Review highlights possible links between TNF blockers and several types of viral infection. The association with viral hepatitis is not included as this has recently been reviewed elsewhere.[10,11]

## HIV infection

Although TNF is known to be involved in the pathogenesis of HIV infection, its exact role is not completely understood.[9] A positive association has been reported between activation of the TNF system *in vivo* and progression of HIV-related clinical disease.[12,13] TNF and death receptors such as Fas ligand are directly and indirectly involved in the activation of T-cell apoptotic processes in HIV infection.[14–16] Several studies have proposed an important role for TNFR signaling in the progression of HIV infection.[14,16,17] Both TNFR1 and TNFR2 can induce apoptosis in peripheral $CD4^+$ and $CD8^+$ T cells in HIV-infected patients.[14] Furthermore, serum levels of TNF and TNFR seem to be elevated in patients with HIV, and could have a critical role in the clinical progression of HIV infection.[18,19] Based on the hypothesis that inhibiting circulating TNF could be a therapeutic strategy, Walker *et al.*[20] examined the safety and efficacy of a chimeric antibody against TNF in six patients with HIV and baseline $CD4^+$ T cell counts of less than 200 per $mm^3$.[20] The investigators found no significant changes in $CD4^+$ T cell counts or plasma HIV RNA levels. Safety concerns remain, however, including whether the use of TNF blockers further increases the risk of opportunistic infection in HIV-infected patients, and whether these agents adversely affect the long-term outcome of HIV infection by further suppressing the host defense system.

Data on the safety of TNF blockers for the treatment of chronic inflammatory conditions in HIV-infected patients are limited and derive mostly from case reports

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**Key Points**

- Little is known about the risk of viral infections associated with the use of tumor necrosis factor (TNF) blockers
- Inhibition of TNF might facilitate the development or reactivation of viral infection through several mechanisms
- Multiple cases of successful TNF-blocking therapy in HIV-infected patients are described in the literature
- Although uncommon, infection with various viruses such as varicella-zoster virus, Epstein–Barr virus, cytomegalovirus, human papillomavirus and JC virus has been reported following TNF-blocking therapy
- The effects of TNF blockade on the long-term sequelae of viral infection such as cancer and latent infectious illnesses might not yet be fully appreciated
- Clinicians should be aware of the current guidelines for adult immunizations with vaccines that can prevent viral infection

(Table 1).[21–31] The majority of the patients included in these case reports received concomitant, highly active antiretroviral therapy. Infliximab infusions, ranging in dose from 2–5 mg/kg, led to marked clinical improvement without associated serious infection or worsening of HIV infection.[22–25,29,30] Furthermore, no serious infectious complications or increases in the HIV viral load were noted in patients given etanercept 50 mg weekly or 25 mg twice weekly.[26–28,30,31] Successful outcomes with etanercept were even noted in patients with both HIV and viral hepatitis infection.[27,28] By contrast, Aboulafia *et al.*[21] reported on a 45 year old HIV-infected male with psoriatic arthritis (PsA) who died of a severe bacterial infection 4 months following etanercept therapy, despite stable CD4 cell count and viral load.[21] Less information is available regarding the safety of adalimumab in HIV-infected patients. Three HIV-positive patients with concomitant PsA in a study by Cepeda *et al.*[30] achieved a partial clinical response to adalimumab, whereas their $CD4^+$ counts and HIV viral loads remained stable.

Whether the relative safety of TNF blocking agents in the cases described above can be generalized to other HIV-infected patients remains unknown. Until there is a better understanding of the long-term safety of TNF blockade in patients with HIV, clinicians should avoid use of these drugs in this population. In circumstances where TNF blockers are required and no alternative treatment exists, these drugs should be used with extreme caution and $CD4^+$ counts, viral loads, and clinical signs and symptoms of infection should be closely monitored.

## Varicella-zoster virus infection

Varicella-zoster virus (VZV) is the cause of primary varicella (also known as chickenpox), herpes zoster (shingles) and postherpetic neuralgia. In children, primary varicella infection is common and usually benign. However, disseminated varicella infection in adults, and particularly in immunocompromised patients, can be severe and potentially fatal.[32] In the general population, the incidence of herpes zoster, which is caused by reactivation of VZV in sensory nerve roots, is reported to be 1.2–4.8 cases per 1,000 person-years.[33,34] Patients with compromised cell-mediated immunity as a result of aging, use of immunosuppressive agents, or concomitant illness are at an increased risk of developing herpes zoster.[34,35] The severity of herpes zoster is related to the degree of immunocompetence in such individuals, which is demonstrated by the greater infection severity observed in patients with organ transplantations, lymphoproliferative diseases (LPD) or AIDS.[36]

A number of commentators have noted that herpes zoster is more common in patients with systemic lupus erythematosus (SLE) or RA than in the general population, because of both the impaired immune system in these patients and the medications used to treat these conditions.[37–40] Several case reports and retrospective studies reporting VZV infection in patients who received TNF blocking therapy for inflammatory conditions are listed in Table 2.[41–52] Data from the Consortium of Rheumatology Researchers of North America (CORRONA) registry showed that VZV infection was the most frequent infection in patients who received methotrexate, TNF blockers or other DMARDs, and accounted for 44% of all cases of opportunistic infection.[53]

A retrospective cohort study using data from the US Veterans' Affairs health system demonstrated an elevated incidence of herpes zoster in patients with RA—9.96 cases per 1,000 patient-years.[54] Correlates of herpes zoster included old age, use of glucocorticoids or DMARDs (including methotrexate, leflunomide, azathioprine, cyclophosphamide, ciclosporin, anakinra and TNF blockers), and the presence of malignancy, chronic lung disease, renal failure, or liver disease. Of 3,661 patients treated with TNF blockers, 96 developed herpes zoster. Among the TNF blockers used, etanercept (hazard ratio [HR] 0.62, 95% CI 0.40–0.95) and adalimumab (HR 0.53, 95% CI 0.31–0.91) were associated with a lower risk of herpes zoster than infliximab (HR 1.32, 95% CI 0.85–2.03).[54] By contrast, a prospective study using data from the German biologics register reported a significantly increased risk of herpes zoster in patients receiving infliximab and adalimumab (HR, 1.82, 95% CI 1.05–3.15) compared with etanercept, even after adjusting for age, severity of RA, and glucocorticoid use.[41] Notably, no significant association was found for etanercept use (HR 1.36, 95% CI 0.73–2.55).

As noted in Table 2, serious morbidity and mortality from VZV infection can occur in patients who receive TNF blocking therapy. Of the six cases of disseminated primary varicella infection reported in the literature,[45,46,48–50,55] one death occurred in a 26-year-old male patient with Crohn disease after a single infusion of infliximab (5 mg/kg).[47]

## Epstein–Barr virus infection

Epstein–Barr virus (EBV), also known as human herpesvirus (HHV)-4, is one of the most common human viruses, infecting as many as 95% of adults aged 35–40 years in the USA.[56] EBV causes infectious mononucleosis, Burkitt lymphoma, nasopharyngeal carcinoma and LPD.[36] The relationship between EBV and autoimmune disease is not completely understood, although EBV has long been considered a possible cause of several autoimmune diseases.[57] Antibodies to EBV are elevated in patients with RA, SLE,

**Table 1** | Use of tumor necrosis factor blockers in patients with HIV

| First author (Country, year) | Patient characteristics | Baseline $CD4^+$ T cell count (cells/$mm^3$) | Drug (duration of therapy) | Concomitant drugs | Results |
|---|---|---|---|---|---|
| Aboulafia (USA, 2000)[21] | 45 year old male with HIV and PsA | <50 | Etanercept 25 mg twice-weekly (6 months) | HAART, steroids, hydroxychloroquine, minocycline | After 6 months of etanercept therapy, skin lesions and arthritis improved considerably, but the patient died of bacterial infection 4 months later |
| Gaylis (USA, 2003)[23] | 41 year old male with HIV and Reiter syndrome | 693 | Infliximab 3 mg/kg (18 months) | HAART, steroids, methotrexate | Marked clinical improvement, with no serious infection; viral loads remained stable |
| Bartke (Germany, 2004)[22] | 46 year old male with HIV, psoriasis and PsA | 68 | Infliximab 3 mg/kg (3 doses) | HAART, acitretin, prednisolone, methotrexate | Dramatic improvement in psoriasis and PsA; HIV status remained stable |
| Wallis (Uganda, 2004)[26] | Phase I study in 16 patients with HIV-associated tuberculosis | >200 (average) | Etanercept 25 mg twice-weekly (8 doses) | Isoniazid, rifampin, ethambutol, pyrazinamide, cotrimoxazole, pyridoxine | 25% increase in $CD4^+$ T cell counts by week 4 and no change in HIV-RNA expression |
| Filippi (France, 2006)[25] | 35 year old female with HIV and Crohn disease | >1,000 | Infliximab* (3 doses) | HAART, azathioprine, steroids | Remission of Crohn disease occurred, but infliximab was discontinued owing to an allergic reaction; no serious infection noted |
| Beltran (Spain, 2006)[24] | 42 year old female with HIV and Crohn disease | >250 | Infliximab* (3 doses) | HAART, steroids | Complete clinical and endoscopic remission of Crohn disease, with no serious infection; HIV status remained stable |
| Sellam (France, 2007)[29] | 2 male patients with HIV, psoriasis, and PsA | 1. 249<br>2. <200 | 1. Infliximab 5 mg/kg (15 doses)<br>2. Infliximab 2 mg/kg (25 doses) | HAART, prednisone, methotrexate | Psoriasis and PsA dramatically improved to almost complete remission; no serious infections occurred and the HIV infection remained well-controlled |
| Linardaki (Greece, 2007)[28] | 43 year old male with hemophilia A, HCV, HIV and PsA | 340 | Etanercept 25 mg twice-weekly (2 years) | HAART, methotrexate, ciclosporin A | Marked improvement in psoriasis and PsA, without serious infection; HCV and HIV status remained stable |
| Kaur (USA, 2007)[27] | 44 year old male with RA, HIV, HBV and HCV | 299 | Etanercept 25 mg twice-weekly (3 months) | HAART, prednisone, sulfasalazine, hydroxychloroquine, infliximab (3 doses before etanercept initiated) | RA improved considerably; HIV, HCV and HBV status remained stable |
| Mikhail (USA, 2008)[31] | 35 year old male with HIV, PsA, and severe pustular psoriasis | 435 | Etanercept 50 mg weekly (20 weeks) | HAART, topical steroids | Skin lesions and arthritis improved dramatically with no serious infection; HIV status remained stable |
| Cepeda (USA, 2008)[30] | 8 patients with HIV and inflammatory arthritis | >600 in 75% of patients | Etanercept, infliximab, adalimumab (average 28 months) | HAART (5 out of 8 patients), steroids, DMARDs | Almost all had an excellent clinical response in arthritis; $CD4^+$ T cell counts and HIV viral loads remained stable; no serious infection was noted |

*Dosage not reported. Abbreviations: HBV, hepatitis B virus; HCV, hepatitis C virus; HAART, highly active antiretroviral therapy; PsA, psoriatic arthritis; RA, rheumatoid arthritis.

or Sjögren's syndrome.[58] A study by Balandraud *et al.*[59] reported that the viral load of EBV in the peripheral blood was associated with high RA disease activity. However, neither methotrexate nor TNF blockers significantly modified EBV load over time.[59]

Several case reports in the literature have described associations between EBV-related conditions and TNF blockade. Sari *et al.*[60] reported a case of a 20 year old male with juvenile ankylosing spondylitis who developed atypical infectious mononucleosis following 8 weeks of infliximab therapy. This patient presented with fatigue, malaise, abdominal discomfort, weight loss and lymphadenopathy; however, fever, pharyngitis, and lymphocytosis were not present. Serologic test showed positive IgM antibodies to the viral capsid antigen of EBV, which was confirmed by a lymph node biopsy. The authors concluded that TNF blockade might have masked the typical symptoms of infectious mononucleosis. In a case report by Park *et al.*[61] a 65 year old Korean female with RA for 4 years developed multiple enlarged lymph nodes, elevated acute phase reactants and anemia several weeks after initiation of etanercept 25 mg twice-weekly. The patients was subsequently diagnosed with EBV-associated diffuse LPD, which gradually resolved after cessation of etanercept therapy. Another case of EBV-associated LPD was reported in a 63 year old Japanese patient with RA following 1 month of treatment with infliximab 3 mg/kg.[62] In this patient, cessation of infliximab therapy also resulted in a dramatic

**Table 2** | Cases of VZV infection following TNF blocking therapy

| First author (Country, year) | Patient characteristics | Drug (duration of therapy) | Concomitant drugs | Results |
|---|---|---|---|---|
| Baumgart (Germany, 2002)[42] | 45 year old male with Crohn disease | Infliximab 5 mg/kg (3 doses) | Azathioprine, prednisone, mesalamine | Acute herpes zoster, resolved with acyclovir |
| Kinder (UK, 2004)[43] | 72 year old male with RA | Infliximab 3 mg/kg (2 doses) | Not reported | Acute severe herpes zoster |
| Leung (USA, 2004)[45] | 26 year old male with Crohn disease | Infliximab 5 mg/kg (1 dose) | Steroids, mesalamine, 6- mercaptopurine | Disseminated primary varicella infection complicated by multiorgan failure, DIC and death |
| Vonkeman (the Netherlands, 2004)[50] | 32 year old male with RA | Infliximab* (1 dose) | Not reported | Disseminated primary varicella infection complicated with respiratory insufficiency, improved with acyclovir |
| Seiderer (Germany, 2004)[49] | 22 year old male with Crohn disease (in a chart review of 100 patients with IBD) | Infliximab 5 mg/kg (1 dose) | Azathioprine | 1 case of generalized primary VZV infection |
| Choi (Korea, 2006)[48] | 63 year old female with RA | Infliximab 3 mg/kg (2 doses) | Methotrexate, bucillamine | Disseminated varicella infection, resolved with acyclovir |
| Lee (Korea, 2007)[55] | 42 year old female with RA | Adalimumab 40 mg biweekly (70 weeks) | Methotrexate, steroids | Disseminated primary varicella infection, resolved with acyclovir |
| Wendling (France, 2008)[51] | 9 patients with inflammatory arthritis (in a chart review of 300 patients who received TNF blocking therapy) | Infliximab* ($n=4$) Adalimumab* ($n=2$) Etanercept* ($n=3$) (6–42 months) | Methotrexate, steroids | Herpes zoster, recovered fully with antiviral treatment and interruption of the TNF blockers |
| Becart (Belgium, 2008)[47] | 58 year old male with psoriasis | Etanercept 50 mg twice-weekly (1 month) | None | Recurrent varicella infection, resolved 2 weeks after discontinuation of Etanercept |
| Balato (Italy, 2009)[46] | 36 year old male with psoriasis | Infliximab 5 mg/kg (15 months) | Not reported | Disseminated primary varicella infection with pulmonary involvement, resolved with acyclovir |
| Tresch (Switzerland, 2009)[52] | 70 year old female with RA | Etanercept* (10 months) | Steroids Methotrexate | Disseminated herpes zoster |

*Dosage not reported. Abbreviations: DIC, disseminated intravascular coagulapathy; IBD, inflammatory bowel disease; RA, rheumatoid arthritis; TNF, tumor necrosis factor; VZV, varicella-zoster virus.

regression of LPD without further treatment. Losco *et al.*[63] described a case of EBV-associated, diffuse, large B-cell lymphoma of the ileum after long-term azathioprine use and a single dose of infliximab (5 mg/kg) in a 42 year old male with Crohn disease. Treatment with surgery and a course of chemotherapy resulted in a successful outcome. The use of TNF blockers is probably not the sole cause of EBV infection. Nevertheless, cessation of these drugs should be considered when EBV infection is suspected, as they could indirectly increase the risk of infection or reactivation of EBV.

## Cytomegalovirus infection

Cytomegalovirus, or HHV-5, is a common viral pathogen that infects 40–60% of the population in developed countries.[36,64] Several cases of cytomegalovirus infection complicating TNF blocking therapy have been reported (Table 3), of which four occurred in patients with inflammatory autoimmune disorders.[65–68] In a case reported by Petersen *et al.*,[66] a 37 year old male with a longstanding history of psoriasis and PsA developed a primary cytomegalovirus infection following 1 month of twice-weekly therapy with etanercept 50 mg (a standard initial dose for plaque psoriasis). Clinical presentations included fever, pneumonia, abnormal liver function tests, and otitis media. After discontinuation of etanercept, the patient recovered spontaneously without antiviral therapy. Six months later, he was restarted on etanercept without cytomegalovirus reactivation. Haerter *et al.*[65] reported a case of severe cytomegalovirus retinitis in the right eye of a 57 year old female with a longstanding history of RA who received infliximab (3 mg/kg) for 2 years. The initial episode of retinitis was treated with intravenous ganciclovir followed by maintenance therapy with oral valganciclovir therapy. Five weeks after stopping valganciclovir, however, she developed recurrent cytomegalovirus retinitis in the contralateral eye. A severe case of cytomegalovirus colitis was noted in a 25 year old male with Behçet disease following the third dose of infliximab (5 mg/kg).[68] This patient had previously been treated with monthly intravenous cyclophosphamide, interferon, ciclosporin and azathioprine. His colitis resolved with cessation of infliximab and treatment with intravenous ganciclovir for 1 month. In a study by Pontikaki *et al.*,[67] of 151 patients with juvenile idiopathic arthritis (95 on etanercept and 56 on infliximab), one patient developed cytomegalovirus pulmonary infection following infliximab therapy.

As most of the patients in the studies listed in Table 3 were on more than one immunosuppressive drug, it is

**Table 3** | Cases of cytomegalovirus infection following TNF-blocking therapy

| First author (Country, year) | Patient characteristics | Drug (duration of therapy) | Concomitant drugs | Results |
|---|---|---|---|---|
| Papadakis (USA, 2001)[120] | 18 year old male with IBD | Infliximab 5 mg/kg (1 dose) | Steroids, ciclosporin, 5-ASA | Cytomegalovirus colitis, treated with colectomy and ganciclovir |
| Helbling (Switzerland, 2002)[121] | 63 year old female with Crohn disease | Infliximab* (1 dose) | Steroids, azathioprine | Disseminated cytomegalovirus infection with gastrointestinal, cutaneous, and CNS involvement, treated with foscarnet and ganciclovir |
| Actis (Italy, 2002)[122] | 8 patients with steroid-refractory ulcerative colitis | Infliximab 5 mg/kg (1 dose) | Steroids, azathioprine | 1 patient developed cytomegalovirus pancolitis |
| Haerter (Germany, 2004)[65] | 57 year old female with RA | Infliximab 3 mg/kg (2 years) | Cyclophosphamide, azathioprine | Severe cytomegalovirus retinitis with visual loss, treated with ganciclovir and valganciclovir; complicated by recurrence of cytomegalovirus retinitis in the contralateral eye |
| Mizuta (USA, 2005)[123] | 45 year old female with Crohn disease | Infliximab 5 mg/kg (1 year) | 6-mercaptopurine, prednisone | Acute cytomegalovirus hepatitis, treated with ganciclovir |
| Kohara[124] (USA, 2006) | 22 year old male with Crohn disease | Infliximab* (4 months) | 6-mercaptopurine | Acute cytomegalovirus ileitis complicated by DIC and hemophagocytic syndrome, treated with ganciclovir and splenectomy |
| Pontikaki (Italy, 2006)[67] | 95 patients with JIA receiving either etanercept or infliximab | Infliximab* (mean 12 months) | Methorexate | 1 patient developed severe cytomegalovirus pulmonary infection |
| Sari (Turkey, 2008)[68] | 25 year old male with Behçet disease | Infliximab 5 mg/kg (3 doses) | Colchicine | Cytomegalovirus, treated with ganciclovir |
| Petersen (Denmark, 2008)[66] | 37 year old male with psoriasis and PsA | Etanercept 50 mg twice-weekly (2 months) | Not reported | Acute primary cytomegalovirus infection; spontaneous resolution after cessation of etanercept |
| D'Ovidio (Italy, 2008)[125] | 15 patients with IBD (11 with Crohn disease, 4 with ulcerative colitis) | Infliximab* (3 doses) | Steroids, azathioprine | 9 patients had cytomegalovirus seropositivity; cytomegalovirus DNA detected in colonic biopsies of 3 patients; no worsening colonic disease |

*Dosage not reported. Abbreviations: 5-ASA, 5-aminosalicylic acid; CNS, central nervous system; DIC, disseminated intravascular coagulopathy; IBD, inflammatory bowel disease; JIA, juvenile idiopathic arthritis; PsA, psoriatic arthritis; RA, rheumatoid arthritis.

difficult to determine whether the use of TNF blockers was directly involved in the development of cytomegalovirus infection. Nonetheless, TNF blockade can theoretically put patients at an increased risk of cytomegalovirus infection.

## Kaposi sarcoma-associated herpesvirus

Kaposi sarcoma, which is caused by HHV-6, is a vascular, multicentric malignant tumor.[69,70] Its occurrence is rare and is usually associated with the presence of AIDS or organ transplantation.[71] A number of cases of Kaposi sarcoma have been noted in non-AIDS patients who are on immunosuppressive therapy for the treatment of rheumatic diseases such as RA, SLE and vasculitis.[72–75] Limited data support an association between TNF blockade and Kaposi sarcoma, with only one case of Kaposi sarcoma reported in a patient with RA who received 12 doses of infliximab (3 mg/kg).[76] A prospective study of 60 patients with Crohn disease found no cases of HHV-6 during 14-weeks of TNF-blocking treatment, as measured by polymerase chain reaction (PCR) assay.[77]

## HPV and MCV

Although anogenital human papillomavirus virus (HPV) infection is the most common sexually transmitted disease in the USA, little is known about the incidence or prevalence of this infection in patients with rheumatic diseases.[78,79] HPV types 1, 2, and 4 cause verrucae vulgaris, also known as benign warts, on the hands and feet. HPV types 6 and 11 usually cause benign condylomata acuminata, whereas types 16, 18, 31, and 33 cause precancerous cervical dysplasia and invasive carcinomas of the anogenital tract. The majority of infections with HPV are subclinical, and in 80% of cases the infection resolves spontaneously within 1 year as a result of a cellular immune response.[79]

The risk of persistent HPV infection, particularly with oncogenic genotypes, might be associated with factors such as increased age, smoking, hormonal status, coexisting infections and family history.[80] Although there is no direct evidence linking the host immunologic response to a risk of HPV persistence, viral reactivation from a latent state in immunocompromised patients has been noted.[81,82] An increased risk of cervical dysplasia, HPV infection and persistence has been repeatedly reported in patients following kidney, lung, and stem cell transplantation.[83–86] A study by Kane *et al.*[87] found that female patients with inflammatory bowel disease (IBD) exposed to immunosuppressive therapy were more likely to have abnormal cervical smears than healthy controls (odds ratio [OR] 4.5, 95% CI 1.5–12.3) or unexposed IBD patients (OR 1.9, 95% CI 1.1–12.1).

Table 4 summarizes cases of cutaneous infections with HPV in patients who received TNF blocking therapy.[88–91]

**Table 4** | Cases of human papillomavirus and molluscum contagiosum virus infection following TNF-blocking therapy

| First author (Country, year) | Patient characteristics | Drug (duration of therapy) | Concomitant drugs | Results |
|---|---|---|---|---|
| Cursiefen (Germany, 2002)[89] | 67 year old female with RA | Infliximab 300 mg (6 months) | Prednisone, methotrexate | Multiple bilateral molluscum contagiosum lesions in upper and lower eyelids |
| Somasekar (UK, 2004)[88] | 23 year old male with Crohn disease | Infliximab* (2 doses) | Steroids, azathioprine | Profuse penile and perianal condylomata acuminata |
| Adams (USA, 2004)[91] | 17 year old female with JIA | Etanercept* (2 years) | Methotrexate | Extensive bilateral plantar warts, which resolved 1 month after discontinuation of etanercept |
| Antoniou (Greece, 2008)[90] | 1. 31 year old female with PsA and severe psoriasis<br>2. 29 year old patient with severe plaque psoriasis | 1. Etanercept 50 mg twice-weekly (3 months); then 25 mg twice-weekly (3 months)<br>2. Infliximab 5 mg/kg (1 dose) | 1. Not reported<br>2. Ciclosporin, efalizumab (both discontinued 1 week before infliximab initiated) | 1. Perianal condylomata acuminata<br>2. Molluscum contagiosum in the abdomen and exacerbation of pre-existing genital condylomata |

*Dosage not reported. Abbreviations: JIA, juvenile idiopathic arthritis; PsA, psoriatic arthritis; RA, rheumatoid arthritis.

Given the available, albeit limited, data in the literature, the use of immunosuppressive agents, including TNF blockers, could potentially increase the risk of persistent HPV infection and ultimately lead to cervical cancer. Future studies should determine the optimal screening strategy for high-risk HPV infection or cervical cancer and the potential benefit of HPV vaccine in immunocompromised patients with rheumatic disease, particularly among patients receiving TNF blockers. Molluscum contagiosum (MCV) is another viral infection of the skin or occasionally of the mucous membranes. This infection is more common in children or in adults with HIV or other immunosuppressed conditions (Table 4).[92]

### Progressive multifocal leukoencephalopathy

Progressive multifocal leukoencephalopathy (PML) is a rare, fatal demyelinating disease of the central nervous system. The incidence of PML has increased with the AIDS pandemic and with the more widespread use of immunosuppressive drugs for organ transplantation or rheumatic disease therapy.[93] PML is caused by reactivation of the JC virus, which is a type of polyomavirus.[94] Up to May 2009, a total of 10 cases of PML have been reported in patients taking natalizumab, a monoclonal antibody against α4 integrin that is used in the treatment of multiple sclerosis and Crohn disease.[95,96] The use of other monoclonal antibodies (efalizumab, rituximab and infliximab) and various transplant drugs such as tacrolimus and mycophenolate has been associated with the development of PML.[97–100] A retrospective cohort study of 734 patients with IBD treated with infliximab showed that a fatal case of PML occurred after the use of both natalizumab and infliximab.[101] Yamamoto *et al.*[102] reported a case of leukoencephalopathy in a 74 year old Japanese patient with RA taking etanercept. Although this patient had characteristics associated with PML such as altered mental status, seizure, and incontinence, the cerebrospinal fluid (CSF) was negative for JC virus DNA, as measured by PCR.

No cases of definite PML following the use of etanercept or adalimumab have been reported. However, the diagnosis of PML is easily missed without a high degree of suspicion. In some patients, features characteristic of the damage caused by PML in the brain can be detected on MRI scans.[93,96] PML can also be confirmed by quantitative PCR assay to detect JC virus DNA in the CSF or in a brain biopsy specimen.[93] The PCR test performed on the CSF has a sensitivity of 76–98% and a specificity of 98–99%.[103,104] Mohan *et al.*[105] reported a series of 19 patients with demyelinating neurologic events following treatment with TNF blockers (17 with etanercept and 2 with infliximab) for rheumatic diseases. None of the patients was diagnosed with PML, but lumbar puncture was performed in only one patient and brain biopsy was done in just two patients. Jarand *et al.*[106] described three cases of neurological complications related to the use of infliximab, but with no specific information on the serology of JC virus. Although JC virus infection is rare and might not be associated with TNF blockers, physicians should maintain a high level of suspicion in immunosuppressed patients with new onset of neurologic symptoms such as disorientation, ataxia, speech disturbance or visual loss.

### Other viral-associated infections

A few case reports have been published regarding viral pneumonia in patients who received TNF blocking therapy for chronic inflammatory diseases. Smith *et al.*[107] reported that following etanercept therapy for RA, a 54 year old female developed severe parainfluenza type 3 pneumonia, which required mechanical ventilation and hospitalization for 3 weeks.[107] A case of severe adenovirus pneumonia following the first dose of infliximab (3 mg/kg) was reported in a 35 year old male with Crohn disease,[108] and Kang *et al.*[109] described a case of severe adenovirus pneumonia in a 55 year old female with RA who took etanercept 25 mg twice-weekly for 2 years. In both of these cases, the patient recovered after prolonged periods of hospitalization and treatment with antiviral agents and intravenous IgG. Most respiratory viral infections are self-limited in immunocompetent

**Table 5** | Viral vaccines recommended for adults in the US[117,126]

| Virus | Vaccine* (manufacturer) | Type | Current recommendations | Contraindicated in pregnancy or immunocompromising conditions (Pregnancy category)‡ |
|---|---|---|---|---|
| Hepatitis A | HAVRIX® (GlaxoSmithKline Biologicals, Rixensart, Belgium)<br>VAQTA® (Merck Sharp and Dohme, Haarlem, the Netherlands) | Inactivated | 2 doses for all adults with risk factors (including immunocompromising conditions) | No (C) |
| Hepatitis B | Engerix-B® (GlaxoSmithKline, Uxbridge, UK)<br>Recombivax HB® (Merck & Co., Whitehouse Station, NJ, USA) | Inactivated | 3 doses for all adults with risk factors (including immunocompromising conditions) | No (C) |
| Measles, mumps, rubella | M-M-R® II (Merck & Co., Whitehouse Station, NJ, USA) | Live, attenuated | 1 or 2 doses for all adults who are not immune, students, healthcare workers, or in an outbreak setting | Yes (C) |
| Varicella zoster | Varivax® (Merck & Co., Whitehouse Station, NJ, USA) | Live, attenuated | 2 doses for all adults without evidence of immunity to varicella zoster virus | Yes (C) |
| Herpes zoster | Zostavax® (Merck & Co., Whitehouse Station, NJ, USA) | Live, attenuated | 1 dose for all adults aged at least 60 years regardless of a prior episode of herpes zoster | Yes (C) |
| HPV | Gardasil® (Merck & Co., Whitehouse Station, NJ, USA) | Inactivated | 3 doses for all females aged between 19 and 26 years regardless of prior history of genital warts, abnormal cervical smear or positive HPV DNA tests | Yes§ (B) |
| Influenza | Afluria® (CSL Biotherapies, King of Prussia, PA, USA)<br>Fluarix® (GlaxoSmithKline, Uxbridge, UK)<br>FluLaval™ (GlaxoSmithKline, Uxbridge, UK)<br>Fluvirin® (Novartis Vaccines and Diagnostics Limited, Liverpool, UK)<br>Fluzone® (Sanofi Pasteur, Swiftwater, PA, USA)<br>FluMist® (MedImmune, LLC Gaithersburg, MD, USA) | Inactivated, except FluMist® (intranasal-live, attenuated) | Recommended annual vaccination | No (except FluMist®) (C) |

*US brand name. ‡Pregnancy risk factor: category A, controlled studies showed no risk in pregnancy; category B, no evidence of risk in humans; category C, risk cannot be ruled out; category D, positive evidence of risk; category X, contraindicated in pregnancy. §Currently not recommended during pregnancy owing to limited safety information. Abbreviation: HPV, human papillomavirus.

individuals. The possibility of disseminated and fatal respiratory viral infection, however, should be considered in the differential diagnosis for immunocompromised patients to ensure that appropriate treatments for these infections are provided.

## Vaccination against viral infection

The appropriate vaccination of immunosuppressed patients, including those with rheumatic disease, is crucial to decrease morbidity and mortality related to infectious diseases (Table 5). In 2008, the American College of Rheumatology (ACR) published their recommendations for the use of nonbiologic and biologic DMARDs in RA.[110] The ACR Task Force Panel recommended periodic pneumococcal vaccinations and annual influenza vaccinations for all patients receiving DMARDs, and completion of a hepatitis B vaccination series for patients at risk of viral infection. These recommendations are in accordance with the general recommendations of the US Centers for Disease Control and Prevention (CDC).[111] Live-virus vaccines such as inhaled influenza and VZV vaccines are contraindicated in immunosuppressed patients.[110,111] Based on the recommendations of the CDC Advisory Committee on Immunization Practices, patients with congenital immunodeficiency, hematologic malignancy, or generalized malignancy, or those undergoing therapy with alkylating agents, antimetabolites, radiation or high-dose corticosteroids (at least 2 mg/kg of body weight or a total of 20 mg/day of prednisone), are considered severely immunocompromised.[111,112] In patients with rheumatic disease who are on high-dose, systemic corticosteroids for more than 2 weeks, live-virus vaccination should be avoided during the therapy, although the vaccine can be given if steroid therapy has been stopped for at least 3 months.[111,112] Patients receiving systemic corticosteroid therapy for less than 2 weeks, low-to-moderate doses of corticosteroids, local steroids injection, low-dose methotrexate (less than 0.4 mg/kg per week) or azathioprine (less than 3.0 mg/kg per day) can receive a live-virus vaccine.[112] Nonetheless, physicians should determine the degree to which an individual patient is immunocompromised before administering a live-virus vaccine. Statements from both the ACR Task Force Panel and the ACR *Hotline* recommend that live-virus vaccines, including VZV vaccine (see below), should be avoided in patients receiving biologic therapy.[110,113] In some patients, the initiation of biologic therapy can be delayed until at least 2 weeks after the zoster vaccine has been administered.[110,113]

Two new vaccines against viral infections have been approved for use in the USA. A live attenuated zoster vaccine (Zostavax®, Merck & Co., Whitehouse Station, NJ, USA) was approved for the prevention of herpes zoster and postherpetic neuralgia in 2006. This vaccine is recommended for all immunocompetent individuals aged 60 years and older, regardless of history of varicella or herpes zoster.[112] Additionally, an inactivated, quadrivalent (types 6, 11, 16 and 18) HPV vaccine, Gardasil® (Merck & Co., Whitehouse Station, NJ, USA), was approved for use in females aged 9–26 years.[78] This vaccine is most efficacious when given before the onset of sexual activity, but some benefit might exist in protecting against other genotypes even in patients with preexisting HPV infection. A recent clinical trial reported the efficacy of the quadrivalent HPV vaccine in women aged 25–45 years with no history of genital warts or cervical disease after 26 months of follow-up.[114] The composite endpoint comprised cervical or external genital disease or type-specific infection that had persisted for at least 6 months. Owing to the lack of long-term studies, the duration of immunogenecity as well as the safety and effectiveness of this vaccine in immunosuppressed patients remain unknown.[115]

Further studies examining the efficacy and safety of these newer vaccines in patients with immunocompromising conditions, including organ transplantation and immunosuppressive therapy for rheumatic diseases, are needed.[116] A reasonable approach could be to offer both immunizations to patients before the initiation of the immunosuppressive therapy, unless contraindicated according to the US CDC recommendations.[117]

## Conclusions

TNF blockade seems to be associated with the occurrence of opportunistic infections, but associations between TNF blockers and most viral infections have not been systematically studied. The multitude of case reports in the literature, however, should raise suspicion for an association with viral infection in patients receiving these agents for the treatment of systemic inflammatory conditions. Given the existence of bias and confounding factors in observational studies and case series, systematic reviews and meta-analyses of randomized clinical trials might be able to provide better information on the potential links between TNF blockers and several viral infections, although the sample sizes and follow-up lengths could be prove problematic. Inactivated viral vaccines are generally well-tolerated and safe even in immunocompromised patients. However, as noted in several studies with influenza and pneumococcal vaccination, the antibody response in the setting of TNF blocking therapy might be altered depending on which agent is used, whether or not traditional DMARDs are used concomitantly, and the timing of vaccination in relation to the last dose of TNF blocker administered.[118,119]

Future research should evaluate the effectiveness and safety of viral vaccinations, as well as appropriate immunization schedules in patients with rheumatic disease receiving immunosuppressives. Nonetheless, vigilant screening and selection of patients appropriate for immunization with both inactivated and live-virus vaccines is required in routine clinical practice. Rheumatologists should be aware of the potential for viral infection or reactivation in therapy with TNF blockers. Education and close surveillance of patients on TNF blockers is critical for timely diagnosis and management of these potentially fatal infections.

### Review criteria

Data for this Review were identified by searching MEDLINE and EMBASE (from 1995 to May 2009) and references from relevant articles. The following search terms were used: "tumor necrosis factor-alpha", "adalimumab", "infliximab", "etanercept", "rheumatic disease", "inflammatory bowel disease", "psoriasis", "virus diseases" or "viral infection", "zoster" or "herpes zoster", "varicella" or "chickenpox", "cytomegalovirus", "human herpesvirus 4" or "Epstein–Barr virus", "infectious mononucleosis", "influenza vaccines or influenza or flu", "HIV or human immunodeficiency virus", "parvovirus or parvovirus B19", "papillomavirus infections or human papillomavirus", and "condylomata acuminata". Only English-language articles were reviewed.


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