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Tumor necrosis factor blockade and the risk of viral infection

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Abstract

Tumor necrosis factor (TNF)-α blockers have been widely used to treat rheumatoid arthritis and other inflammatory diseases. An increased risk of tuberculosis and opportunistic infections with TNF-α blockers has been well reported because of the primary role of TNF-α in host defense and immune response. However, little is known about the association between TNF-α blockers and viral infections. Because interferon-γ and TNF-α play critical roles in the control of viral infection, depletion of TNF by treatment with TNF-α blockade may facilitate the risk of or reactivation of viral infection. Several large observational studies have recently found an increased risk of herpes zoster in patients receiving TNF-α blockers for rheumatoid arthritis. This review draws attention to several important viral infections such as human immunodeficiency, varicella-zoster and Epstein-Barr viruses, cytomegalovirus, and human papillomavirus in patients receiving TNF-α blocking therapy, their implications in clinical practice, and possible preventative approach with vaccination.

Keywords

tumor necrosis factor-alpha; rheumatoid arthritis; inflammatory bowel disease; infection; viral disease; vaccination; adalimumab; etanercept; infliximab; tumor necrosis factor-alpha blocker

INTRODUCTION

Tumor necrosis factor (TNF)-α plays an essential role in host defense and immune response [1]. TNF receptors (TNFR) are found on virtually all cell types and TNF-α affects many physiologic processes. TNF-α blockers effectively treat rheumatoid arthritis (RA) and several other chronic inflammatory conditions. The increasingly widespread use of these agents highlights the importance of understanding their safety. Much attention has been paid to the risks of opportunistic infections (i.e., tuberculosis and fungal infections) [2, 3]. Some conflicting data exist on the association between the use of TNF-α blockers and serious infection [4-6]. A recent meta-analysis by Bongartz *et al* reported that the number needed to harm for up to one year of therapy with infliximab or adalimumab was 59 (95% confidence interval (CI): 39-125) for serious infections [7]. Most prior studies have focused on bacterial or opportunistic infections, with few assessing a possible association between viral infections and these agents. Since interferon-γ and TNF-α play critical roles in the control of

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viral infection – recruiting and activating macrophages, NK cells, T cells, and antigen presenting cells –depletion of TNF by treatment with TNF-α blockade may facilitate the risk of or reactivation of viral infection [8]. We reviewed several important viral infections and their possible link with these agents. Viral hepatitis was not inclu[9]ded because it has recently been reviewed [10, 11].

A. Human Immunodeficiency Virus (HIV) infection

TNF is involved in the pathogenesis of HIV infection, but, to date, the exact role of TNF-α in HIV infection is not completely understood [9]. A positive association between activation of the TNF system in vivo and progression of HIV-related clinical disease has been reported [12, 13]. TNF and death receptors such as Fas ligand are directly or indirectly involved in the activation of T cell apoptotic processes in HIV infection [14-16]. Several studies proposed the important role of TNFR signaling in HIV infection [14, 16, 17]. Both TNFR1 and TNFR2 can induce apoptosis in peripheral T cells among HIV-infected persons, involving both CD4 and CD8 T cells [14].

Several case reports showed successful use of TNF-α blocking drugs in HIV-infected patients for chronic inflammatory conditions, including Crohn's disease (CD), psoriatic arthritis (PsA), and RA (Table 1) [18-28]. Most patients in these reports concomitantly received HAART. Infliximab, ranging 2 to 5 mg/kg per infusion, achieved marked clinical improvement without causing serious infection or worsening the status of HIV infection [19-22, 26, 27]. No serious infectious complication or increase in the HIV viral load was noted in most cases where etanercept, either 50 mg weekly or 25 mg twice weekly, was administered [23-25, 27, 28]. Successful outcomes with etanercept were noted even in patients with both HIV and viral hepatitis infection [24, 25]. In contrast, Aboulafia *et al* reported on a 45-year-old male with HIV and PsA, who died of severe bacterial infection 4 months after the use of etanercept [18]. In this case, the patient's CD4 T cell count and HIV viral load remained stable. His skin lesions and arthritis improved significantly, but he developed recurrent polymicrobial bacterial infections. 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* achieved partial clinical response to adalimumab while their CD4 counts and HIV viral loads remained stable [27]. However, it is unknown whether the relative safety of TNF-α blocking agents in these cases can be generalized to other HIV-infected patients. Until there is a better understanding of the long-term safety of TNF- α blockers in this specific population, clinicians should avoid use of these drugs in HIV-infected patients. Under specific circumstances where TNF- α blockers are clinically needed with no other alternative treatment options, the use of these drugs should be extremely cautious with close monitoring of CD4 counts, viral loads, and any clinical signs and symptoms for infection.

B. Varicella-Zoster Virus (VZV) infection

VZV is the cause of primary varicella, herpes zoster and post-herpetic neuralgia. Primary varicella infection is common and usually benign in children. However, disseminated varicella infection in adults and particularly immunocompromised patients can be severe and potentially fatal [29]. In the general population, the incidence of herpes zoster, caused by reactivation of VZV in sensory nerve roots, is reported at 1.2 to 4.8 cases per 1,000 person-years [30, 31]. Patients with compromised cell-mediated immunity due to aging, immunosuppressive agents, or concomitant illness are at an increased risk for development of herpes zoster [31, 32]. Severity of herpes zoster is related to the degree of immunocompetence, evidenced by greater severity among patients with organ transplantations, lymphoproliferative diseases or the acquired immunodeficiency syndrome (AIDS) [33].

It has been noted that herpes zoster is more common in patients with systemic lupus erythematosus (SLE) and RA, because of their impaired immune system as well as medications to treat the rheumatic conditions [34-37]. In a recent study from the Consortium of Rheumatology Researchers of North America (CORRONA) registry, VZV infection was the most frequent opportunistic infection – 44% of all cases of opportunistic infections — in patients who received methotrexate (MTX), TNF-α blockers or other disease modifying anti-rheumatic drugs (DMARDs) [38].

A retrospective cohort study using the U.S. Veterans Affairs Health system data demonstrated an elevated incidence of herpes zoster in RA – 9.96 cases per 1,000 patient-years [39]. Correlates of herpes zoster include older age, glucocorticoid use, traditional and biologic DMARDs including methotrexate, leflunomide, azathioprine, cyclophosphamide, cyclosporine, anakinra and TNF-α blockers, malignancy, chronic lung disease, renal failure, and liver disease. Of the 96 patients treated with TNF-α blockers developed herpes zoster. Among the TNF-α blockers, etanercept (hazard ratio (HR) 0.62, 95% CI: 0.40–0.95) and adalimumab (HR 0.53, 95% CI 0.31–0.91) appeared to have a lower risk of herpes zoster, compared with infliximab (HR 1.32, 95% CI 0.85-2.03). A prospective study using the data in the German biologics register reported a significantly increased risk of herpes zoster in patients receiving treatment with the monoclonal antibodies – infliximab and adalimumab – (HR, 1.82, 95% CI 1.05-3.15), even after adjusting for age, RA severity, and glucocorticoid use [40]. Notably, no significant association was found for etanercept use (HR 1.36, 95% CI 0.73-2.55) [40].

Several case reports and retrospective studies reporting VZV infection in patients who received TNF-α blocker treatment for inflammatory conditions are listed in Table 2 [40-51]. In the majority of the reported cases, the patients were treated with TNF-α blockers and concomitant immunosuppressive agents such as MTX and azathioprine for a period ranging 1 month. As noted in Table 2, serious morbidity and mortality from VZV infection can occur in patients who received treatment with TNF-α blockers. Of the 6 disseminated primary varicella infection cases [44, 45, 47-49, 52], 1 death occurred in a 26-year-old male patient with CD who received the first infusion of infliximab (5 mg/kg) [44]. Immunization with the VZV vaccine is an effective approach to prevent both primary varicella infection and herpes zoster. However, the VZV vaccine is a live, attenuated vaccine generally contraindicated in immunocompromised patients. The use of the VZV vaccine in such patients is discussed further below.

C. Epstein-Barr Virus (EBV) infection

EBV, also known as HHV-4, is one of the most common human viruses infecting as many as 95% of adults aged 35 to 40 years in the U.S [53]. EBV causes infectious mononucleosis, Burkitt's lymphoma, nasopharyngeal carcinoma, and lymphoproliferative disease (LPD) [33]. The relationship between EBV and autoimmune diseases are not completely understood, although EBV has been considered as a possible cause of several autoimmune diseases for many years [54]. Antibodies to EBV are elevated in patients with RA, SLE, or Sjogren's syndrome [55]. A study by Balandraud *et al* reported that peripheral blood EBV viral load was associated with high disease activity in RA [56]. However, neither MTX nor TNF-α blockers significantly modified EBV load over time [56].

Several case reports in the literature described EBV-related conditions associated with TNF-α blocking therapy. Sari *et al* reported a 20-year-old male with juvenile ankylosing spondylitis, who developed atypical infectious mononucleosis following infliximab treatment for 8 weeks [57]. This patient presented with fatigue, malaise, abdominal discomfort, weight loss and lymphadenopathy, however fever, pharyngitis, and lymphocytosis were not present. His serologic test revealed positive IgM antibodies to the

viral capsid antigen of EBV, also confirmed in the lymph node biopsy. The authors concluded that blockade of TNF-α might have masked the typical symptoms of infectious mononucleosis. In a case report by Park *et al*, 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 25mg twice weekly [58]. Subsequently, she was diagnosed with EBV-associated diffuse LPD, which gradually resolved after stopping etanercept. Another case of EBV-associated LPD was reported in a 63-year-old Japanese patient with RA following a month of infliximab (3mg/kg) therapy [59]. In this case, cessation of infliximab therapy also resulted in a dramatic regression of LPD without further treatment. Losco *et al* described a case of EBV-associated, diffuse large B-cell lymphoma of the ileum in a 42-year-old male with CD, after long-term use of azathioprine and a single dose of infliximab (5mg/kg) [60]. His treatment was successful with a surgery and a course of chemotherapy. The use of TNF-α blockers is probably not the sole cause of EBV infection. Nevertheless, cessation of the drugs should be considered when suspected, as these drugs may indirectly increase risk of infection or reactivation of EBV.

D. Cytomegalovirus (CMV) infections

CMV or HHV-5 is a common viral pathogen that infects 40-60% of the population in developed countries [33, 61]. Several cases of CMV infection complicating TNF-α blocking therapy were reported (Table 3). Of those, 4 cases occurred in patients with inflammatory arthritis [62-65]. In a case by Petersen *et al*, a 37-year-old male with a long standing history of psoriasis and PsA developed a primary CMV infection following a month of therapy with etanercept 50mg twice weekly (a standard initial dose for plaque psoriasis) [63]. His clinical presentations included fever, pneumonia, abnormal liver function tests, and otitis media. After discontinuation of etanercept, the patient recovered spontaneously with no antiviral therapy. Six months later, he was restarted on etanercept without CMV reactivation. Except for this patient, all other patients in Table 3 were treated with infliximab for either IBD or inflammatory arthritis [62, 64-71]. Haerter *et al* reported a case of severe CMV retinitis in a 57-year-old female with a longstanding history of RA who received infliximab (3mg/kg) for 2 years [62]. This patient was concomitantly on oral cyclophosphamide 150mg daily and azathioprine 150mg daily due to refractory RA. Her initial episode of retinitis in the right eye was treated with intravenous ganciclovir followed by a maintenance therapy with oral valganciclovir. However, she developed a recurrent CMV retinitis in the contralateral eye 5 weeks after stopping valganciclovir. A case of severe CMV colitis was noted in a 25-year-old male with Behcet's disease after the 3rd dose of infliximab (5mg/kg) [65]. He was previously treated with monthly intravenous cyclophosphamide, interferon, cyclosporine and azathioprine. His colitis resolved with cessation of infliximab and intravenous ganciclovir for a month. In a study by Pontikaki *et al*, one of 151 patients with juvenile idiopathic arthritis (95 on etanercept and 56 on infliximab) developed CMV pulmonary infection following infliximab therapy [64]. Most patients in Table 3 were using more than one immunosuppressive drug, and thus, it is difficult to determine whether the use of TNF-α blockers was directly involved in CMV infection. Nonetheless, TNF-α blockade can theoretically put patients at an increased risk of this viral infection.

E. Kaposi's sarcoma-associated herpesvirus infection

Kaposi's sarcoma, caused by HHV-6, is a vascular, multicentric malignant tumor [72, 73]. It is rare and usually associated with the AIDS and organ transplantations [74]. A number of cases of Kaposi's sarcoma have been noted in non-AIDS patients on immunosuppressive therapy for the rheumatic diseases such as RA, SLE and vasculitis [75-78]. There is almost no data supporting an association between TNF-α blocking therapy and Kaposi's sarcoma, with only one case of Kaposi's sarcoma reported in a patient with RA who received 12 doses of infliximab (3mg/kg). One prospective study of 60 patients with CD found no patients

turning positive by polymerase chain reaction for HHV-6 during 14-weeks of follow-treatment. [79]

F. Human papillomavirus (HPV) and molluscum contagiosum virus (MCV) infection

Table 4 summarizes cases of cutaneous infections with either HPV or MCV in patients who received TNF-α blocking therapy (3 patients with infliximab and 2 patients with etanercept) [80-83]. Little is known about the incidence or prevalence of HPV infection in patients with rheumatic diseases although anogenital HPV infection is the most common sexually transmitted disease in the U.S [84, 85]. HPV types 1, 2, and 4 cause verrucae vulgares, also known as benign warts, on the hands and feet. HPV types 6 and11 usually cause benign condylomata acuminata, while types 16, 18, 31, and 33 cause precancerous, high-grade squamous intraepithelial neoplasia and invasive carcinomas of the anogenital tract. The majority of infections with HPV are subclinical. In 80%, the infection resolves spontaneously within a year as a result of a cellular immune response [85]. The risk of persistent HPV infection, particularly with oncogenic genotypes, may be associated with factors such as age, smoking, hormonal status, coexisting infections, and family history [86]. Although there is no direct evidence linking host immunologic response to risk of HPV persistence, viral reactivation from a latent state in immunocompromised patients has been noted [87, 88]. An increased risk of cervical dysplasia, HPV infection and persistence has been repeatedly reported in patients following kidney, lung, and stem cell transplantation [89-92]. A study by Kane *et al* found that women with IBD were also more likely to have higher-grade cervical dysplasia caused by HPV infection than controls (odds ratio (OR) 4.3, 95% CI 2.2-10.5). In addition, those women exposed to immunosuppressive therapy were more likely to have abnormal Pap smears than controls (OR 4.5, 95% CI 1.5-12.3) as well as unexposed IBD patients (OR 1.9, 95% CI 1.1-12.1) [93]. Given the available, albeit limited, data in the literature, it is possible that use of immunosuppressive agents including TNF-α blockers increases the risk of persistent HPV infection and ultimately cervical cancer. Future study 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 those receiving TNF-α blockers. Molluscum contagiosum is another viral infection of the skin or occasionally of the mucous membranes. It is more common in children or in adults with HIV or other immunosuppressed conditions [94].

G. JC virus infection or progressive multifocal leukoencephalopathy (PML)

PML, a fatal demyelinating disease of the central nervous system, is a very rare disease. The incidence has increased with the AIDS pandemic and the more common use of immunosuppressive drugs for organ transplantation or rheumatic diseases [95]. It is caused by reactivation of the JC virus, a type of polyomavirus [96]. As of May 2009, a total of 10 cases of PML were reported in patients who took natalizumab, a monoclonal antibody against α4 integrin, used for multiple sclerosis and CD [97, 98]. Use of other monoclonal antibodies--efalizumab, rituximab, and infliximab-- and various transplant drugs such as tacrolimus and mycophenolate has been associated with PML cases [99-102]. A recent study reviewed 57 cases of PML after rituximab therapy between 1997 and 2008 [103]. Of those, 2 patients had SLE and 1 had RA. A retrospective cohort study of 734 patients with IBD on infliximab showed that a fatal case of PML after the use of both natalizumab and infliximab [104]. Yamamoto *et al* reported a case of leukoencephalopathy in 74-year-old Japanese patient with RA on etanercept. Although this patient had characteristics of PML, the PCR for the JC virus-DNA was negative in the cerebrospinal fluid (CSF) [105].

No definite case of PML has been reported following the use of etanercept or adalimumab in published literature. However, the diagnosis of PML is easily missed without a high degree

of suspicion. In some cases, characteristic evidence of the damage caused by PML in the brain can be detected on MRI scans [95, 98]. PML can be confirmed by quantitative PCR for JC virus DNA in the CSF or in a brain biopsy specimen [95]. The PCR test performed on the CSF has a sensitivity between 76-98% and a specificity of 98-99% [106, 107]. Mohan *et al* reported a series of 19 patients with demyelinating neurologic events following treatment with TNF-α blockers (17 for etanercept and 2 for infliximab) for rheumatic diseases [108]. None was diagnosed as PML, but lumbar puncture was only performed in 1 patient and brain biopsy was done in just 2 patients. Jarand *et al* described 3 cases of neurological complications related to the use of infliximab, but with no specific information on the serology of JC virus [109]. Although JC virus infection is very rare and may not be associated with TNF-α blockers, physicians should still maintain a very high level of suspicion for any immunosuppressed patient with new neurologic symptoms, such as disorientation, ataxia, speech disturbance or visual loss.

E. Other viral-associated infections

A few case reports have been published regarding viral pneumonia in patients who received TNF-α blockers for chronic inflammatory diseases. Smith *et al* reported that, after using etanercept for RA, a 54-year-old female developed severe parainfluenza type 3 pneumonia requiring mechanical ventilation and a prolonged hospitalization for 3 weeks [110]. A case of severe adenovirus pneumonia following the first dose of infliximab (3 mg/kg) was reported in a 35-year-old male with CD [111]. Kang *et al* also 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 [112]. In both cases of adenovirus pneumonia, the patients recovered with antiviral treatment and intravenous immunoglobulin G after prolonged hospitalizations. Most respiratory viral infections are self-limited in immunocompetent subjects. However, the possibility of disseminated and fatal respiratory viral infection should be considered in the differential diagnosis for immunocompromised patients, to ensure appropriate treatments for these infections.

F. Vaccinations against virus infections

Table 5 summarizes all available viral vaccines recommended for adults in the U.S. The appropriate vaccination of immunosuppressed patients including those with rheumatic disease is crucial to decrease morbidity and mortality related to vaccine-preventable infectious diseases. In 2008, the American College of Rheumatology (ACR) published their recommendations for the use of non-biologic and biologic DMARDs in RA [113]. The ACR Task Force Panel recommended periodic pneumococcal vaccinations and annual influenza vaccinations for all patients receiving non-biologic and biologic DMARDs and completion of a hepatitis B vaccination series for the patients with risk factors. These recommendations are in accordance with the Centers for Disease Control and Prevention (CDC) general recommendations [117]. Live-virus vaccines such as inhaled influenza and varicella-zoster vaccines are contraindicated in immunosuppressed patients [113, 114]. Based on the recommendations of the Advisory Committee on Immunization Practices (ACIP), patients with congenital immunodeficiency, hematologic malignancy, generalized malignancy or therapy with alkylating agents, antimetabolites, radiation or high dose of corticosteroids – 2mg/kg of body weight or a total of 20mg/day of prednisone— are considered severely immunocompromised [114, 115]. With regard to patients on high-dose, systemic corticosteroids for more than 2 weeks to control rheumatic diseases, a live-virus vaccine should be avoided during the therapy, although it can be given after stopping the therapy for at least 3 months [114, 115]. Patients receiving systemic corticosteroid therapy less than 14 days, low-to-moderate dose of corticosteroids, local steroids injection, low-dose methotrexate (less than 0.4 mg/kg/week) or azathioprine less than 3.0 mg/kg/day can receive a live-virus vaccine [115]. The ACR Task Force Panel recommends live-virus vaccines including zoster

vaccine should also be avoided in patients receiving biologic therapy [113]. The ACR Hotline suggested that rheumatologists should avoid the zoster vaccine in patients actively receiving TNF blockers, as well as abatacept, rituximab and anakinra or delay the initiation of biologic therapy until at least two weeks after the zoster vaccine is given in some patients [116]. The American Society of Transplantation 2004 guidelines for vaccination of solid organ transplant candidates recommends varicella, measles, mumps, rubella, and rabies vaccines before organ transplantation [113, 117]. No guideline for the use of vaccination prior to initiating biologic therapy for rheumatic diseases has been issued yet. Nonetheless, it is important to note that a physician should determine the degree to which an individual patient is immunocompromised prior to administering a live-virus vaccine.

Over the last several years, two new vaccines against viral infections were licensed in the U.S. Zostavax, a live, attenuated varicella-zoster vaccine, has been approved for prevention of herpes zoster and post-herpetic neuralgia in 2006. Currently, it is recommended for all immunocompetent persons aged 60 years and older, regardless of history of varicella (chickenpox) or herpes zoster [118]. As well, an inactivated, quadrivalent (type 6, 11, 16, and 18) HPV vaccine, Gardasil, was approved for females aged 9 to 26 years in the U.S [84]. A bivalent (type 16 and 18) HPV vaccine is not yet available in the U.S. This vaccine is most efficacious when given before the onset of sexual activity, but some benefit may exist in protecting against the other genotypes even in a patient with preexisting HPV infection. A recent randomized, double-blind trial reported the efficacy of the quadrivalent HPV vaccine in women aged 25 to 45 years with no history of genital warts and cervical disease after 26 months of follow-up using a composite endpoint comprising cervical or external genital disease or type-specific infection that had persisted for at least 6 months [119]. Due to the lack of long-term studies at the present time, the duration of immunogenecity is not known. It is also unknown whether this vaccine is safe and effective in immunosuppressed patients [120]. Further studies examining the efficacy and safety of the newer vaccines in patients with immunocompromising conditions including organ transplantation and immunosuppressive therapy for rheumatic diseases are needed [121]. It may be reasonable to offer both immunizations for patients before initiation of the immunosuppressive therapy unless contraindicated according to the CDC recommendations [122].

CONCLUSIONS

TNF-α blockade seems clearly associated with tuberculosis and opportunistic infections; however the associations between TNF-α blockers and most viral infections have not been systematically studied. The multitude of case reports should raise the suspicion for viral infections for physicians recommending these agents for systemic inflammatory conditions. Given the existence of bias and confounding in observational studies and case series, systematic reviews and meta-analyses of randomized clinical trials may be able to provide better information on potential links between TNF-α blockers and several important viral infections. Vaccination with inactivated viral vaccines is safe even in immunocompromised patients although the antibody response may be altered. Future research should evaluate the effectiveness and safety of viral vaccinations in patients with rheumatic disease on immunosuppressive therapy. 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-α blockers as discussed in this review. Education and close surveillance of patients on TNF-α blockers is critical for timely diagnosis and management of these potentially fatal infections.

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Search Strategy

Data for this review were identified by searching electronic databases -- 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, herpesvirus 4, human 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 papilloma virus, and condylomata acuminata*. Only English language articles were reviewed.

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Key points

- Little is known about the association between TNF-α blockers and viral infections.
- TNF-α blockade may facilitate the risk of or reactivation of viral infection through several mechanisms.
- Several successful cases of TNF-α blocking therapy in HIV patients were reviewed.
- Cases of infection with varicella-zoster virus, Epstein-Barr virus, cytomegalovirus, human papillomavirus and JC viruses in patients who received TNF-α blocking therapy were reviewed.
- Currently available viral vaccines and the guidelines for adults were summarized.

Table 1

Use of TNF-α blockers in Human Immunodeficiency Virus (HIV)-infected patients

Author (Yr/Country)	Patient characteristics	Baseline CD4 count (cells/mm^3)	Drug (duration of therapy)	Concomitant drugs	Results
Aboulafia [18] (2000/USA)	45-year-old male with HIV and PsA	< 50	ETA 25mg twice a week (6 months)	HAART Steroids Hydroxychlor oquine Minocycline	After 6 months of ETA therapy, his skin lesions and arthritis improved significantly, but the patient died of bacterial infection 4 months later.
Gaylis [20] (2003/USA)	41-year-old male with HIV and Reiter's syndrome	693	INF 3mg/kg (18 months)	HAART Steroids MTX	Marked clinical improvement was achieved with no serious infection. Viral loads remained stable.
Bartke [19] (2004/Germany)	46-year-old male with HIV, psoriasis and PsA	68	INF 3mg/kg (3 doses)	HAART Acitretin Prednisolone MTX	Dramatic improvement in psoriasis and PsA occurred while his HIV status remained stable.
Wallis [23] (2004/Uganda)	Phase I study to determine the safety of ETA in 16 patients with HIV-associated TB	> 200	ETA 25mg twice a week (8 doses)	Isoniazid Rifampin, Ethambutol Pyrazinamide Cotrimoxazole Pyridoxine	25% increase in CD4 cell counts by week 4 and no change in HIV-RNA occurred.
Filippi [22] (2006/France)	35-year-old female with HIV and CD	> 1000	INF (3 doses)	HAART Azathioprine Steroids	Remission of CD occurred, but INF was discontinued due to an allergic reaction. No serious infection was noted.
Beltran [21] (2006/Spain)	42-year-old female with HIV and CD	> 250	INF (3 doses)	HAART Steroids	Complete clinical and endoscopic remission of CD occurred with no serious infection. Her HIV status remained stable.
Sellam [26] (2007/France)	2 male patients with HIV, psoriasis, and PsA	1. 249 2. < 200	1. INF 5mg/kg (15 doses) 2. INF 2mg/kg (25 doses)	HAART Prednisone MTX	Psoriasis and PsA dramatically improved to almost complete remission. No serious infections occurred and the HIV infection remained well-controlled.
Linardaki [25] (2007/Greece)	43-year-old male with hemophilia A, HCV, HIV, and PsA	340	ETA 25mg twice a week (2 years)	HAART MTX Cyclosporin A	Marked improvement in psoriasis and PsA occurred without serious infection. His HCV and HIV status remained stable.
Kaur [24] (2007/USA)	44-year-old male with RA, HIV, HBV, and HCV	299	ETA 25mg twice a week (3 months)	HAART Prednisone Sulfasalazine Hydroxychlor oquine (INF 3 doses prior to ETA)	RA improved significantly while HIV, HCV and HBV status remained stable.
Mikhail [28] (2008/USA)	35-year-old male with HIV, PsA, and severe pustular psoriasis	435	ETA 50mg weekly (20 weeks)	HAART Topical steroids	Both skin lesions and arthritis improved dramatically with no serious infection. His HIV status remained stable.

Author (Yr/Country)	Patient characteristics	Baseline CD4 count (cells/mm^3)	Drug (duration of therapy)	Concomitant drugs	Results
Cepeda [27] (2008/USA)	8 patients with HIV and inflammatory arthritis	> 600 in 75 % of the patients	ETA INF ADA (average 28 months)	HAART (5 out of 8 patients) Steroids DMARDs	Almost all had an excellent clinical response in arthritis. CD4 counts and HIV viral loads remained stable. No serious infection was noted.

PsA: psoriatic arthritis, RA: rheumatoid arthritis, CD: Crohn's disease, TB: tuberculosis, HCV: hepatitis C virus, HBV: hepatitis B virus, INF: infliximab, ETA: etanercept, ADA: adalimumab, HAART: highly active antiretroviral therapy, MTX: methotrexate, CD4: cluster of differentiation 4, DMARDs: disease modifying antirheumatic drugs

Table 2

Cases of varicella zoster virus (VZV) infection following TNF-α blocking therapy

Author (Yr/Country)	Patient characteristics	Drug (duration of therapy)	Concomitant drugs	Results
Baumgart [41] (2002/Germany)	45-year-old male with CD	INF 5mg/kg (3 doses)	Azathioprine Prednisone Mesalamine	Acute herpes zoster, resolved with acyclovir
Kinder [42] (2004/UK)	72-year-old male with RA	INF 3mg/kg (2 doses)	Not reported	Acute severe herpes zoster
Leung [44] (2004/USA)	26-year-old male with CD	INF 5mg/kg (1 dose)	Steroids Mesalamine 6-MP	Disseminated primary varicella infection complicated by multi-organ failure, DIC and death
Vonkeman [49] (2004/Netherlands)	32-year-old male with RA	INF (1 dose)	Not reported	Disseminated primary varicella infection complicated with respiratory insufficiency, improved with acyclovir
Seiderer [48] (2004/Germany)	22-year-old male with CD (in a chart review of 100 patients with IBD)	INF 5mg/kg (1 dose)	Azathioprine	1 case of generalized primary VZV infection
Choi [47] (2006/Korea)	63-year-old female with RA	INF 3mg/kg (2 doses)	MTX Bucillamine	Disseminated varicella infection, resolved with acyclovir
Lee [52] (2007/Korea)	42-year-old female with RA	ADA 40mg biweekly (70 weeks)	MTX Steroids	Disseminated primary varicella infection, resolved with acyclovir
Wendling [50] (2008/France)	9 patients with inflammatory arthritis (in a chart review of 300 patients who received TNF-α blocking therapy)	INF – 4 patients ADA – 2 patients ETA – 3 patients (6-42 months)	MTX Steroids	Herpes zoster, recovered fully with antiviral treatment and interruption of the TNF-α blockers
Becart [46] (2008/Belgium)	58-year-old male with psoriasis	ETA 50mg twice a week (1 month)	none	Recurrent varicella infection, resolved 2 weeks after discontinuation of ETA
Balato [45] (2009/Italy)	36-year-old male with psoriasis	INF 5mg/kg (15months)	Not reported	Disseminated primary varicella infection with pulmonary involvement, resolved with acyclovir
Strangfled [40] (2009/Germany)	A study of 5040 RA patients in the German biologic registry	INF ETA ADA (average 1.9 years)	Steroids DMARDs	28 cases of herpes zoster; Adjusted HR 1.82 (95%CI: 1.05-3.15) for both INF and ADA, and 1.36 (95%CI: 0.73-2.55) for ETA
Tresch [51] (2009/Switzerland)	70-year-old female with RA	ETA (10 months)	Steroids MTX	Disseminated herpes zoster

RA: rheumatoid arthritis, CD: Crohn's disease, IBD: inflammatory bowel disease, TNF: tumor-necrosis factor, INF: infliximab, ETA: etanercept, ADA: adalimumab, 6-MP: 6-mercaptopurine, MTX: methotrexate, DMARDs: disease modifying antirheumatic drugs, HR: hazard ratio, CI: confidence interval

Table 3

Cases of cytomegalovirus (CMV) infection following TNF-α blocking therapy

Author (Yr/Country)	Patient characteristics	Drug (duration of therapy)	Concomitant drugs	Results
Papadakis [68] (2001/USA)	18-year-old male with IBD	INF 5mg/kg (1 dose)	Steroids Cyclosporine 5-ASA	CMV colitis; treated with colectomy and ganciclovir
Helbling [67] (2002/Switzerland)	63-year-old female with CD	INF (1 dose)	Steroids Azathioprine	Disseminated CMV infection with GI, cutaneous, and CNS involvement, treated with foscarnet and ganciclovir
Actis [66] (2002/Italy)	A study of 8 patients with steroid-refractory UC	INF 5mg/kg (1 dose)	Steroids Azathioprine	1 patient developed CMV pancolitis
Haerter [62] (2004/Germany)	57-year-old female with RA	INF 3mg/kg (2 years)	Cyclophosphamide Azathioprine	Severe CMV retinitis with visual loss; treated with ganciclovir and valganciclovir; complicated by recurrence of CMV retinitis in the contralateral eye
Mizuta [70] (2005/USA)	45-year-old female with CD	INF 5mg/kg (1 year)	6-MP Prednisone	Acute CMV hepatitis; treated with ganciclovir
Kohara [69] (2006/USA)	22-year-old male with CD	INF (4 months)	6-MP	Acute CMV ileitis complicated by DIC and hemophagocytic syndrome; treated with ganciclovir and splenectomy
Pontikaki [64] (2006/Italy)	A study of 95 patient with JIA on either ETA or INF	INF (mean: 12 months)	MTX	1 patient developed severe CMV pulmonary infection
Sari [65] (2008/Turkey)	25-year-old male with BD	INF 5mg/kg (3 doses)	Colchicine	CMV colitis; treated with ganciclovir
Petersen [63] (2008/Denmark)	37-year-old male with psoriasis and PsA	ETA 50mg twice a week (2 months)	Not reported	Acute primary CMV infection; spontaneous resolution after cessation of ETA
D'Ovidio [71] (2008/Italy)	A study of 15 patients with IBD (11 with CD and 4 with UC)	INF (3 doses)	Steroids Azathioprine	9 patients had CMV seropositivity; CMV DNA from the colonic biopsies in 3 patients; no worsening colonic disease

CD: Crohn's disease, UC: ulcerative colitis, RA: rheumatoid arthritis, BD: Behcet's disease, PsA: psoriatic arthritis, GI: gastrointestinal, CNS: central nervous system, DIC: disseminated intravascular coagulopathy, IBD: inflammatory bowel disease, INF: infliximab, ETA: etanercept, 6-MP: 6-mercaptopurine, MTX: methotrexate

Table 4

Cases of human papilloma virus (HPV) and molluscum contagiosum virus (MCV) infection following TNF-α blocking therapy

Author (Yr/Country)	Patient characteristics	Biologic drug (duration)	Concomitant drugs	Results
Cursiefen [81] (2002/Germany)	67-year-old female with RA	INF 300mg (6 months)	Prednisone MTX	Multiple bilateral molluscum contagiosum lesions in upper and lower eyelids
Somasekar [80] (2004/UK)	23-year-old male with CD	INF (2 doses)	Steroid Azathioprine	Profuse penile and perianal condylomata acuminata
Adams [83] (2004/USA)	17-year-old female with JIA	ETA (2 years)	MTX	Extensive bilateral plantar warts, which resolved a month after discontinuation of ETA
Antoniou [82] (2008/Greece)	31-year-old female with PsA and severe psoriasis	ETA 50mg twice a week (3 months); then 25mg twice a week (3 months)	Not reported	Perianal condylomata acuminata
	29-year-old patient with severe plaque psoriasis	INF 5mg/kg (1 dose)	Cyclosporine Efalizumab (both were discontinued a week prior to INF)	Molluscum contagiosum in the abdomen and exacerbation of preexisting genital condylomata

RA: rheumatoid arthritis, CD: Crohn's disease, JIA: juvenile idiopathic arthritis, PsA: psoriatic arthritis, INF: infliximab, ETA: etanercept, MTX: methotrexate

Table 5

Available viral vaccines recommended for adults in the United States [*] [122]

Vaccine	U.S. brand name	Type	Current guidelines for adults	Contraindicated in pregnancy or immunocompromising conditions (Pregnancy category [§])
Hepatitis A	HAVRIX®; VAQTA®	Inactivated	Recommended 2 doses for all adults with risk factors (including immunocompromising conditions)	No (C)
Hepatitis B	Engerix-B®; Recombivax HB®	Inactivated	Recommended 3 doses for all adults with risk factors (including immunocompromising conditions)	No (C)
Measles, mumps, rubella	M-M-R® II	Live, attenuated	Recommended 1 or 2 doses for all adults who are not immune, students, health-care workers, or in an outbreak setting	Yes (C)
Varicella	Varivax®	Live, attenuated	Recommended 2 doses for all adults without evidence of immunity to varicella	Yes (C)
Herpes zoster	Zostavax®	Live, attenuated	Recommended 1 dose for all adults aged 60 or older regardless of a prior episode of herpes zoster	Yes (C)
HPV	Gardasil®	Inactivated	Recommended 3 doses for all females aged between 19 and 26 regardless of prior history of genital warts, abnormal Pap smear or positive HPV DNA tests	Yes [†] (B)
Influenza	Afluria®; Fluarix®; FluLaval™; Fluvirin®; Fluzone®; FluMist®	Inactivated, except FluMist® (intranasal- live, attenuated)	Recommended annual vaccination	No (except FluMist®) (C)

[*] More information for all the vaccines is available at http://www.cdc.gov/vaccines/recs/schedules/default.htm.

[§] 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, due to limited safety information