

Biologics in psoriasis: Complications and precautions

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ABSTRACT

The use of biological agents as a new alternative treatment for psoriasis and other chronic inflammatory diseases is expanding worldwide. Acute and chronic adverse effects of biologics are becoming increasingly recognized. Careful pretreatment monitoring and follow-up will allow early recognition and treatment of adverse effects like opportunistic infections, reactivation of TB, malignancy/lymphoma, congestive heart failure, demyelination, injection/infusion reactions, development of auto antibodies, lupus-like disease and cutaneous adverse events. Early recognition of the clinical manifestations of any complication in patients treated with biologic therapy enables dermatologists to appropriately treat or refer patients to relevant specialist for diagnostic workup, disease confirmation, and any necessary treatment. In this review, we propose a concise overview of the adverse events of biologics drugs currently being used in the dermatologic field with a guide for monitoring and assessment.

INTRODUCTION

Psoriasis vulgaris is a chronic, systemic, inflammatory disorder which can be altered by genetic and environmental factors. It may be associated with other inflammatory disorders such as psoriatic arthritis, inflammatory bowel disease, coronary artery disease, and components of the metabolic syndrome.¹ Psoriasis causes physical and mental disability comparable or in excess of that found in patients with other chronic illnesses such as cancer, arthritis, hypertension, heart disease, diabetes, and depression.²

The significant reduction in quality of life and the psychosocial disability suffered by patients underline the need for prompt, effective treatment, and long-term disease control. Localized, limited

disease can usually be managed satisfactorily with topical agents. Those with moderate to severe disease often require systemic treatment.³ Phototherapy and traditional 'standard' systemic therapies, while often effective, can be associated with long-term toxicity; some are expensive, and some patients have treatment resistant disease.⁴ Also, phototherapy is not available to many due to geographical, logistical or other constraints. Patients themselves demonstrate high levels of dissatisfaction with standard approaches to treatment.⁵ Biologic therapies for psoriasis utilize molecules designed to block specific molecular steps important in the pathogenesis of psoriasis and now comprise a number of well-established, licensed, treatment options for patients with severe disease.⁶

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Table 1 Biologic agents approved for treatment of psoriasis^{7,8,9}

Drug name	Trade name	Mechanism	FDA approval for psoriasis
TNF α -blockers			
Adalimumab	Humira®	Recombinant human IgG1 nonoclonal antibody	2008
Infliximab	Remicade®	Chimeric human IgG1 nonoclonal antibody	2006
Etanercept	Enbrel®	Dimeric fusion protein linked to Fc portion of human IgG1	2004
T cell modulators			
Alefacept	Amevive®	Dimeric fusion protein of CD2/LFA3 linked to Fc portion of human IgG1	2003
Efalizumab	Raptiva®	Recombinant humanized nonoclonal antibody against LFA-1(CD11a)	withdrawn in 4/2009
Cytokine inhibitors			
Ustekinumab	Stelara®	IL-12 and IL-23 blocker	2009

COMPLICATIONS

Although most of biologics are relatively safe when correctly used and monitored, there are known side effects and adverse events that occur. The FDA has issued warnings related to biologic agents used in the management of psoriasis over the past two years. These warnings have focused on infectious,¹⁰ neurologic,¹¹ and malignancy related concerns.¹² Evaluating the true risk of complications of biologic agents in the management of psoriasis is challenging because many reports of complications from use of these agents have occurred in the management of other diseases, such as rheumatoid arthritis and inflammatory bowel disease, rather than psoriasis. These diseases may have a greater inherent risk for developing infections or malignant complications compared to psoriasis. Many complications of these biologic agents have occurred in patients on concomitant

immunosuppressive therapies.¹³ Reported adverse effects include opportunistic infections, reactivation of tuberculosis (TB), malignancy/lymphoma, congestive heart failure, demyelination, injection/infusion reactions, development of auto antibodies, lupus-like disease and cutaneous adverse events.^{7,8, 13-18}

MALIGNANT COMPLICATIONS

Overall Cancer Rates

Long-term studies concerning the malignancy risks associated with these immunosuppressive agents have been most extensively explored in the RA population rather than in psoriasis. Bongartz et al¹⁹ carried out a meta-analysis of nine trials of patients with RA treated with infliximab or adalimumab. The data included 3493 patients who received TNF antagonist treatment and 1512 patients who received placebo and demonstrated a

pooled odds ratio for malignancy of 3.3 (95% CI 1.2–9.1) and the incidence of cancer was associated with higher doses of the biologic. This paper raised a variety of methodological concerns and subsequent studies have given reassurance that biases in the previous meta-analysis might inflate cancer risk.^{20,21}

Analysis of a Swedish registry by Geborek et al²² and Askling²³ revealed no increase in the overall cancer risk in patients receiving anti-TNF therapy compared with those that are not. In support of above studies, the most recent data from a large US observational study concluded that biologics use in RA was not associated with increased overall risk of any malignancy.²⁴ However, when examined separately, the risks for both nonmelanotic skin cancer and melanoma were increased with biologic therapy.^{24,25} In the meta-analysis of Bongartz et al¹⁹, many malignancies in the anti-TNF arms of the trials were NMSC (nine out of 35). The Swedish Biologic Register signals a possible increased occurrence of NMSC in RA cohort treated with anti-TNF.²³

Determining the risk of developing malignancies with the use of biologic agents in the treatment of psoriasis is difficult due to the nature of the disease and the concomitant use of immunosuppressive agents. Psoriasis is a chronic inflammatory disorder that may inherently place the patient at risk of developing certain cancers. In a British cohort study, patients with psoriasis who were over the age of 64 had a three-fold increased risk of developing lymphoma as compared to those without psoriasis.²⁶ Another study demonstrated that all patients with psoriasis faced an increased risk of lymphoma with higher relative risks for Hodgkin's lymphoma (HL) and cutaneous T-cell lymphoma (CTCL). Patients with severe psoriasis had

a higher relative risk of of developing lymphoma than mild psoriasis.²⁷

Lymphoma

To date, there is no robust evidence of increased risk of malignancy with TNF antagonists in patients with psoriasis. Data from clinical trials are reassuring, and there is no indication from registry data in rheumatology populations of increased risk of solid tumours and lymphoma with TNF antagonist therapy as compared with standard disease-modifying antirheumatic drugs (DMARDs) to date.²⁸ However, uncertainty and conflicting evidence remain around the possible increased risk of lymphoma, possibly because lymphomas are more common in patients with severe RA.¹⁹⁻²¹ In addition, both infliximab and adalimumab have been rarely associated with hepatosplenic T-cell lymphoma.²⁹ There are also reports of cases of early onset of lymphoma after introduction of TNF antagonist therapy^{22,24,30} and regression of lymphoma following withdrawal of TNF antagonist therapy.^{22,24,30}

The association between lymphoma and biologic therapy was weakened by data reported by Askling et al.³¹ The lymphoma risk in those treated with TNF-blockers was no higher versus the other RA cohorts. According to a recent review article, the current data is not sufficient to completely rule out or firmly establish a causal relationship between biologics and lymphoma. Short-to intermediate term treatment with biologics (up to four years) appears to be very safe with respect to lymphoma risk.³²

Safety concerns regarding anti-TNF- α blockers and lymphoma arose after the US FDA's post-marketing spontaneous adverse event reporting system received reports of lymphoma. The

FDA issued an alert on August 4, 2009, warning healthcare professionals of the increased risk of lymphoma and other malignancies in children and adolescents treated with TNF blockers.³³ The FDA reviewed 48 cases of malignancy in children and adolescents. Approximately 50 percent of the malignancies were lymphoma (Hodgkin's, non-Hodgkin); other malignancies included leukemia, melanoma, and solid organ cancers.. The majority of patients (88%) were on other immunosuppressive medications, especially azathioprine and methotrexate.. The FDA concluded that there was an increased risk of malignancy in children and adolescents with the use of TNF blockers but was unable to fully characterize the strength of the association.³³

The combination of TNF- α blockers with other immunosuppressants has also been documented to cause T-cell proliferation as well as lymphoma in those being treated for psoriasis. A case report documented by Mahe et al³⁴ concerns a patient with erythrodermic psoriasis treated with CsA and infliximab who developed CD30-positive T-cell lymphoma that regressed after these treatments were stopped. In patients with psoriasis for which CsA is a usual second-line therapy, dermatologists must be aware of the putative risks of lymphoproliferative disorder when an anti-TNF- α therapy is initiated. Adams et al³⁵ reported one case of CTCL that developed in a patient who had been treated for 18 months with etanercept for psoriatic arthritis, as well as a case of systemic anaplastic large-cell lymphoma with cutaneous involvement that developed after 3 doses of infliximab and concomitant treatment with 6-mercaptopurine for a presumptive diagnosis of early Crohn disease.. Other 3 case of CTCL were reported also in patients during infliximab and adalimumab therapy

for ankylosing spondylitis,³⁶⁻³⁸

Skin cancers

With respect to skin cancer, data on TNF antagonists in RA are inconsistent and the relationship between the administration of anti-TNF agents and cutaneous carcinogenesis remains an issue of debate. Retrospective analysis of patients with RA treated with etanercept did not show any link between squamous cell carcinoma (SCC) development and etanercept^{39,40} However, an increased risk of nonmelanoma skin cancer (NMSC) and a trend towards increased risk of melanoma has recently been reported in a large observational study comparing rates of malignancy in patients with RA on biologic therapies with population rates.²⁴ In addition, rapid development of multiple keratoacanthomas and squamous cell carcinomas have been described in patients with RA and psoriasis following the initiation of either etanercept or infliximab.^{41,42}

It is well known that patients with psoriasis have a higher risk of skin cancer, largely because of previous carcinogenic treatments and their cumulative toxicities. A multitude of recent case reports in psoriasis have begun to strengthen the link between anti-TNF- α therapy and induction or rapid reactivation of NMSCs such as SCC, BCC, and keratoacanthoma. Most of the patients had been previously unsuccessfully treated with multiple drug therapies including MTX, CsA, and PUVA.⁴³ Until further analysis of long-term data from clinical trials and post-marketing surveillance is available, skin cancer screening at regular intervals has been suggested for patients with psoriasis receiving anti-TNF therapy, particularly those with severe actinic damage, a history of multiple (>2) skin cancers, especially SCCs, and a record

of high cumulative doses of PUVA therapy, given the previous example of enhanced PUVA-induced skin carcinogenesis by cyclosporine.¹⁷

The development or recurrence of melanoma is a potential concern in patients undergoing immunosuppressive therapy including TNF inhibitors. A case report of eruptive latent metastatic melanoma after initiation of etanercept was first reported in 2007 by Fulchiero et al.⁴⁴ Inhibition of active immune surveillance by TNF inhibitors may augment malignant cell proliferation in previously treated melanomas. Even after several years, disease reactivation or recurrence with anti-TNF therapy remains a possibility in patients with a previous diagnosis and treatment of melanoma.^{44,45} Interestingly, recent reports described the occurrence of eruptive nevocellular nevi on the palms and soles during treatment with biologic agents including infliximab, alefacept, and etanercept.⁴⁶

Leukemia

On August 4, 2009, the FDA also warned of the possible association of leukemia and TNF blockers.³³ The FDA reviewed 147 post-marketing reports of leukemia in patients using TNF blockers. Most patients who developed leukemia were also receiving other immunosuppressive therapies. The FDA concluded there was a possible association between treatment with TNF blockers and the development of leukemia.

Guidelines to avoid malignancy:⁶⁻⁸

1. All patients should be fully assessed prior to, and during treatment with, biologic therapy with respect to their past or current history of malignancy and/or any future risk of malignancy; the risks and benefits of biologic therapy should be considered in this context.

2. In addition, a thorough oncologic history, family history, skin examination, and, baseline blood tests attempting to identify any hematologic abnormalities is warranted before starting patients with psoriasis on either the newer biologics or the more traditional systemic therapies.
3. Biologic therapy should be avoided in patients with a current or recent past history of malignancy unless the malignancy has been diagnosed and treated more than 5 years previously and/or where the likelihood of cure is high (this includes adequately treated NMSC).
4. All patients should be encouraged to participate in national cancer screening programs appropriate for their age and gender.
5. Regular, comprehensive dermatological assessment for skin cancer, including melanoma, is recommended before and at regular intervals during therapy.
6. Biologic therapy is relatively contraindicated in patients who have had prior therapy with > 200 PUVA and/or > 350 UVB treatments, especially when it has been followed by cyclosporin.

INFECTIOUS COMPLICATIONS

Increased rates of infection have been reported in patients being treated with all of the TNF blockers, alefacept, and ustekinumab but overall rates of infection are no greater than with placebo.⁴⁷⁻⁵¹ Upper respiratory infections are the most common infection. Each of the TNF inhibitors has a black box warning concerning the occurrence of mycobacterium tuberculosis (TB), bacterial sepsis, invasive fungal disease, and other opportunistic infections. Rheumatology registry data do suggest an increased risk of skin and soft tissue

infections compared with standard disease-modifying antirheumatic drugs (DMARDs), and although these are poorly characterized, they have included erysipelas, cellulitis, furunculosis, folliculitis, paronychia and wound infections.^{51,52}

Reactivation of Tuberculosis (TB)

TNF plays a key role in host defence against mycobacterial infection, particularly in granuloma formation (and hence containment of mycobacteria) and inhibition of bacterial dissemination. Destabilization of granulomas in patients infected with TB can result in disseminated disease.⁵⁴ TB has occurred at higher rates than in controls during clinical trials with the monoclonal antibodies infliximab and adalimumab.^{48,49} The risk of tuberculosis may be greater with the monoclonal antibodies (infliximab and adalimumab) as compared with etanercept with incidences of tuberculosis in patients with RA reported to the BSRBR of 39 per 100 000 patient-years for etanercept, 103 per 100 000 patient-years for infliximab and 171 per 100 000 patient-years for adalimumab.⁵⁵

Even when latent tuberculosis is identified and treated prior to TNF antagonist therapy, patients may develop clinical evidence of infection. Thus a high index of suspicion throughout treatment is required. The clinical presentation of infection is often atypical, with at least 50% of cases associated with infliximab^{56,57} and etanercept⁵⁸ being extrapulmonary. Late diagnosis, development of disseminated disease and concomitant immunosuppressive therapy may all contribute to high rates of morbidity, and associated mortality.⁵⁶

The FDA recommends screening all the patients before starting any TNF inhibitor or ustekinumab, however, the Medical Board of the National Psoriasis Foundation recommends screening for TB

in patients who are placed on any of the biologics that may cause immunosuppression.⁵⁹ The mode of action of ustekinumab predicts that it would also facilitate reactivation of tuberculosis. All the trials conducted with this agent excluded patients with latent tuberculosis.⁷

Before starting treatment, patients should be screened for latent TB by taking a history of travel, recent sick contacts, physical exam, and a tuberculin skin test (PPD). Patients who are Bacille Calmette-Guerin (BCG) vaccinated are good candidates for the QuantiFERON-TB Gold assay, which has a greater specificity, and at least as good sensitivity as the PPD.⁶⁰ If infection is suspected or the PPD is positive, a chest radiograph should be obtained. If there is a high suspicion for infection, contact a physician with expertise in the treatment of tuberculosis to help in the treatment process.⁶¹ Debate over how long one should wait before starting anti-TNF therapy for psoriasis after beginning treatment for latent TB continues. Recommendations range from two weeks to six months.⁶¹

Assessment for risk of tuberculosis in patients considered for TNF antagonist therapy is based on American guidelines the British Thoracic Society guidelines.^{7,8,62,63} In the U.S.A, the Centers for Disease Control and Prevention advocate tuberculin skin testing in all patients irrespective of whether or not they are on immunosuppressant therapy and this is reflected in the American Academy of Dermatology guidelines on tuberculosis screening for patients considered for TNF antagonist therapy.^{7,8,63} Current recommendations from the CDC state that skin indurations of 5 mm or more at 48 to 72 hours should be interpreted as a positive result in any patient considered for anti-TNF therapy.^{7,8,63} However, it should be noted that

there is global variation in the diameter of skin induration that is interpreted as a positive result based on frequency of TB in the population and BCG vaccination, which can cause false-positive tuberculin skin test results. For example, the British Thoracic Society recommends the use of a threshold diameter of 15 mm in any person with a history of BCG vaccination and 6 mm in any patient without history of BCG vaccination.^{62,63}

The *in vitro* interferon gamma release assay (IGRA) tests became increasingly available. These tests (QuantiFERON®-TB Gold) and T-SPOT®.TB) are both *in vitro* tests, based on release of interferon gamma following stimulation by *Mycobacterium tuberculosis*-specific antigens. These tests have some advantages in being more specific in that there is no cross-reactivity with either BCG or most (but not all) clinically relevant atypical mycobacteria. They have proven utility in identifying latent tuberculosis but their place in screening low-risk individuals is still unclear. Repeated tuberculin skin testing may lead to a boosting of the *in vitro* interferon gamma release, and result in a false-positive result.⁷ The tests may be a suitable alternative to tuberculin skin testing for screening in BCG-vaccinated individuals and also for assessment of patients who are immunosuppressed, in whom tuberculin skin testing is unreliable. Latent TB is diagnosed in cases with PPD-positive (better confirmed by T-SPOT®.TB test) and negative chest X-ray. Refer to pulmonologist to rule out active tuberculosis. Initiate isoniazid therapy for 9 months once active disease ruled out. Initiate TNF therapy after 4 weeks of isoniazid, possibly 8–12 weeks for infliximab.⁶³

Once the patient is started on a biologic therapy, a majority of dermatologists recommend performing an annual PPD, particularly in those at high-

est risk of infection.⁶⁰ Monitoring for signs and symptoms of infection during and after treatment is warranted as well. There are reports of patients with false negative PPDs who developed infection while being treated with TNF inhibitors.⁶¹ If a patient develops any signs or symptoms of TB while being treated it is currently recommended that the drug be withheld and expert opinion in the treatment of TB be obtained. In cases of seroconversion during treatment (PPD or T-SPOT®.TB test converted from negative to positive),withhold TNF until active disease is ruled out. Then, re-initiate TNF agent concurrently with tuberculosis prophylaxis (isoniazid therapy for 9 months) in a fully compliant patient demonstrating benefit from treatment.⁶³

Opportunistic Infections

Rare opportunistic infections, including histoplasmosis, listeriosis, coccidioidomycosis, cryptococcosis, aspergillosis, candidiasis, and pneumocystis,⁶⁴⁻⁶⁶ have been reported more often in patients treated with anti-TNF antibodies such as infliximab or adalimumab than etanercept. However, many of these patients were also treated with other immunosuppressive agents, such as methotrexate, systemic corticosteroids, or both. Second to *Staphylococcus aureus*, fungal infections are among the most common serious infections encountered during treatment with TNF inhibitors.⁶⁷

In September of 2008, the FDA issued a warning that healthcare professionals were not recognizing invasive fungal infections early enough in patients treated with the TNF inhibitors.⁶⁸ Maintaining close follow up with patients and recognizing risk factors should aid in earlier diagnosis of fungal infections in this patient population.

At this time, there is no reliable screening method for fungal infections before starting biologic therapy because most patients acquire the disease after starting treatment rather than reactivation of latent infection.⁶⁹ Patients who present with signs and symptoms of possible invasive fungal infection, and live or have recently traveled to an endemic area should be carefully evaluated. An infectious disease specialist should be involved in the treatment of infected patients and the biologic agent should be stopped immediately.

Hepatitis

Reactivation of hepatitis B or worsening of symptoms has been reported with all of the TNF inhibitors, and in some cases patients died.^{70,71} The FDA states that limited data are available, and all patients prescribed these medications should be evaluated for Hepatitis B virus prior to starting therapy. Infiximab more often causes HBV reactivation, compared to patients treated with etanercept and adalimumab. This is not unique, as it also is more likely to cause reactivation of TB and other opportunistic infections, when compared to etanercept and adalimumab.⁷² TNF antagonist therapy should be avoided in chronic carriers of hepatitis B because of the risk of reactivation. TNF plays a role in hepatitis C-induced hepatocyte injury and treatment resistance to interferon alfa-2b. Patients infected with Hepatitis C have not been found to experience the same complications as those with Hepatitis B during anti-TNF alpha treatment.^{72,73} However, long-term safety of TNF inhibitors in patients with chronic hepatitis C is not well known.⁷² The few studies that have reviewed patients with HCV infection and psoriasis treated with etanercept have demonstrated no change in HCV load or LFTs.⁷⁴⁻⁷⁶ These studies

suggest that etanercept is currently the safest of the TNF inhibitors to use in this patient population. Although infliximab has been shown to be effective and safe in patients with psoriasis and HCV, fewer data are available.⁷⁵

Human Immunodeficiency Virus

The safety of biologic therapy in the context of HIV infection is unknown but particular caution should be exercised in this group given the risks of infection. Paradoxically, perhaps, TNF has been implicated in HIV disease progression in HIV-associated tuberculosis, and therefore the benefit of etanercept as adjunctive therapy for this indication has been investigated.⁷⁷ There are several case reports of successful use of TNF antagonist therapy for rheumatological indications in patients who are HIV positive. Alefacept is known to inhibit T lymphocyte activation and reduce the number of circulating CD4+ and CD8+ T-cells, so, it is contraindicated for use in patients with HI).⁵⁰

Herpesviruses

The risks of reactivation of latent herpesviruses in patients with psoriasis are unknown, although there are sporadic case reports of severe disseminated infections with both CMV and varicella-zoster⁷⁸ in the context of TNF antagonists. In a short-term (6-14-week) and long-term evaluation of patients with Crohn's disease and RA treated with infliximab and etanercept, no evidence for reactivation of Cunningham virus (JCV), Epstein-Barr virus (EBV), human herpesvirus (HHV)-6, HHV-7, HHV-8 or CMV was identified in serum using polymerase chain reaction (PCR).^{79,80} Risks of herpes reactivation in the context of efalizumab and ustekinumab are unknown. However, with respect to efalizumab, recent reports of PML indi-

cate that John Cunningham virus (JCV) reactivation can occur.⁹

Recommendations: Biologic therapy and infection risk

- During biologic treatment of psoriasis, patients should be advised to seek immediate medical attention if they develop signs or symptoms of infection. In the event of any serious infection (one in which antibiotic therapy is necessary) the biologic therapy should be discontinued until complete resolution of the infection.
- Patients on biologic interventions should be monitored for early signs and symptoms of infection throughout treatment.
- Patients on biologic interventions should be warned against risk factors for Salmonella and Listeria and should not consume raw or partially cooked dairy, fish or meat produce or unpasteurized milk or milk produce. Salads should be washed

Recommendations: Assessment and monitoring for tuberculosis.^{7,8,63}

- A pretreatment chest X-ray and Mantoux skin test currently remain the preferred screening tests in patients not on immunosuppression.
- Annual tuberculin skin testing has been recommended in the U.S.A. for both dermatology and rheumatology practice.^{7,8} Where there is a low incidence of tuberculosis in the community annual testing is unnecessary but in patients with risk factors annual checks for conversion of IGRA may be useful.
- Tuberculin testing is not valid in patients already established on immunosuppressive therapy (e.g. methotrexate). IGRA tests may have a role in this group and can be used if

practicable, although the positive and negative predictive values are unknown. The T-SPOT. TB test may be more sensitive in patients on immunosuppressive.

- Patients with signs to suggest tuberculosis or a history of previous treatment for tuberculosis should be referred to a tuberculosis physician.
- Patients with active tuberculosis should receive treatment prior to initiating biologic therapy.
- Patients with test(s) to support latent tuberculosis should be stratified for risk and considered for prophylactic antituberculous therapy; further advice should be sought from a tuberculosis physician when necessary.
- When antituberculous therapy is indicated, patients should complete 2 months of treatment before commencing biologic therapy with either isoniazid (total treatment course 9 months) or rifampicin plus isoniazid (total treatment course 3 months) or rifampicin alone (total treatment course at least 4 months).
- A high index of suspicion for tuberculosis should be maintained during therapy and for 6 months after discontinuation, with special emphasis on extrapulmonary, atypical and disseminated forms of the infection, and in those patients on additional immunosuppressant agents.
- During treatment, and for 6 months following discontinuation, a high index of suspicion for tuberculosis should be maintained, especially in those at high risk. Those at particular risk include recent immigrants from high-prevalence countries, injection drug users residents and employees of high-risk congregate settings (e.g. prisons, homeless shelters), mycobacteri-

ology laboratory personnel, and persons with high-risk medical conditions (diabetes mellitus, chronic renal failure, some haematological conditions, conditions requiring prolonged high-dose corticosteroid or other immunosuppressive therapy, mastectomy/jejunoileal bypass)

NEUROLOGICAL DISEASE

TNF antagonist therapy has been associated with the development of, or worsening of demyelinating disease, although evidence for causality is inconclusive. Cases of demyelination have been reported with all three TNF blockers available for psoriasis.^{16,81} A detailed review of cases reported to the FDA in 2001 identified 17 due to etanercept and two due to infliximab. Partial or complete resolution of symptoms on discontinuation, and with recurrence of symptoms, was documented in at least one case following rechallenge.⁸¹

Efalizumab was voluntarily withdrawn from the market by Genentech after three confirmed cases of progressive multifocal leukoencephalopathy (PML).⁹ PML is a progressive neurologic disorder associated with the John Cunningham virus (JC virus). It is associated with scattered demyelination of the brain. PML should be suspected in patients on biologic agents who demonstrate acute onset of visual deficits, mental impairment, dementia, personality changes, confusion, and motor weakness. PML has been associated with 57 patients treated with rituximab.⁸²

All the TNF- α inhibitors and efalizumab have been associated with reports of new or exacerbated symptoms of demyelinating disorders.⁴⁷⁻⁴⁹ The demyelinating conditions have included transverse myelitis, Guillian-Barre syndrome, multiple sclerosis (MS), optic neuritis, seizures and

central nervous system manifestations of systemic vasculitis. All the TNF- α biologic agents used in the treatment of psoriasis urge caution in the treatment of patients with pre-existing or recent onset of central nervous system (CNS) demyelinating disorders.⁴⁷⁻⁵¹ It has been demonstrated that siblings of patients with MS have a significantly higher risk of predisposition to developing MS.⁸²

Recommendations: Demyelination and TNF antagonists.^{7, 8, 16}

- It is important to obtain a pre-treatment family history for demyelinating disorders prior to therapy and to inform the patients of potential risks
- TNF antagonist therapy must be avoided in patients with a personal history of, or a first-degree relative with a demyelinating disorder
- Demyelinating disorders should be considered in patients on biologics experiencing one of the followings: subacute (hours to days) unilateral vision loss, pain with eye movement, color vision, diplopia, sensory loss, paresthesias, limb weakness, acute areflexic motor paralysis, ascending paralysis evolving over hours to days, ataxia, gait disorder, seizures, speech disorder, and cranial nerve palsies, facial palsy, “band-like” of tightness around the torso, of pain in the neck, shoulder, back, or spine, progressive neck weakness.
- If neurological symptoms suggestive of demyelination develop during TNF antagonist therapy, treatment should be withdrawn and specialist advice sought.

CARDIOVASCULAR DISEASE

Patients with congestive heart failure who were concurrently treated with TNF inhibitors were

found to have worsening of heart failure in several reports. The risks of TNF antagonist therapy in the context of heart failure were first highlighted when trials in severe congestive cardiac failure [New York Heart Association (NYHA) class III and IV, left ventricular ejection fraction < 35%,] were prematurely discontinued due to an excess mortality with high-dose infliximab; a similar trial of etanercept failed to show benefit.⁸³ Forty-seven spontaneous reports to the U.S. Food and Drug Administration (FDA) of new onset or worsening of pre-existing heart failure following either infliximab or etanercept have been reviewed in detail with the possibility of drug-induced pathology. Complete resolution or substantial improvement of symptoms seen on withdrawal of drug in younger patients (< 50 years. Clinical trial data in psoriasis and other diseases⁸⁴ show no excess risk of heart failure, although selection bias (i.e. exclusion of those at risk) may account for this.⁸⁵

Patients with psoriasis have an increased risk of cardiovascular disease including myocardial infarction.⁸⁶ Increased predilection for cardiovascular disease in this patient population has caused debate over the use of potentially cardiotoxic drugs in patients with mild to severe heart failure.

Recommendations: Cardiovascular disease and TNF antagonists.⁷

- TNF antagonist therapy should be avoided in patients with severe (NYHA class III and IV) cardiac failure
- Patients with well-compensated (NYHA class I and II) cardiac failure should have a screening echocardiogram and those with an ejection fraction < 50% of normal

HEMATOLOGICAL COMPLICATIONS

Alefacept is a recombinant fusion protein that works by binding to the T-cell lymphocyte antigen CD2. It is known to inhibit T lymphocyte activation and reduce the number of circulating CD4⁺ and CD8⁺ T-cells in a dose-dependent relationship.⁵⁰ For this reason, the patients with below normal CD4⁺ T-cell counts should not be started on alefacept. It is also contraindicated for use in patients with human immunodeficiency virus (HIV).⁵⁰ In patients treated with alefacept, a baseline complete blood cell count should be obtained and CD4⁺ T-cell counts monitored every two weeks throughout the 12 week course of dosing. In the intramuscular study conducted, lymphocytopenia was more common after six to eight weeks of therapy.⁷² If the CD4⁺ count falls below 250 cells/uL, dosing should be withheld and weekly monitoring initiated. Alefacept treatment should be discontinued if the CD4⁺ count does not normalize within a month.^{8,50}

The anti-TNF alpha agents have been rarely associated with anemia, leukopenia, neutropenia, thrombocytopenia, pancytopenia and aplastic anemia.⁴⁷⁻⁴⁹ Due to the current lack of evidence and possibly related fatalities following hematologic complications while being treated with TNF inhibitors, caution is advised.⁴⁷⁻⁴⁹ Patients who develop easy bruising, prolonged bleeding, pallor or fever should be evaluated for a hematologic cause.

Drug-induced thrombocytopenia is a rare but potential side effect of anti-TNF- α therapy (infliximab and etanercept) which was reported in a recent study. Thrombocytopenia appeared to be a class-effect adverse event probably associated with autoimmunity, but these findings should be validated in larger studies.⁸⁷ The authors recom-

mended that monitoring of platelet counts should be performed every 4 weeks in patients receiving anti-TNF- α therapies in order to detect early asymptomatic thrombocytopenia.⁸⁷ Clinicians should be aware that autoimmune syndromes with cutaneous and systemic manifestations, including thrombocytopenia, may occur in patients receiving anti-TNF- α therapies. In cases in which autoimmunity is suspected, a platelet count should be determined immediately, with prompt drug withdrawal at the onset of thrombocytopenia.⁸⁷

HEPATIC DISEASE

Hepatotoxicity has been reported with the use of alefacept, efalizumab, adalimumab, etanercept and infliximab.⁴⁷⁻⁵⁰ Asymptomatic increases in alanine aminotransferase (ALT) and aspartate aminotransferase (AST) are the most commonly reported hepatic finding.⁴⁷⁻⁵⁰ These increases in liver enzymes rarely required discontinuation of the medication. However, the use of infliximab has been associated with greater liver complications than the other biologic agents listed. In 2004, the FDA issued a warning that hepatic disease, including severe hepatic failure, might complicate infliximab therapy.⁸⁸ These cases included patients who were also taking multiple concomitant drugs, some of which were known to be hepatotoxic.

Current guidelines for monitoring liver function while taking any biologic agent include baseline chemistry screening and LFTs. Any abnormal results should prompt assessment for the underlying cause. During treatment with infliximab, some experts suggest LFTs should be repeated before each infusion.^{59,88} If either the AST or ALT rise to greater than five times the upper limit of normal, treatment should be withheld and any rise in liver enzymes should prompt repeating the test before

the next infusion.^{59,88}

IMMUNOLOGIC COMPLICATIONS

The use of TNF alpha blocking agents has been associated with the development of auto-antibodies. Antinuclear antibodies (ANA) and anti-dsDNA antibodies were found at different prevalence rates among the various agents but rarely manifest clinical symptoms of lupus erythematosus (LE). Infliximab is associated with the highest occurrence rate of ANA with approximately 50 percent of patients tested testing positive.⁴⁸ In comparison, only 12% and 11% of patients tested ANA positive that were treated with adalimumab and etanercept, respectively.^{49,47} In all three medications, incidence of ANA or anti-dsDNA antibodies did not correlate with development of Lupus-like syndromes.

Lupus like syndrome

In symptomatic patients, anti-TNF-induced lupus manifests as systemic, subacute cutaneous or discoid lupus erythematosus. The clinical and laboratory findings of drug-induced lupus are similar to those of the idiopathic disease; however, central nervous system and kidney involvement are extremely rare.⁸⁹ In a recent French national survey conducted in more than 11,000 patients receiving either infliximab or etanercept for rheumatic diseases, the incidence of drug-induced lupus was found to be the same for both agents (approx 0.18%). In these patients all systemic lupus erythematosus symptoms resolved within 16 weeks of discontinuation of the drug. These patients most commonly present with rash, purpura, myalgia, serositis, and pneumonitis.⁸⁹ Paradoxically, therapeutic TNF blockade has been shown to have differential effects, alleviating, for instance, lupus

nephritis or subacute LE in some patients, but inducing typical SLE in others.⁸⁹

Although clinicians treating patients with anti-TNF agents need to be aware of this lupus-like condition, it is not necessary to evaluate patients for antinuclear antibodies or to conduct other serologic tests before or during anti-TNF therapy unless clinical symptoms warrant.⁵⁹ If a patient develops signs or symptoms of lupus, the biologic agent should be withheld, and resolution of symptoms most often occurs.⁵⁹

Antibodies against biologics

Development of antibodies to alefacept and etanercept has been reported to occur in 3% and 6% of patients respectively.^{90,47} The formation of antibodies to either of these medications has not been found to correlate with clinical response or adverse events.

Clinical studies have shown that patients with psoriasis who are treated with infliximab are more likely to develop antibodies against infliximab at lower doses. It has also been demonstrated that low dose methotrexate can lower the percentage of patients who develop these antibodies. Approximately 1% of patients treated with infliximab will experience a serum sickness reaction that can occur as early as the second infusion and will recur if treatment is reinitiated.⁴⁸ Clinical findings include fever, rash, myalgia, arthralgia, headache, facial edema, and/or dysphagia.⁹¹ Prior to treatment, antihistamines, corticosteroids, and epinephrine should be available and used promptly, if a reaction occurs. Use of infliximab should not be continued in that patient.

The formation of antibodies to adalimumab has also been shown to result in neutralization of the medication and likely decreased efficacy. In con-

trast to infliximab, there have been no adverse reactions associated with these antibodies.⁴⁹ In the three controlled trials reviewed, antibodies against adalimumab were detected in 12% of patients treated for rheumatoid arthritis.⁴⁹ The use of methotrexate concomitantly with adalimumab resulted in only one percent of patients developing antibodies to adalimumab.

Infusion reactions

The most common adverse events associated with infliximab are infusion reactions. Infusion reactions appear in 3–22% of patients with psoriasis who are treated with infliximab.^{18,48} The reactions can be subdivided into mild, moderate or severe reactions. Most reactions are mild or moderate and only few are severe.^{18,92} Mild reactions can be defined as reactions that are self-limiting and resolve spontaneously after temporary cessation of the infusion or reduction of the infusion speed. Moderate reactions are those that require closer attention and an extended observation period and often discontinuation of the infusion. Serious reactions involve respiratory symptoms or a symptomatic blood pressure drop and need for close monitoring, often for 24 h and occasionally requiring hospital admission. Adverse events occurring during the infusion or in the first 24 hours following the infusion are defined as acute reactions. Those manifesting 24 hours to 14 days post infusion are considered to be delayed-type reactions.^{17, 18}

Acute reactions occur in approximately 3% to 6% of treated patients with infliximab.⁹³ These reactions typically consist of hypotension or hypertension, chest pain, palpitations, dyspnea, fever, skin eruptions, headache, nausea, and vomiting.⁹⁴ Cutaneous symptoms may vary from a burning

sensation with minimal erythema, to a flushing and/or urticarial rash.. Less than 1% of these reactions are severe enough to interrupt treatment and to require immediate intervention. In most cases, reduction of infusion rate leads to the resolution of the symptoms. Serious infusion reactions occurred in less than one percent of patients and included anaphylaxis, convulsions and erythematous rash. Interestingly, patients who developed antibodies to infliximab were two to three times more likely to develop an infusion reaction than those who did not.⁴⁸

The exact mechanisms of infusion reaction development, however, are not yet clear, although several factors and possible mechanisms have been suggested.¹⁸ Mechanisms involved include anaphylactoid, non-IgE mediated reaction (in acute infusion reaction), serum sickness-like reaction, or due to development of antibodies to infliximab (ATI), which develop soon after initiation of treatment and are usually associated with mild to moderate infusion reactions, not with the severe reactions.¹⁸

Premedication is often routinely given before infusions, consisting of paracetamol, antihistamines and/or corticosteroids, to prevent the occurrence of infusion reactions. However, solid evidence that prophylactic medication can prevent infusion reactions is lacking.^{18, 95} It has also been reported that loading the infliximab therapy with three infusions at weeks 0, 2 and 6 followed by maintenance treatment (an infusion every 8 weeks) is associated with low ATI formation and infusion reaction. Co-medication with low dose methotrexate has the same effect.^{96,97} Most importantly, patients who experience a severe infusion reaction should discontinue therapy with infliximab indefinitely, as future reactions may occur if treatment

is resumed.

The usual management of infusion reactions focuses on alleviating symptoms. In most cases an acute reaction is sufficiently treated by slowing the infusion rate, administering intravenous fluids and giving paracetamol and antihistamines. In severe reaction, the infusion must be stopped immediately and treat as a case of anaphylaxis with IM antihistamines, corticosteroids, and adrenaline in addition to other measures In a delayed infusion reaction administration of paracetamol, antihistamine and, if necessary, steroid is advised. A complete treatment proposal was advised by Lecluse et al.¹⁸

Injection site reactions

Etanercept and Adalimumab have been associated with injection site reactions in 14% and 20 % respectively.^{47,49} The most common reactions are mild to moderate in severity and include erythema, itching, hemorrhage, pain or swelling at the injection site. These adverse events rarely necessitate discontinuing the TNF inhibitor, and often reduce in severity and frequency following the first month of therapy.⁹⁸ In order to decrease the likelihood of injection site reactions, one should vary the site of injection.

There was also a one percent incidence of hypersensitivity reactions, including allergic rash, anaphylactoid reactions, fixed drug reaction or urticaria.. Alefacept is associated with injection site reactions in 16 percent of patients. The most common injection site reactions include inflammation, bleeding, edema, and non-specific reactions.⁵⁰

CUTANEOUS COMPLICATIONS

Paradoxical events (Psoriasis and psoriasiform eruptions)

The TNF alpha inhibitors approved for treatment of psoriasis have paradoxically been reported in numerous case studies to be associated with new onset or exacerbation of cutaneous psoriasis. The T-cell inhibitor alefacept has not been associated with these same complications. The FDA reviewed 69 cases in which patients receiving TNF inhibitor therapy for various rheumatologic conditions developed new onset psoriasis.⁹⁹ The overall prevalence of induced psoriasiform lesions is estimated by several authors to be about 1.0-5.3% in various rheumatologic diseases.¹⁰⁰⁻¹⁰⁴ A positive personal or family history was noted in 25 patients, leaving a significant portion of patients with no previous disease association or family history.¹⁰³ The time from induction of therapy to exacerbation or new onset of psoriasis varied considerably, but occurred at a mean 9.5 months in these cases.¹⁰³ After discontinuation of the TNF inhibitor alone or in association with other psoriatic therapy, the majority of patients experience complete or partial improvement.^{99,103}

The most characteristic pattern of psoriasis associated with anti-TNF-alfa treatment, is a localized pustular eruption occurring symmetrically on the palms and soles, resembling palmoplantar pustulosis. The eruption has been reported in approximately one third of all reported cases and consists of painful or itchy pustular lesions based on erythematous areas of the acral sites, with or without concomitant psoriatic plaques or pustular lesions in other cutaneous sites.⁹⁹⁻¹⁰⁴ Other cases appear with the typical psoriatic morphology, consisting of scaly erythematous plaques on the trunk, extremities, or scalp. New onset of nail psoriasis has also been noted.⁹⁹⁻¹⁰⁴

Overall, the reported cases of psoriasis or psoriasiform eruptions have differed with respect

to their severity and treatment response. In most cases, topical treatment was sufficient to control the eruption.^{103,105} In other cases, psoralens and ultraviolet A treatment or UVB phototherapy were initiated,¹⁶² while, in more severe or persistent cases, discontinuation of anti-TNF therapy or switching to an alternative anti-TNF regimen was necessary.^{103,105} The improvement of the eruption after discontinuation of the anti-TNF agent in some cases and relapse upon re-treatment with the same agent (positive rechallenge) further supports the causal association of anti-TNF agents with the development of psoriasiform eruptions.¹⁰⁵ The pathogenic mechanisms accounting for this paradoxical adverse effect are still unclear, but several possible explanations have been proposed, including an imbalance of the dynamic interplay between TNF and interferon- α , or a change in T cell function following TNF- α inhibition.

Vasculitis

An association between TNF inhibitors and vasculitis has been established during the post-marketing marketing experience with infliximab, etanercept and adalimumab.¹⁰⁶ The Adverse Events Reporting System of the US Food and Drug Administration documented 35 patients with leucocytoclastic vasculitis (LCV), out of 116,000 and 344,000 individuals treated with etanercept and infliximab, respectively.¹⁰⁶ Both studies revealed that the majority of cases occurred in the treatment of rheumatoid arthritis and presented with cutaneous manifestations. These cutaneous lesions included purpura, petechiae, nodules, bullae and urticarial wheals.^{106, 107} Although, rheumatoid arthritis and other autoimmune disorders are known to be associated with vasculitis, the temporal relationship between cutaneous lesion onset with initiation of

anti-TNF therapy and the resolution with discontinuation gives strong evidence that the drug is at fault. This is also supported by the reoccurrence of LCV in five patients who were retried on etanercept after initially experiencing a vasculitis.¹⁰⁶ Although cutaneous manifestations represent a majority of the vasculitis presentations, involvement of the peripheral nervous system, kidney, central nervous system, pleura, heart and lung have also been reported.^{106,108} The diagnosis can be confirmed by skin biopsy. Culture may be needed also to exclude infectious agents.¹⁰⁶ Discontinuation of the drug was shown to result in resolution of the vasculitis in 50% of patients in one study.¹⁰⁸ The remaining required high-dose glucocorticoids and/or immunosuppressants for symptom resolution over several weeks. The pathogenesis of LCV in anti-TNF-treated cases remains unknown. Antibodies against infliximab or etanercept have been described as a consequence of anti-TNF therapy and may play a role in developing an immune complex-mediated hypersensitivity vasculitis or a direct antigen-mediated hypersensitivity reaction in cases of vasculitis at etanercept-injected sites.^{17,96}

Eczema-dermatitis

Eczematous skin lesions have been reported with the use of anti-TNF therapy for rheumatic diseases. In the prospective study of Flendrie et al¹⁰⁹ which included 289 patients with RA on TNF-alfa blocking therapy. Twenty cases of eczema were documented, 5 of which were confirmed by histopathology. These cases included dyshidrotic eczema, contact dermatitis, nummular eczema, atopic dermatitis, papular lesions, and a nonspecific eruption. Atopic dermatitis-like reactions have been reported also in several patients receiving

anti-TNF agents.¹¹⁰⁻¹¹²

In most cases, eczema-like reactions occurring in the context of anti-TNF therapy were of moderate intensity and responded well to topical treatment with topical steroids, alone or in combination with calcineurin inhibitors, with no need to discontinue anti-TNF treatment. Severe cases, however, necessitating hospitalization or discontinuation of therapy have been described.¹⁰⁹

Interface dermatitis (erythema multiforme and lichenoid eruptions)

Anti-TNF agents have been implicated in several cases of erythema multiforme and lichenoid drug eruptions, clinically manifested by papular erythematous lesions and histologically consistent with an interface dermatitis pattern.¹¹³⁻¹¹⁵ The reported cases were treated for RA and ankylosing spondylitis. Histopathologic features revealed a diffuse lymphocytic infiltrate in the superficial dermis with a liquefactive degeneration of the basal cell layer and foci of epidermal necrosis, a pattern implying an immune-mediated cytotoxic mechanism.

Erythema multiforme-like drug reactions described with TNF- α blockers are intriguing, given the suggestive role of anti-TNF agents for the treatment of toxic epidermal necrolysis and acute generalized exanthematous pustulosis caused by drugs.¹¹⁶ Once again, we encounter the same dual action of anti-TNF agents exhibiting a therapeutic effect in some patients, while inducing the same pathology in others. It has been hypothesized that the underlying inflammatory disease could constitute an appropriate setting in which immune complexes between TNF- α and its antagonists propagate a cytotoxic immune reaction in the skin, leading to the development of lichenoid or

erythema multiforme-like lesions or there is a paradoxical overproduction of TNF- α .

Granulomatous reactions

Noninfectious cutaneous granulomatous reactions, including cutaneous sarcoidosis, interstitial granulomatous dermatitis, and disseminated granuloma annulare, have been documented in a total of 20 patients during anti-TNF therapy.

Paradoxically, TNF-blocking therapy has been used as an off-label treatment of refractory sarcoidosis with contradictory results.¹¹⁸ Infliximab and adalimumab have been found to be efficacious in the majority of cases; however, 11 of 16 patients with progressive pulmonary sarcoidosis treated with etanercept had worsening of the disease.¹¹⁸⁻¹²⁰

Interstitial granulomatous dermatitis (IGD, also known as atypical granuloma annulare, and palisaded neutrophilic and granulomatous dermatitis) has been associated with the use of infliximab, etanercept, and adalimumab in patients with RA or psoriatic arthritis. Skin lesions had a rapid onset and presented as asymptomatic annular macules or indurated papules or plaques, some with a clear center and a slightly elevated border. The trunk, shoulders, and upper extremities were affected. Skin biopsy revealed diffuse interstitial granulomatous infiltrates of lymphocytes, histiocytes, and eosinophils palisading around degenerated collagen. Withdrawal of the anti-TNF agent led to complete resolution of the skin lesions.¹²¹⁻¹²²

The close temporal relation, between IGD development and anti-TNF administration, as well as the resolution of the dermatosis upon drug discontinuation, support an inducing or triggering role of anti-TNF therapy in the development of IGD.

In addition, 9 cases of disseminated granuloma

annulare (2 with infliximab, 6 with adalimumab, 1 with etanercept) have been documented during anti-TNF therapy in 197 RA patients. The lesions were successfully treated with topical corticosteroids, and treatment discontinuation was necessary in only 2 patients.¹²³

Cutaneous infections

In a retrospective study of 709 patients treated with a TNF-blocker for RA, spondyloarthropathy, or other inflammatory disorder, skin infections comprised 21% of all diagnosed infections, which were caused by bacteria in 53%, viruses in 30.5%, and fungi in 6.5% of cases. In cases with serious infections, the most frequent sites of involvement were skin and skin-associated tissues (40.4%).¹²³⁻¹²⁵

The frequency of infections in patients with RA who received TNF inhibitors (infliximab or etanercept) was reported to be higher than in patients who received disease-modifying antirheumatic drugs (DMARDs). The total rate of bacterial skin infections was significantly higher in the TNF group, including erysipelas, furuncles, abscesses, and paronychia, fungal skin infections herpes simplex skin infections, and herpes zoster skin infections. Atypical mycobacterial infections of the skin have also been reported, including two cases of cutaneous *Mycobacterium marinum* infection that developed during infliximab treatment for ankylosing spondylitis and Crohn's disease, respectively.^{126,127}

Similar rates of infections have been reported in patients with psoriasis treated with infliximab versus placebo.¹²⁸ Clinical studies of infliximab and etanercept in psoriatic patients reported mild cutaneous infections, including lower leg and breast cellulitis, furuncles, and cutaneous abscesses.^{124,125}

Case reports of human papillomavirus recurrence and molluscum contagiosum appearance have also been described with infliximab treatment in psoriatic patients.¹²⁸

RECOMMENDED PRETREATMENT AND MONITORING INVESTIGATIONS:⁷

1. Thorough History: Consider risk factors for tuberculosis; sexual history; drug abuse; history of blood transfusions; any past or current chronic infection, any past or current malignancy
2. Clinical examination (full skin check; assessment for lymphadenopathy; hepatosplenomegaly): pretreatment and at 3- to 6-monthly intervals.
3. Echocardiogram only in cases with well-compensated NYHA class I and II: pretreatment and clinical assessment at 3- to 6-monthly intervals .
4. Exclude demyelination: pretreatment and at 3- to 6-monthly intervals.
5. Tuberculin skin test and/or T-SPOT®.TB test before treatment and T-SPOT®.TB test every year.
6. Blood chemistry (full blood count, creatinine, urea, electrolytes, liver function tests): pretreatment, at 3 months, then every 6 months
7. Hepatitis B serology: pretreatment and Periodically in those at risk
8. Hepatitis C serology: pretreatment and periodic assessment of hepatitis C viral load if positive
9. Human immunodeficiency virus serology : pretreatment and periodically in those at risk
10. Autoantibodies (ANA, anti-DNA antibodies: pretreatment and repeated only if symp-

toms suggest development of autoimmune phenomena, e.g. abnormal liver function tests.

11. Urine pregnancy test: pretreatment and Periodically in those at risk
12. Chest X-ray: pretreatment and repeated Only if clinically indicated .

CONCLUSION

The use of biological agents as a new alternative treatment for psoriasis and other chronic inflammatory diseases is expanding worldwide. Acute and chronic adverse effects of these drugs are becoming increasingly recognized. All dermatologists must be aware of the potential risks of such therapy. Dermatologists must know how to inform patients about medication risks; as such discussions will allow those seeking treatment to make educated decisions regarding their disease management as well as potentially increase patient awareness of any complications if any were to develop. Careful pretreatment monitoring and follow-up will allow early recognition and treatment of adverse effects as malignancy, TB, infections, demyelinating diseases, cardiac or cutaneous adverse events. Safety can be improved also with good clinical practices, including modification of infusion rates, appropriate doses, reduction of pre- or concomitant immunosuppressive therapy, and avoidance of irregular or long intervals between doses. As both the number of patients on anti-TNF treatment and the duration of treatment are increasing, a new adverse event may appear at any time, so the clinician must keep high index of suspicion to pick up any unexpected adverse reaction or complication. Early recognition of the clinical manifestations of any complication in patients treated with biologic therapy enables der-

matologists to appropriately treat or refer patients to relevant specialist for diagnostic workup, disease confirmation, and any necessary treatment. It is worthwhile mentioning that the majority of all previously described adverse events are of mild or moderate severity, and the documented benefits of these drugs must be weighed against the uncertain preventable risks. It is imperative that larger prospective studies should be conducted to shed light on the prevalence of these reactions, to define their underlying mechanisms, and to provide guidelines for their prevention and management.

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