Opportunistic infections associated with TNF-\(\alpha\) treatment

The therapeutic agents known as TNF-\(\alpha\) inhibitors have been widely adopted as effective and standard therapy for many rheumatic diseases. Since their introduction into clinical practice, there has been concern that these agents that blunt host immunity to intracellular pathogens would lead to the development of opportunistic infections. Early reports of extrapulmonary tuberculosis, listeriosis, *Pneumocystis jiroveci* pneumonia and invasive fungal diseases seemed to confirm this association. Prospective and retrospective studies, registries, adverse reporting databases and experience from clinical practices indicate at least a twofold risk of serious bacterial infections with TNFs versus standard DMARDs but data are limited on opportunistic infections (OIs). This article will review the available data on OIs describing these risks and studies that have been done to reduce that risk.

Opportunistic infections (OIs) are infections caused by organisms that ordinarily do not lead to disease unless the host is immunodeficient, when they may cause significant morbidity and mortality [1]. The predisposition to OIs often relates to an inherited, acquired or medication-induced defect in immune function. Often, multiple defects are present due to the underlying illness of the host and its treatment. The host defects induced by various immunosuppressive agents differ and their effects may be multiplicative. One of the challenges in defining opportunistic infections in this group of patients is their underlying risk for granulomatous and intracellular infections, even in the absence of therapy.

Many OIs are due to intracellular pathogens, whereby the principal host defect lies in the initiation of the cellular immune response. These include tuberculosis (TB), atypical mycobacterial infection, salmonellosis, listeriosis, invasive and endemic fungal disease, legionellosis, parasitic diseases (*Strongyloides*, *Leishmania*, *Toxoplasma*) and opportunistic viruses such as cytomegalovirus (CMV) varicella zoster virus (VZV), herpes simplex virus (HSV) and Epstein–Barr virus (EBV).

TNF-\(\alpha\) inhibitor therapy has become widely used in the management of autoimmune disorders, including rheumatoid arthritis, Crohn's disease, ankylosing spondylitis and psoriatic arthritis. The currently available anti-TNF agents infliximab, etanercept and adalimumab vary in structure, pharmacology, effect duration, specific targets, effectiveness and side effects.

TNF plays several critical roles in the host immune response: affecting cytokine regulation, neutrophil recruitment, T-cell activation and the innate immune system [2]. It is critical in the formation and maintenance of granulomas and production of IFN-\(\gamma\). The complete inhibition of TNF may allow for the dissolution of granulomas and inability to maintain latency. On the other hand, less potent inhibition may affect granuloma formation but not maintenance, thus allowing for acute infection but not reactivation.

TNF is required for defense against intracellular pathogens, is involved in the Th1-mediated immune response and affects apoptosis. In mice, TNF induces apoptosis of macrophages, which may provide sanctuary sites to intracellular organisms.

In these mice, the absence of TNF-\(\alpha\) may lead to dissolution of granulomas that previously contained mycobacteria [3,4]. Infliximab may induce apoptosis in monocytes potentially inhibiting the memory T-cell immune response for maintenance of granulomas [5,6]. Studies in mice in whom the ability to produce TNF-\(\alpha\) was genetically blocked demonstrated enhanced susceptibility to intracellular pathogens and dissemination of previously contained granulomatous infections [7].

TNF is important in chemokine regulation; increasing adhesion molecule expression; mediating macrophage apoptosis and limiting excessive type 1 immune activation during intracellular infection [8,9]. It has a direct impact on the innate immune system by affecting specific Toll-like receptors (TLRs) and decreasing the presentation of antigens to T-cells [10]. Although we tend to generalize about the role of TNF-\(\alpha\), the specific actions upon inflammatory and immune function may vary depending upon the component which is blocked. Blockade of the soluble portion
of TNF activity may inhibit the inflammatory response without adversely impacting the innate immune response to infection [11,12]. Conversely, blockade of both transmembrane and soluble TNF may blunt both.

The risk of infections associated with TNF blockade may also be related to genomic and pharmacodynamic factors. Specific polymorphisms in the TNF-α gene may predispose to more serious or frequent infections in certain individuals, which may also be dose dependent [13].

Because of TNF-α’s central role in host defenses, several clinically important questions impact those receiving TNF-blocking agents:

- Are there more infections in patients receiving these agents?
- Which specific infections are most frequently seen?
- Are these infections serious or opportunistic?

**Serious infections & TNF inhibitors**

The precise degree to which TNF inhibitors are associated with increased infection risks is difficult to ascertain due to a host of study design limitations. From experience in clinical practice, it is apparent that patients receiving these agents develop serious and disseminated infections often early in their use.

While this review focuses on OIs, any infection that requires hospitalization, intravenous anti-infectives or causes significant morbidity or death is defined as a serious infection. The frequency and types of infection may vary with the host’s underlying disease. Patients with RA have an increased baseline risk of serious infection 1.8-times that of non-RA patients [14]. In a large primary care cohort of patients with polyarthritis, the overall infection incidence was greater than 2.5-times that of the general population. Smoking, corticosteroid use and a positive rheumatoid factor were independent predictors of infection-related hospitalization. Those with all three risk factors were seven-times more likely to be hospitalized [15].

In clinical trials of the three TNF inhibitors, the observed serious infection event (SIE) rate is two to six serious infections/100 patient-years [16-21]. The incidence of serious infections was 4.1 per 100 patient-years (1%) with etanercept [16], four per 100 patient-years with adalimumab and both similar to placebo [17]. The overall serious infection risk from most clinical trials is approximately five events/100 patient-years. Despite this apparent low risk, there are numerous case reports and series of serious and opportunistic infections in recipients of TNF blocking agents. In an attempt to clarify the confusion between serious infection rates reported from clinical trials and that of clinical practice, Salliot and colleagues looked at a large-clinic practice of patients with rheumatic diseases treated before and after the use of TNF inhibitors, using the patients themselves as controls. In this study of 709 patients, they found the incidence of serious infections in the TNF inhibitor-treated group was increased threefold. They calculated a number needed to harm (NNH) of only 14 for the first year of treatment [22]. The serious infections were evenly distributed amongst the three agents. Serious skin and soft-tissue infections and pulmonary infections predominated. Bacterial infections accounted for 74.5%, viral for 10.6%, mycobacterial for 4.2%, parasitic for 2.1% and fungal for 2.1% of serious infections. In a multivariate model, the risk factors most often associated with serious infections were previous joint surgery and high previous cumulative steroid dose.

In a meta-analysis of randomized controlled trials of infliximab and adalimumab in RA, the overall risk of serious infections in TNF inhibitor-treated patients was twice that of those treated with standard therapies, even excluding the granulomatous infections, although the relative risk of OIs could not be assessed [22]. In a stratified analysis according to dose, higher doses of adalimumab and infliximab appeared to be associated with an increased risk. These authors calculated the NNH was 59 within a treatment period of 3–12 months [23].

Case reports and passive surveillance provide another window to the infectious morbidity associated with these agents. In a review of the US FDA’s MedWatch Adverse Event Reporting System for reports of granulomatous infections associated with infliximab or etanercept use, from 1998 to 2002, a total of 639 granulomatous infections were reported among 197,000 patients who had received infliximab and 113,000 etanercept respectively [24,25]. Of these patients, 40% received concomitant immunosuppression with either methotrexate or corticosteroids. The overall rate of granulomatous infection was 129/100,000 treated patients for infliximab and 60/100,000 for etanercept. The most frequently reported granulomatous infections were tuberculosis (TB) followed by histoplasmosis, candidiasis, listeriosis, nontuberculous mycobacteria and
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aspergillosis. The median time to onset of infection was 40 days for the infliximab group and 236 days for etanercept [24,25]. Of infliximab-associated infections, 72% occurred within the first 90 days of treatment, compared with 28% for etanercept [24,25]. The same was true for TB, with the median time to onset of 190 days in the infliximab arm and 511 days in the etanercept group; 44% of the infliximab-associated TB cases occurred within 90 days of treatment versus 10% for etanercept [24,26]. Granulomatous infections were three-times more frequent in the infliximab group versus etanercept.

Several large patient registries were established in the late 1990s in Sweden, Germany, Spain, France and Great Britain to monitor the use, effectiveness and safety of these agents [26–29]. The British Society of Rheumatology (BSR) Biologics Registry is the largest reported prospective observational cohort study of TNF-inhibitor use in RA patients. Rates of serious infections were compared, including site-specific and bacterial intracellular infections in 7664 patients who received a TNF inhibitor for RA with a comparison group of 1354 on only DMARDs. A total of 525 serious infections occurred in the TNF-treated group compared with 56 in the DMARD group with a median follow-up of approximately 1 year. The incidence rate ratio (IRR) was 1.28 [30]. When controlled for disease severity, baseline steroid use and smoking there was no difference in infection risk. However, when adjusted for just the first 90 days of treatment with the TNF inhibitor, the adjusted incidence rate rose to 4.6 [31]. There were 19 intracellular (opportunistic) bacterial infections – ten TB, two Legionella, three Listeria, one M. fortuitum and three Salmonella – all of which occurred only in the TNF inhibitor-treated group [30,31].

In the prospective cohort of RA patients from Germany (the Rheumatoid Arthritis Observation of Biologic Therapy [RABBIT] cohort), infections occurred in 204/1529 (13%) of patients overall; 15% in the etanercept, 21% in the infliximab, and 6% among the controls who received DMARDs alone [29]. The relative risk of serious infections was 2.7–2.8-times higher in the TNF inhibitor-treated group compared with those treated with DMARDs alone. Another study using administrative data found the risk of hospitalization for infection was twofold higher in the TNF-treated group and fourfold higher in the initial 6 months of treatment as compared with the methotrexate (MTX) alone group [32]. Most of these infections were pneumonias and cellulitis.

Bacterial opportunists
One of the most commonly reported intracellular bacterial infections in these patients is listeriosis, occurring in three per 10,000 patient-years [33]. Listeria monocytogenes is a facultative intracellular food-borne pathogen that affects hosts with impaired cellular immunity. TNF-α protects mice against listerial infection and TNF blockade may lead to overwhelming listerial infection. Several reports of disseminated listeriosis and deaths have been reported in persons receiving TNF blockade [33,34]. These cases occurred between 4 and 290 days after receipt of the first infliximab infusion with most occurring following the sixth infusion [35]. Because this subset at risk cannot be easily identified and the overall event rate is low, antimicrobial prophylaxis for listeria cannot be routinely recommended. Patients receiving TNF antagonists should be counseled to avoid soft cheeses, unpasteurized milk products and ‘ready-to-eat’ meat products to decrease their exposure to Listeria. Disseminated salmonellosis is another food-borne opportunistic infection occasionally reported in patients on anti-TNF therapy [36,37].

Mycobacterial infections
Both atypical and tuberculous mycobacterial infections have been described with the TNF inhibitors. In early experiments, it was found that TNF-α deficient mice had poorly formed granulomas and extensive necrosis when infected with mycobacterium tuberculosis [3]. Thus, it was anticipated that disseminated mycobacterial infections might occur in humans receiving these agents. As of December 2004, 82 cases with etanercept (27.1/100,000 patients), 633 (33/100,000 patients) with infliximab and 15 (27.1/100,000 patients) with adalimumab had been reported worldwide [16–18,38].

Tuberculosis incidence rates from MedWatch data are: 54 cases/100,000 patients treated with infliximab, and 28/100,000 patients treated with etanercept [24,25] compared with the baseline rate of TB in the USA of 6.2/100,000 [3,39]. Several of the early clinical trials enrolled patients in countries with high endemic TB rates. The incidence rate of TB in trials of infliximab was 0.4%. TB risk in patients receiving adalimumab appears to be dose-dependent; the calculated incidence rate of TB in patients receiving adalimumab prior to PPD screening was 1.3/100,000 patient-years and 0.19/100,000 patient-years after screening [38]. The median time to TB onset was 167 days and 65% cases were extrapulmonary [21,38,40].
In a review of the US National Databank for Rheumatic Diseases of 10,782 patients with RA during 1998–1999 and 6460 infliximab-treated patients during 2000–2002, the TB incidence rate prior to TNF-inhibitor use was 6.2/100,000 patient-years versus 52.5/100,000 patient-years with infliximab use [41]. The US baseline TB incidence rate for years 1999 and 2000 was 6.4 and 5.8 per 100,000 patient-years, respectively [41]. These numbers differ in Europe where endemic TB rates are higher. In an analysis of data from 2000 to 2004 in Spain, the baseline TB rate was 21/100,000 patients and the rate among 4102 patients treated with etanercept, adalimumab and infliximab was 20-fold higher than the background rate [26]. Following the implementation of recommended TB screening, rates fell 78% from 522/100,00 patient-years to 117/100,000 [26].

In most patients treated with TNF inhibitors, TB presents as a reactivation disease. In cases associated with infliximab, the median age was 57 years, and the median time to onset was 12 weeks versus 46 weeks for etanercept, and 30 weeks for patients on adalimumab [24,25,38,39]. Only a small number of patients reported a past history of TB exposure. Two-thirds of the patients had extrapulmonary disease (EPTB) and 25% had disseminated disease (DTB) [38,42]. This contrasts with the usual 18% EPTB and 2% DTB in non-HIV-associated TB. The diagnosis of TB in these patients may be difficult due to atypical and extrapulmonary presentations and in some circumstances poor granuloma formation [38].

As latent TB infection may present a significant risk to patients on TNF inhibitors, US guidelines recommend screening for TB risk with a focused history, purified protein derivative (PPD) skin test and a chest radiograph. A PPD skin test of more than 5 mm induration should be considered as evidence of tuberculous infection. In these patients, active TB should be excluded and, if so, receive preventive therapy for latent TB infection (LTBI) for 9 months. Two-step TB skin testing is not recommended. Because many patients qualifying for TNF-inhibitor therapy have been on immunosuppression, which increases the risk of a falsely negative PPD, a negative test needs to be interpreted with caution [43]. Screening of at-risk patients appears to have reduced the incidence rate of TB [26,44,45]. In RA patients treated with steroids who had a positive PPD skin test, the incidence of TB was reduced by 70% by this strategy [46]. The role of the IFN-γ ELISPOT assay, (QuantiFERON®-TB-Gold Cellestis Ltd.), has not yet been validated in this population. However, it appears to have improved sensitivity in immunosuppressed hosts (including HIV) and might prove useful in those who have received Bacillus of Calmette and Guérin (BCG) immunization [47].

If tuberculosis develops while receiving a TNF inhibitor, it is recommended that the anti-TNF agent be discontinued and a standard course of antituberculous therapy be administered [42,48]. Anti-TNF therapy should not be resumed until the completion of therapy if possible. If the underlying disease is progressive, TNF inhibition should be withheld for at least 2 months after antituberculous therapy has been started and there has been an adequate response. Patients who then resume TNF inhibitors must be closely monitored for disease recurrence. Physicians should also be aware of the potential for a paradoxical worsening of TB after initial improvement to anti-TB therapy following discontinuation of TNF inhibitors [49]. This may be similar to the immune reconstitution observed in antiretroviral treated HIV patients [50].

Histoplasmosis

Macrophage apoptosis plays an important role in control of endemic fungal infections. Resolution of histoplasma infection is dependent upon an effective cellular immune response. In vitro infliximab inhibits T-cell proliferation when alveolar macrophages are the antigen-presenting cells and results in a significant reduction in IFN-γ production [51,52]. In murine models, TNF-α blockade after infection results in fatal disseminated histoplasmosis [53]. A total of 39 cases of histoplasmosis associated with infliximab and three with etanercept had been reported to the MedWatch as of September 2002 and additional cases have been noted since [24,25,54,55].

Histoplasmosis presents from 1 week to 6 months after initiating anti-TNF treatment. Patients may present with an acute and fulminant course characterized by fever, malaise, cough, dyspnea and interstitial pneumonitis [54]. The infection may mimic the underlying inflammatory disease being treated (Crohn’s, RA) [51]. Patients treated with infliximab may be at higher risk for developing histoplasmosis than those treated with etanercept or adalimumab [24]. Although most cases of histoplasmosis during anti-TNF therapy have been diagnosed via bronchoalveolar lavage or lung biopsy, the urine histoplasma antigen may be a potentially...
useful tool in those suspected of disseminated disease and for follow-up [51]. Its role in monitoring at risk patients in highly endemic areas is not established.

Patients who develop histoplasmosis should stop their TNF inhibitors until they have completed their histoplasma treatment. Initial therapy should include a liposomal formulation of amphotericin B for 1–2 weeks followed by itraconazole at 200–400 mg daily for 1 year [56]. Itraconazole levels should be monitored to ensure efficacy. If the patient had a positive urinary histoplasma antigen, this should be followed to ensure adequate therapy and monitor for relapse. Since histoplasmosis is a rare event, even in chronically immunosuppressed patients living in endemic areas, and because screening by serology has not proven predictive of who will acquire the disease, the role of screening and prophylaxis remains unclear [57,58]. It is prudent to advise patients receiving TNF-α inhibitors to avoid activities that increase their risk of exposure to histoplasma, such as exploring caves or cleaning chicken coops and to wear a mask when working in soil. Further data are needed to optimize preventive strategies.

Coccidioidomycosis
Like histoplasmosis, this granulomatous infection has been reported in endemic areas in patients treated with TNF inhibitors. The estimated annual risk of coccidioidomycosis in Tucson, AZ, USA is 3%. The majority of these infections are asymptomatic. In patients with impaired cell-mediated immunity, 7% per year are symptomatic [59]. The risk of developing symptomatic coccidioidomycosis on TNF inhibitors may be increased by fivefold compared with patients suffering from inflammatory arthritis [59]. The cumulative incidence of coccidioidomycosis in RA, reactive arthritis and patients with psoriatic arthritis is 1%.

Coccidioidomycosis in TNF inhibitor-treated patients mimics TB with a median onset at week 7 [59]. Of the 13 patients with coccidioidomycosis reported by Bergstrom, 12 received infliximab and one etanercept. Of 12 patients, 11 were taking MTX. All 13 developed pneumonia, four had disseminated disease, 11 of 13 had positive coccidoidal serology, five were hospitalized and two died [59].

Screening patients receiving TNF inhibitors in endemic areas for coccidioidomycosis is controversial. In transplant patients, screening in hyperendemic areas and use of azole prophylaxis reduces the morbidity from coccidioidomycosis [60]. It is recommended that patients receiving TNF inhibitors from endemic areas for coccidioidomycosis have a screening chest radiograph and coccidioides serologies. Unlike histoplasmosis, targeted antifungal prophylaxis with fluconazole has been effective in transplant recipients with a history of coccidioidomycosis infection or positive coccidioidomycosis serology in endemic areas [60]. More data are needed to determine whether fluconazole should be considered in patients receiving TNF inhibitors who are at increased risk for this infection. Those who acquire infection should discontinue their anti-TNF therapy and be treated with azole therapy. Whether anti-TNF therapy can be safely re-instituted with or without azole secondary prophylaxis is unknown and not advised in cases of CNS coccidioidomycosis where the risk for relapse is high [61].

Pneumocystis jiroveci pneumonia
Though rarely reported in patients only on TNF inhibitors, there are potential mechanisms by which this may occur [62,63]. Cases of Pneumocystis pneumonia (PCP) have occurred in patients on infliximab and five on etanercept [64–66]. The FDA-Adverse Event Reporting System (AERS) safety database contained 84 cases of PCP in patients receiving infliximab between January 1998 and December 2003. Most of these patients were on other concomitant immunosuppressives, including prednisone, MTX, azathioprine, 6-mercaptopurine and cyclosporin A, all of which have previously been associated with PCP. The mean time to onset of PCP was 21 days; 27% died [66]. The time to onset was within 1 month of initiation of infliximab and 2 months of etanercept therapy, suggesting these patients were already moderately immunosuppressed. At present, PCP prophylaxis is not warranted unless other risk factors for this infection are present.

Other reported infections
A variety of other opportunists, including Toxoplasma, Nocardia, Cryptococcus, atypical mycobacteria, Leishmania, Bartonella, Legionella, Aspergillus, Sporobolomyces and Microsporidiosis have been reported in patients receiving TNF inhibitors [67].

In the few reported cases of aspergillosis, the disease was localized and invasive within the lungs; its onset was rapid, within 5 days and culture positive within 1 week. Cases have occurred.
in patients on infliximab therapy alone [68,69]. Several cases of unusual and severe complications such as Brachiola myositis [70] and disseminated sporotrichosis [71] illustrate the need for appropriate counseling regarding exposure risks, and a meticulous search for infections prior to intensification of immunosuppression in patients with inflammatory diseases.

**Viral diseases**

A variety of opportunistic and nonopportunistic viral diseases have been reported in patients receiving these drugs including CMV [72], hepatitis B and C [73–75], EBV [76], recurrent herpes simplex, varicella zoster [77,78] and severe molluscum contagiosum [79]. It is not clear that these occur more frequently in patients receiving TNF inhibitors than with other forms of immunosuppression.

CMV disease is rarely encountered [72]. The diagnosis of CMV is usually by tissue biopsy, pp65 antigenemia or quantitative PCR. It has been suggested that patients on TNF inhibitors who demonstrate elevated quantitative measures of CMV receive treatment with antiviral therapy; however, there is a lack of data to support this recommendation [72].

The risk for zoster is increased with prednisone doses above 10 mg daily, the use of cyclophosphamide and the combination of both a DMARD and a TNF inhibitor. There appears to be no higher risk in patients on TNF inhibitors alone [78]. Severe disease is treated with intravenous acyclovir whereas mild or localized disease may be treated with an oral agent such as valacyclovir, famciclovir or acyclovir. Since there are no data on use of zoster vaccine (Zostavax®) in immunosuppressed hosts, this new vaccine should not be used.

Patients who are candidates for TNF-inhibitor therapy should be screened for hepatitis B and immunized prior to immunosuppression. For those with chronic hepatitis, hepatology consultation is needed. The European Association for the Study of the Liver (EASL) recommends that antiviral therapy begins 2–4 weeks prior to the start of a TNF inhibitor in patients with inactive hepatitis B [75]. The duration of therapy is unknown. For those requiring lifelong immunosuppression, lifelong antivirals may be needed.

Hepatitis C infection may also coexist with the patient’s underlying disease, such as RA or psoriasis. Hepatitis C screening is prudent, although several reports indicate no worsening, and potential benefit of etanercept in some patients with hepatitis C infection [75,80].

**Conclusion**

Patients receiving TNF inhibitors may be at risk for opportunistic infections. Some of these infections may be prevented by personal protective measures, some via immunization and others by antimicrobial prophylaxis (Table 1 & Box 1). A pretreatment assessment of infectious risks and directed risk reduction may be reasonable. The development of monitoring systems to determine the risk factors and absolute risk for OIs will help to better target preventive measures including antimicrobial prophylaxis. Current recommendations based principally upon expert opinion [1,81,82] suggest a pretreatment chest radiograph and PPD skin test only. It is recommended that all age-appropriate immunizations be given prior to initiation of anti-TNF therapy. Live virus vaccinations should be avoided [83]. As patients with rheumatic disease treated with TNF inhibitors are at increased risk for respiratory infections and because of increased morbidity due to pneumococcal disease, the annual inactivated influenza vaccine, and pneumococcal vaccine are recommended [84,85].

Patients need to be aware that their physician may recommend interruption of therapy for serious infections. How long to hold them remains unclear, especially for OIs. Most authorities suggest holding these agents until the OI has been cleared.

**Future perspective**

As this review illustrates, there remain many unanswered questions regarding the infectious risks associated with these therapies. There will be a proliferation of newer agents affecting other immunomodulatory pathways and therapeutic indications will continue to expand. As in

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**Table 1. Precautions when using TNF-blocker therapy.**

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<td>Active Hep B or C, or treated with Hepatitis B/C, treated</td>
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<td>Liver cirrhosis</td>
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transplantation, future research will help us better define those at greatest risk of infectious morbidity and predict the timing of such events. Though at first this will involve traditional risk-factor analysis, this area will be ripe for genomic exploration. We will likely be able to search for specific polymorphisms that might place patients at risk for infectious complications. Future studies will also better define the pharmacologic and pharmacogenomic parameters which might reduce infectious risks. We will better define the impact of specific agents on infection risk, including the role of TNF-receptor specificity. Since a significant proportion of patients with RA and Crohn’s as well as psoriasis and various forms of spondylarthropathies may have inadequate long-term responses to individual TNF inhibitors, we will begin to see the use of sequential or combination therapy with other biological agents. Whether the infectious risks are the same with sequential or combination therapies will need to be determined. We will begin to explore the risk across the diverse populations receiving these agents. Pre-treatment risk assessment will be standardized and preventive measures will be provided for those at highest risk. Lastly, our experience thus far is limited with respect to long-term adverse effects. We will continue to monitor for the development of immunomodulatory virus induced malignancies.

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Executive summary

**Risk of opportunistic infection with anti-TNF treatment**
- The TNF-α inhibitors have begun to revolutionize the treatment of inflammatory diseases. Like their predecessors, these new agents carry an increased risk of serious and granulomatous infections, the timing and frequency of which may vary between the specific agents.
- Patients receiving TNF inhibitors will be at variable risk for opportunistic infection, depending upon their underlying disease and prior immunosuppression.
- Granulomatous and intracellular infections may occur with TNF inhibition, and the risks for opportunistic infections are cumulative with multiple immunosuppressives.
- Infections may present atypically and be disseminated at time of diagnosis. The first 3–6 months appear to be the period of greatest risk.

**Measures for infection risk reduction**
- Patients in whom anti-TNF therapy is being initiated should undergo pretreatment screening for exposure risks, including TB.
- Appropriate immunizations including pneumonia vaccination, seasonal influenza vaccination and hepatitis B vaccination in patients at risk for this infection should be performed prior to initiation of therapy.
- Patients with infection should undergo an aggressive diagnostic evaluation that considers the possibility of opportunistic infection.

**Future perspective**
- Many practical questions remain unanswered such as the most appropriate screening, optimal timing of vaccines, need for discontinuation of TNF inhibitors, and role of opportunistic infection monitoring and prophylaxis.
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Papers of special note have been highlighted as either of interest (*) or of considerable interest (**) to readers.


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1. Humira®, Package insert. Abbott Laboratories, IL, USA.

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1. Systematic review of the risks associated with infliximab and adalimumab. The key finding is the twofold increased risk of serious infections and a number needed to harm of 59 within the first 3–12 months of treatment.


1. Original descriptive review of the US FDA adverse event database describing granulomatous infections in patients receiving TNF inhibitors.


Largest prospective cohort study showing a 4.6-fold relative risk of infection within the first 3 months of TNF-inhibitor use.


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