6

Infectious Complications of Anti-Tumour Necrosis Factor-α Therapy in Rheumatoid Arthritis

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1. Introduction

In the last decade the use of Tumor Necrosis Factor- α inhibitors including infliximab, etanercept, adalimumab; and lately certolizumab and golimumab, has revolutionized the treatment of rheumatoid arthritis (RA). These agents have been effective in reducing inflammatory activity and limiting joint destruction in patients with RA however their application has raised a number a safety concerns. Increased risk of infections is of predominant importance given these factors' major role in altering host defense mechanisms.

2. Infections in rheumatoid arthritis patients

2.1 Background infection risk in patients with RA

As infection adverse effects are common in patients with RA due to the underlying disease itself and/or concurrent medications used in its treatment such as immunosuppressants, it is of great importance to identify whether biological treatments increase this risk further (Furst 2010).

Epidemiological studies prior the introduction of biological treatments have shown that patients with RA are at increased risk of certain types of infections including pulmonary infection, generalized sepsis, osteomyelitis, cellulitis, and septic arthritis with relative risks of infection - related mortality ranging from 5 to 15 (Mitchell, Spitz et al. 1986; Wolfe, Mitchell et al. 1994; Symmons, Jones et al. 1998). Nevertheless, the confounding influence of treatment with glycocorticoids and other disease –modifying antirheumatic drugs (DMRDs) is difficult to interpret. Disease it self leads to alterations in cellular immunity, including a decline in the number and function of T-suppressor and natural killer (NK) cells (Dobloug, Forre et al. 1982; Fox, Fong et al. 1984; Young, Adamson et al. 1984); changes that may predispose patients to infection. Other studies have suggested a genetic component to the risk of infection in RA. For example the incidence of urinary tract infection in patients with rheumatoid arthritis patients has been correlated with the number of risk alleles defined by single nucleotide polymorphisms in the genes for TNF-α, lymphotoxin–α and the Fcγ receptors 2A, 3A and 3B (Hughes, Criswell et al. 2004).

2.2 Bacterial infections

2.2.1 Randomised controlled trials and extension studies of anti-TNF agents

Infliximab

The 1- year anti- TNF trial in Rheumatoid Arthritis with concomitant Therapy (ATTRACT study) reported similar incidences of infections among patients treated with infliximab (3 or 10 mg/kg, given every 4 weeks or every 8 weeks) [1-5 patients (1–6%)] compared to patients receiving methotrexate (MTX) alone [5 patients (6%)]. (Maini, St Clair et al. 1999). The serious infections were described as bacterial infections, bronchitis, cellulitis, peritonitis, pneumonia, pyelonephritis and urinary tract infection, sepsis and tuberculosis, although the relative incidence of each of these infections was not reported. Notably, the frequency of any infection was significantly increased in patients receiving 10 mg/kg of infliximab, but not in those receiving 3 mg/kg. Similar incidence of serious infections was reported when ATTRACT was extended to 2 years (10-13%) (Maini, Breedveld et al. 2004). On the contrary, the incidence of serious infections in the 54 weak active controlled study of patients receiving infliximab for treatment of early onset RA (ASPIRE study) was significantly higher in the group receiving infliximab (3 or 6 mg/kg, given every 8 weeks in combination with MTX than in the group of patients receiving MTX monotherapy (St Clair, van der Heijde et at 2004. More specifically, serious infections included pneumonia, tuberculosis (TB), sepsis, bronchitis and septic bronchitis and occurred more commonly in patients receiving MTX -3 mg/kg infliximab [21 patients (5.6%)] or MTX -6 mg/kg infliximab [19 patients (5.0%)] than in those receiving MTX alone [6 patients (2.1%)] (P=0.02 and P=0.4, respectively). Among the serious infections, pneumonia occurred more frequently in the infliximab-treated patients than in those treated with MTX alone [15/749 (2.0%) versus 0/291 (0.0%)]. According to the authors of the ASPIRE study most of these cases were community-acquired pneumonias that responded appropriately to antibiotic therapy. It has been suggested that the apparent differences in the incidence of severe infections between the ASPIRE and ATTRACT trials may reflect, at least partially, differences in study design. ASPIRE had substantially more patients enrolled (N=291-377 per treatment arm, compared with 81-88 in ATTRACT) and in addition ASPIRE excluded patients that had prior treatment with MTX or anti-TNF while all patients in ATTRACT were receiving MTX at the time of the enrollment (Furst 2010).

Etanercept

With regards to etanercept, a 1 year study comparing MTX with 10 mg or 25 mg etanercept twice weekly reported similar number of patients with one or more infections in all treatment groups (Bathon, Martin et al. 2000). Interestingly, when the number of events that occurred per patient-year was analyzed, the rate of all types of infection was significantly higher among patients who received MTX than among those who received either dose of etanercept (1.9 vs. 1.5 events per patient-year, P=0.006). The frequency of upper respiratory tract infections was similar in the MTX group and the group assigned to receive 25 mg of etanercept, while the rate of infections at other sites in the respiratory tract was higher in the MTX group (1.3 vs. 1.0 events per patient-year, P=0.006). Infections requiring hospitalization or the intravenous administration of antibiotics occurred in less than 3% of patients in each group. There were no opportunistic infections, and no deaths from infections. When this study was extended to 2 years, similar incidences of serious infections in each treatment arm

were reported and did not increase in frequency during the second year of the study (Genovese, Bathon et al. 2002). Over the 2-year study period, 21 patients had infections that required hospitalization or use of intravenous antibiotics, including 9 patients in the MTX group, 5 patients in the 10 mg etanercept group, and 7 patients in the 25 mg group. The types of serious infection observed in the second year were similar to those reported in the first year and included cellulitis (1 patient each in all 3 treatment groups), bronchitis (1 patient in the 10 mg group), pneumonia (1 patient in the 10 mg group), and cystitis (2 patients in the 25 mg group); no cases of TB and no opportunistic infections were seen. Similarly, in a double-blind, randomized, clinical efficacy, safety, and radiographic study (TEMPO) involving 686 patients with active rheumatoid arthritis randomly allocated to treatment with etanercept 25 mg (administered subcutaneously twice a week), oral MTX (up to 20 mg every week), or the combination, similar incidences of infections and serious infections have been recorded in all treatment arms with no reports of TB or opportunistic infections (Klareskog, van der Heijde et al. 2004). Those results were sustained into the 2 year follow up of the TEMPO trial showing similar rates of serious infections among all treatment groups (van der Heijde, Klareskog et al. 2006). Again, no cases of TB were reported but there was one case of bronchopulmonary aspergillosis in the combination therapy group. A similarly favorable safety profile for etanercept was reported from the ADORE study, which evaluated the efficacy and safety of combination etanercept and MTX versus etanercept alone in patients with RA with an inadequate response to MTX. The study showed comparable incidence of infections in the two arms and notably no cases of opportunistic infections or TB were reported in the combination group (van Riel, Taggart et al. 2006).

Adalimumab

The safety profile of adalimumab was initially evaluated in 3 double blind placebo controlled short term (24-26 weeks) trials reporting low incidence of serious infections (Furst, Schiff et al. 2003; van de Putte, Atkins et al. 2004; Weinblatt, Keystone et al. 2006). In a subsequent 52 weeks - long study comparing treatment with adalimumab (40mg every other week or 20 mg every week) plus concomitant MTX in patients with active RA who had an inadequate response to MTX, the proportion of patients with serious infections was higher in the group receiving adalimumab (3.8%) than in those receiving MTX (0.5%) ($P \leq 0.02$), and was highest in the patients receiving 40 mg adalimumab every other week (Keystone, Kavanaugh et al. 2004). Adjusting for exposure time, serious infections occurred at a rate of 0.06 patients / patient-year with adalimumab 40 mg every other week, 0.03 patients per patient-year with adalimumab 20 mg weekly, and 0.01 patients per patient-year with MTX alone. One patient treated with adalimumab 40 mg every other week was diagnosed as having primary TB of the cervical lymph nodes, and nodes, was withdrawn from the study and successfully treated. At baseline, this patient had a negative tuberculin purified protein derivative (PPD) test result and a normal chest radiograph. One patient treated with adalimumab 40 mg every other week plus MTX was diagnosed with histoplasmosis infection after 78 days of treatment, and was subsequently withdrawn from the study and successfully treated with antifungal therapy. This patient lived in an area which was endemic for histoplasmosis infection. One patient treated with adalimumab 40 mg every other week was diagnosed as having herpes zoster and developed encephalitis, which resolved but resulted in mild lower extremity weakness. In the 2- year multicenter, double

blind, active Comparator-controlled study designed to compare the efficacy and safety of adalimumab plus MTX versus MTX monotherapy or adalimumab monotherapy in patients with early, aggressive RA who had not previously received MTX treatment (PREMIER study), the overall rate of infectious adverse events (AEs) did not differ significantly among the 3 treatment groups (123, 110, and 119 events per 100 patient-years in the combination therapy, adalimumab monotherapy, and MTX monotherapy groups, respectively) (Breedveld, Weisman et al. 2006). The rate of serious infections in the adalimumab monotherapy group was significantly lower than that in the combination treatment group, but not significantly different compared with the MTX monotherapy group. Notably, serious infections were more common in the combination therapy arm with 9 serious infections reported, including 3 pulmonary infections (1 case of pleural TB) and 1 case each of sinus infection, wound infection, septic arthritis, infected hygroma, cellulitis, and urinary tract infection. In the adalimumab monotherapy arm, serious infections included 1 case each of pneumonia, cellulitis, and septic arthritis. In the MTX monotherapy arm, the 7 serious infections consisted of 2 cases of pneumonia and 1 each of septic arthritis, sinusitis, abscess, bacteremia, and parotitis. The long term safety of adalimumab was investigated in the 4-year open-label extension of the ARMADA trial (Weinblatt, Keystone et al. 2006). The rate of serious infections was slightly lower throughout the entire study than in the blinded period alone with the most common serious infections reported being pneumonia, urinary tract infections and septic arthritis. A PPD skin test was performed at the screening visit for all patients. Standard chest radiographs were also taken at the screening visit and at week 24. Notably, at baseline, 11/271 (4.1%) randomized patients had positive PPD results at screening, including 9/209 (4.3%) adalimumab treated patients and 2/62 (3.2%) placebo treated patients. These patients were treated with TB prophylaxis in accordance with routine medical practice. No cases of TB or other opportunistic infections were reported. The safety profile of adalimumab was analyzed further in a cumulative analysis of data from 10050 patients who participated in randomized controlled trials, open label extensions, and two phase IIIb open label trials, representing 12506 patient-years (PYs) of adalimumab exposure (Schiff, Burmester et al 2006). The rate of serious infections in the clinical trial safety database as of April 2005 was 5.1/100 PYs. This rate is nearly identical to that observed in August 2002 (4.9/100 PYs) and was similar to rates reported for the general RA population. Four cases of histoplasmosis were reported, all in endemic areas (0.03/100 PYs). No cases of coccidioidomycosis have been reported in RA clinical trials.

2.2.2 Registry data, observational data and chart reviews

The safety profile of anti-TNF agents in the everyday clinical practice was elucidated further by registry data analysis, observational studies and chart reviews. Data derived from these studies could be highly informative; however the lack of a standard comparator, strict inclusion and exclusion criteria and the inherent differences in patient characteristics with respect to ethnic, geographical and socio-economical characteristics often reduce their credibility and, produce desperate results and do not allow direct comparisons among different studies. Nevertheless, these studies become important when they investigate specific or relatively rare types of infections and raise specific concerns with regards to infections in certain population groups (Furst 2010).

In the German registry study, data of 512 patients receiving etanercept, 346 patients receiving infliximab, 70 patients receiving anakinra, and 601 control patients treated with disease-modifying antirheumatic drugs were analyzed. After adjusting for confounding factors, the relative risks of serious AEs were 2.2 [95% CI (confidence interval) 0.9–5.4] for patients receiving etanercept and 2.1 (95% CI 0.8–5.5) for patients receiving infliximab, compared to those treated with DMARDs. Respiratory tract infections were the most frequent followed by skin and subcutaneous tissue infections, influenza like illness, herpes virus infections, and urinary tract infections. Lower respiratory tract infections were the most common serious infections (Listing, Strangfeld et al. 2005). Updated results from the British Register for Biologic Therapies (BSRBR) (Galloway, Hyrich et al. 2011) also showed in contrary to previous reports (Dixon, Watson et al. 2006) that anti-TNF therapy is associated with a small but significant overall risk of serious infections. The adjusted hazard ratio (adjHR) for serious infections in the anti-TNF cohort was 1.2 (95% CI 1.1, 1.5). The risk did not differ significantly between the three agents adalimumab, etanercept and infliximab and it was highest during the first 6 months of therapy [adjHR (Hazard Ratio) 1.8, 95% CI 1.3-2.6]. This was in accordance with the work of Askling and Dixon who reviewed all available studies on infection risk associated with anti-TNF therapy in RA and found that the risk was highest in the first few months but declined later during the course of treatment (Askling and Dixon 2008). It has been proposed that this variation in risk may reflect biological functions (anti-TNF therapy causing early infections in susceptible individuals), or bias (clinicians having a lower threshold for treating infections early in therapy). In addition the depletion of susceptible individuals (a healthy user effect) by withdrawing patients who develop an infection from the anti-TNF cohort may reduce the apparent risk of the drug through subsequent patient selection bias. Furthermore, as patients become established on anti-TNF therapy, their RA becomes better controlled and other confounding factors such as mobility may improve or their dose of steroids may be reduced thus contributing to the complexity of interpretation (Askling and Dixon 2008; Galloway, Hyrich et al. 2011).

Registries and chart reviews can be particularly useful in identified specific infectious risks for susceptible patients. For example, data from the French registry estimated the relative risk of legionellosis when receiving treatment with a TNF-α antagonist to be between 16.5 and 21.0, compared with the relative risk in France overall (Tubach, Ravaud et al. 2006).

2.2.3 Case reports

Numerous case reports have raised awareness to rare bacterial infections in RA patients treated with anti-TNF. These included reports on reactivation of brucellosis (Jimenez, Colmenero et al. 2005), *Capnocytophaga cynodegmi*-related cellulitis (Gerster and Dudler 2004), *Roseomonas mucosa* induced septic arthritis (Sipsas, Papaparaskevas et al. 2006), and *Propionebacterim acnes*-related endogenous endophthalmitis (Montero, Ruiz-Moreno et al. 2006).

2.2.4 Meta-analyses

One solution to the lack of precision in the estimates of harm derived from individual randomized trials is to pool their results using meta-analysis. Results however from the two

existing meta-analyses studies on anti-TNF therapy and risk of infection are disparate. A meta-analysis of nine randomized, controlled studies including 3493 patients with RA who received anti-TNF antibody treatment (infliximab and adalimumab) and 1512 patients who received placebo reported a doubled risk of serious infection [odds ratio (OR) 2.0, 95% CI 1.3–3.1] and a tendency towards a dose–response association (Bongartz, Sutton et al. 2006). On the contrary, a second meta-analysis of five published, placebo-controlled trials involving a total of 2945 randomized patients, who received at least one dose of abatacept (0.5, 2 or 10 mg/kg) (n=1960) or placebo (n=985) for a duration of treatment ranging between 24 and 48 weeks did not reveal a statistically significant increased risk of serious infection for abatarcept (Salliot, Dougados et al. 2009). The 49 serious infections reported in the abatacept cohort were mainly broncho-pulmonary, streptococcal and pyogenic septicaemia, staphylococcal arthritis, abscesses, gastrointestinal infections (6 of whom 3 diverticulitis), dermatological infections (six of whom one was a cellulitis) and pyelonephritis. One case of unconfirmed TB and one case of pulmonary aspergillosis were reported. The last patient (who had a history with TB and pulmonary fibrosis) died with aspergillosis and *Pseudomonas aeruginosa* septicaemia.

2.3 Tuberculosis and opportunistic infections

As shown earlier, the incidence of TB in pre-registration clinical trials has been low. It was only after licensing of these medications that post-marketing surveillance registers showed results suggestive a strong association between ant-TNF treatment and TB. Keane *et al* analysed data from the US Food and Drug Administration's (FDA) Adverse Event Reporting System (AERS) for reports of TB with infliximab from its licensure in 1998 through May 29, 2001 (Keane, Gershon et al. 2001). There were 70 reported cases of TB after treatment with infliximab for a median of 12 weeks. In 48 patients, TB developed after three or fewer infusions and 40 of the patients had extrapulmonary disease (17 had disseminated disease, 11 lymph-node disease, 4 peritoneal disease, 2 pleural disease, and 1 each meningeal, enteric, paravertebral, bone, genital, and bladder disease). An estimated rate of 24.4 cases of tuberculosis per 100 000 in the USA compared with a background rate in American patients with RA who had not received the drug of 6.2 cases per 100000 was calculated. The rather atypical presentation of the disease (e.g. extrapulmonary dissemination), the temporal relation between development of active tuberculosis and the start of therapy, the age of the patients (median, 57 years), the small number of cases with reported recent exposure to TB, and the low incidence of TB in the countries from which the reports were received suggested reactivation of the disease (Keane, Gershon et al. 2001).

As of March, 2002, 121000 patients had been treated with etanercept worldwide with about 94% of the use in the USA. In a search of the FDS's AERS database reported up to March 2002, Mohan and co-workers detected 25 cases of tuberculosis that occurred during or after etanercept therapy (Mohan, Cote et al. 2004). Patients with etanercept-associated TB were fewer but clinically similar to those with infliximab-associated TB (Keane, Gershon et al. 2001). The numbers of patients who had been exposed to etanercept and infliximab were roughly similar, yet the TB rate for US patients using etanercept was lower than that for patients using infliximab (~10 vs. ~41 cases/100000 patient-years of exposure). It has been proposed that this difference might be due to the divergent ways in which the 2 agents neutralize TNF-α, the use of MTX concurrently with infliximab (as indicated for RA in the

infliximab package insert), differences in proportions of international patients treated with the 2 agents, or other factors (Gardam, Keystone et al. 2003; Mohan, Cote et al. 2004). Overall, in a large systematic review of infectious complications of TNF antagonists extracted from 35275 distinct reports from the AERS database between for January 1998–September 2002, granulomatous infections were reported at rates of ~239 per 100000 patients who received infliximab and ~74 per 100,000 patients who received etanercept (P <0.001) (Wallis, Broder et al. 2004). TB was the most frequently reported disease, occurring in ~144 and ~35 per 100,000 infliximab-treated and etanercept-treated patients, respectively P<0.001. Candidiasis, coccidioidomycosis, histoplasmosis, listeriosis, nocardiosis, and infections due to nontuberculous mycobacteria were reported with significantly greater frequency among infliximab-treated patients. 72% of these infection occurred 90 days after starting infliximab treatment, and 28% occurred after starting etanercept treatment P<0.001. These data indicated a relative risk of granulomatous infection that was >3 among patients who received infliximab compared to those who received etanercept. The clustering of reports shortly after initiation of treatment with infliximab was consistent with reactivation of latent infection.

Geographical associations between anti-TNF therapy and specific granulomatous diseases have been suggested. For example, disseminated histoplasmosis has been reported more frequently in endemic regions in the US (Lee, Slifman et al. 2002). In a review of the FDA passive surveillance database, nine cases of invasive disseminated histoplasmosis associated with infliximab and 1 associated with etanercept were reported. In patients treated with infliximab, manifestations of histoplasmosis occurred within 1 week to 6 months after the first dose and typically included fever, malaise, cough, dyspnea, and interstitial pneumonitis. All patients had received concomitant immunosuppressive medications in addition to infliximab or etanercept, and all resided in histoplasmosis endemic regions of central US (Lee, Slifman et al. 2002). Similarly, anti-TNF therapy was shown to be associated with increased reports of leishmaniasis in endemic areas in Europe (Xynos, Tektonidou et al. 2009).

A major factor that has influenced data relating to the risk of TB associated with biological treatments has been the introduction of vigorous screening of patients participating in clinical trials; hence rates for newer biological agents such as abatarcept may be biased. Screening for TB exposure with PPD skin testing or newer interferon-based serum tests (although their optimal use in this setting is not yet clear) should be performed before beginning therapy with anti-TNF agents (Winthrop and Chiller 2009). Anergy is known to occur in patients with RA or Crohn's disease, and the possibility of false-negative skin tests should be taken into consideration. Nevertheless from a therapeutic point of view, since the implementation of strict guidelines (e.g. BTS recommendations, 2005) with regards to screening patients for exposure risks and treating latent TB prior to initiation of any biological treatment, the risk of tuberculosis has decreased. This is depicted in the data from the Spanish Registry showing that these strategies have resulted in dropping the rates of active TB in RA patients by 83% reaching those observed for RA patients not treated with TNF antagonists (Carmona, Gomez-Reino et al. 2005).

2.3.1 TNF-α pathophysiology and infections

TNF is essential for granuloma formation and maintenance which are key components of host defences against intracellular pathogens (Furst, Wallis et al. 2006). TNF can support

host immunity through the secretion of chemokines, up-regulation of adhesion molecules and the induction of macrophage apoptosis. While TNF blockers may therefore interfere with these important immune functions, other less predictable immune effects have been seen with these agents. In particular, TNF-blockers have been shown to diminish interferon (IFN)-γ effects and stimulate apoptosis of key immune cells, including monocytes, $CD4^+$ T helper cells and Mtb-reactive $CD8^+$ T cells. Anti-TNF therapy is also associated with increased regulatory T cell (T_{reg}) function, which has been linked with susceptibility to TB (Harris and Keane 2010). TNF-α neutralization in mice has resulted in fatal reactivation of persistent tuberculosis characterized by a moderately increased tissue bacillary burden and severe pulmonic histopathological deterioration that was associated with changes indicative of squamous metaplasia and fluid accumulation in the alveolar space (Mohan, Scanga et al. 2001).

2.4 Postoperative infections

Although several studies have attempted to address the risk of postoperative infection, limited statistical precision has been a major concern. The largest study reported a 50% (but not statistically significant) increased risk of surgical site infections for those patients who continued therapy peri-operatively (den Broeder, Creemers et al. 2007). Nevertheless, considering the morbidity of orthopedic surgical site infections (especially prosthesis infections) as compared to a transient surge in disease activity, withholding anti-TNF agents peri-operatively appears to be the most reasonable and prudent approach at present (Bongartz 2007).

2.5 Viral infections

Reactivation of Hepatitis B (HBV) infection is a well described complication of immunosuppression in the setting of organ transplantation or cancer chemotherapy, occurring in up to 50% of patients where concomitant anti-viral treatment is not applied (Shale, Seow et al. 2010). The use of anti-TNF medications has been reported in isolated case reports, case series and chart reviews with a variety of outcomes ranging from apparent viral clearance to fatal hepatitis. In a comprehensive review of these cases by Zingarelli *at al* involving 27 HBV-infected patients treated with anti-TNF agents, HBV reactivation was documented in 14% of patients treated with lamivudine compared with 73% of patients not receiving HBV prophylaxis (Zingarelli, Frassi et al. 2009) thus suggesting that the use of prophylactic lamivudine could help reducing the risk of HBV reactivation. More recently, interesting data with regards to the relative safety of anti-TNF agents in HBV carriers were presented by Charpin *et al* (Charpin, Guis et al. 2009). Their cohort included 21 patients with serologically cured HBV infection, that is HBsAg –ve plus anti-HBc +ve patients and results were suggestive that anti-TNF therapy appeared to be safe during the a limited follow up period of three years. Nevertheless, about 30% of patients involved in this study had significant lower antibody titers over the follow up period which may be relevant during long-term follow up (Jansen 2010). Similar findings we reported by others over a shorter follow up period of 2 years (Vassilopoulos, Apostolopoulou et al. 2010) yet the decrease in antibody titers observed in the later study was comparable to that observed in a control group of patients treated with MTX alone, indicating no apparent specific effect of anti-TNF on HBV protective immunity.

Anti-TNF therapy for RA in the setting of Hepatitis C (HCV) infection could be of particular interest in light of the existing evidence suggesting a role for inflammatory cytokines including TNF-α in the mediating hepatocyte destruction in chronic CMV (Parke and Reveille 2004). It may therefore carefully assumed that anti-TNF agents may be safer in patients infected with HCV rather than HBV (Shale, Seow et al. 2010) and furthermore this notion has been tested in a phase 2 randomised, double-blind, placebo-controlled study where etanercept given for 24 weeks as adjuvant therapy to interferon and ribavirin was shown to significantly improve virological response among patients with chronic HCV and was associated with decreased incidence of most adverse effects associated with interferon and ribavirin (Zein 2005). Although overall experience to date with anti-TNF agents in the chronic HCV setting suggests an acceptable short-term safety profile (Marotte, Fontanges et al. 2007), long-term issues remain to be clarified.

The safety of anti-TNF therapy in HIV is a controversial subject. TNF inhibition in the setting of HIV induced immunosuppression does not appear appealing in view of the potential role for TNF-α in the host defence against infections. Notably, in an early report, the use of etanercept in HIV positive patient with psoriasis and CD4 count of $<200/mm^3$ was associated with polymicrobial infections prompting termination of the treatment (Aboulafia, Bundow et al. 2000). Subsequent reports though have shown a favourable safety profile (Kaur, Chan et al. 2007; Cepeda, Williams et al. 2008), yet clinical decisions should be taken cautiously; careful consideration of the risks and benefits for the individual patient would be needed and close clinical and virological monitoring should always be warranted.

The safety of TNF inhibitors in patients with herpes virus (HSV) infections has also been considered. In particular the risk of herpes zoster infection in patients with RA is twice as much even in the absence of therapy (Wolfe, Michaud et al. 2006; Smitten, Choi et al. 2007) and severe herpes zoster infections have been reported in randomised controlled trials and their open-label follow up studies in patients with RA receiving the TNF inhibitors infliximab or adalimumab (Lipsky, van der Heijde et al. 2000; Furst, Schiff et al. 2003; Keystone, Kavanaugh et al. 2004; Maini, Breedveld et al. 2004). A study by Strangfeld *et al* (Strangfeld, Listing et al. 2009) addressed the question whether this association actually represents a true association between TNF inhibitors reactivation of latent viral infections or simply reflects the increased risk of herpes zoster infection in RA patients (Bongartz and Orenstein 2009). In this prospective cohort the investigators identified 86 episodes of herpes zoster among 5040 patients from the German biologics register RABBIT, receiving anti-TNF agents or conventional DMARDs. Adjusted for age, RA severity and glucocorticoid use, a significant increased risk was observed for treatment with the monoclonal antibodies (HR, 1.82 [95% CI, 0.73-2.55]), although this risk was lower than the threshold (of 2.5) for clinical significance. No significant associations were found for etanercept use (HR 1.36, 95% CI 0.73-2.55) or for anti-TNF treatment (HR 1.63, 95% CI 0.97-2.74) as a class. Equally important, the incidence rate of multidermatomal and ophthalmic zoster was higher in patients taking TNF inhibitors implying severe disease often requiring hospitalisation (Bongartz and Orenstein 2009). Nevertheless, anti-TNF therapy can generally be restarted following temporary interruption and conventional anti-viral therapy until the skin lesions are completely healed (Wendling, Streit et al. 2008). Isolated varicella infections have also been reported in RA patients receiving anti-TNF therapy (Vonkeman, ten Napel et al. 2004; Choi, Kim et al. 2006; Lee, Kim et al. 2007). Notably the rash in one of these cases was

atypical (Choi, Kim et al. 2006) stressing the need for high index of suspicion upon diagnosing primary varicella infection in susceptible patients with atypical skin lesions.

Finally, although a prospective study involving 15 patients with refractory forms of RA under treatment with infliximab (3 mg/kg) did not show evidence of lymphotropic herpesviruses reactivation (CMV, HHV-6, HHV-7, HHV-8, EBV) in RA patients (Torre-Cisneros, Del Castillo et al. 2005), two isolated case reports have associated infliximab with HHV8 related Kaposi's sarcoma (Cohen, Horster et al. 2003) and cytomegalovirus (CMV) retinitis (Haerter, Manfras et al. 2004).

2.6 Response to vaccination

As patients with RA receiving conventional DMARDs and biologics are at increased risk of vaccine preventable diseases such as respiratory tract infections caused by *H. Influenza* and *S. Pneumoniae*, safety and efficacy evaluation of vaccines in this setting is of paramount importance. The use of TNF inhibitors in particular has raised specific concerns with regards to their potential influence on antibody responses to vaccination. The potential influence of anti-TNF inhibition on the efficacy of influenza vaccination was evaluated in a prospective cohort study involving 149 patients with RA including 50 patients treated with TNF blockers (etanercept or infliximab) in combination with MTX, 62 patients receiving TNF blockers alone or with other DMARDs and 37 patients treated with MTX alone plus 18 healthy controls (Kapetanovic, Saxne et al. 2007). Vaccination with trivalent vaccine resulted in better serological response in RA patients treated with MTX without TNF inhibitors compared with those receiving TNF inhibitors alone or in combination with MTX and/or other DMRDS. Nevertheless, the immune response according to the authors was sufficiently large to warrant influenza vaccination to all RA patients regardless of treatment. Similar results were reported by others (Fomin, Caspi et al. 2006). Equally reassuring were results from studies investigating the efficacy of pmeumococcal vaccine in RA patients receiving anti-TNF therapy. In one study, immune response to 23-valent pneumococcal vaccine was better in patients treated with TNF inhibitors without MTX compared to those treated with TNF inhibitors in combination with MTX or MTX alone. Response rates were 50, 31 and 13% for the TNF inhibition without MTX, TNF inhibition with MTX and MTX groups respectively (Kapetanovic, Saxne et al. 2006). In a different prospective cohort of RA patients receiving either adalimumab or placebo, investigators reported that following pneumococcal vaccination, the percentage of patients achieving a vaccine response were similar in the adalimumab and placebo groups [37.4% and 40.4%, respectively; 95% CI -16.2%, 10.3%]. Equally similar was the percentage of patients with protective antibody titres in both treatment groups (adalimumab: 85.9%, placebo: 81.7%) (Kaine, Kivitz et al. 2007). Thus, anti-TNF therapy should not deter physicians from offering patients with RA vaccination against *H. Influenza* and *S. Pneumoniae*.

3. Conclusions and future directions

TNF-α blockade strategies have revolutionized the treatment RA, raising though safety concerns with regards to increased risk for infections. Although pre-registration clinical trials for TNF inhibitors showed no clear increased risk for infections, long term clinical trials and post registrations studies have shown a small but consistent increase in infection

risk in patients treated with anti-TNF therapy compared to those treated with conventional DMARDs. Common infections involve sites as the respiratory tract, skin and soft tissue and the urinary tract. The risk of *M. tuberculosis* infection also appear to be increased with the use of these agents and is highest during the first 6 months of therapy, most probably reflecting reactivation of latent TB. Screening patients for exposure risks and latent TB prior to the initiation of anti-TNF therapy and administration of standard chemo-prophylaxis has decreased the incidence of new TB cases. Other opportunistic infections such as histoplasmosis, coccidioidomycosis and leishmaniasis may occur following geographical criteria, indicating increased incidence of these illnesses in endemic areas. In view of the increased infectious risk associated with these agents, we should reiterate the importance of efficient pre-treatment screening and close monitoring of patients throughout their treatment. Physicians should be aware of infectious diseases endemic to their geographic area and be vigilant for unusual presentation of symptoms and signs of infectious illnesses. They should stop biologic therapy when these occur, treat those infectious complications promptly and report such cases to regulatory or public health authorities where appropriate. As new biological agents are developed and reach the market place, large scale post marketing surveillance with registry studies and other observational studies will be needed to establish the long term safety profile of these novel therapies.

4. References

Aboulafia, D. M., Bundow, D., Wilske, K., & Ochs, U. I. (2000). Etanercept for the treatment of human immunodeficiency virus-associated psoriatic arthritis. *Mayo Clin Proc*, 75(10), 1093-1098.

Askling, J., & Dixon, W. (2008). The safety of anti-tumour necrosis factor therapy in rheumatoid arthritis. *Curr Opin Rheumatol*, 20(2), 138-144.

Bathon, J. M., Martin, R. W., Fleischmann, R. M., Tesser, J. R., Schiff, M. H., Keystone, E. C., Genovese, M. C., Wasko, M.C., Moreland, L. W., Weaver, A.L., Markenson, J., & Finck, B. K. (2000). A comparison of etanercept and methotrexate in patients with early rheumatoid arthritis. *N Engl J Med*, 343(22), 1586-1593.

Bongartz, T. (2007). Elective orthopedic surgery and perioperative DMARD management: many questions, fewer answers, and some opinions. *J Rheumatol*, 34(4), 653-655.

Bongartz, T., & Orenstein, R. (2009). Therapy: The risk of herpes zoster: another cost of anti-TNF therapy*? Nat Rev Rheumatol*, 5(7), 361-363.

Bongartz, T., Sutton, A. J., Sweeting, M. J., Buchan, I., Matteson, E. L., & Montori, V. (2006). Anti-TNF antibody therapy in rheumatoid arthritis and the risk of serious infections and malignancies: systematic review and meta-analysis of rare harmful effects in randomized controlled trials. *JAMA*, 295(19), 2275-2285.

Breedveld, F. C., Weisman, M. H., Kavanaugh, A. F., Cohen, S. B., Pavelka, K., van Vollenhoven, R., Sharp, J., Perez J. L., & Spencer-Green, G. T. (2006). The PREMIER study: A multicenter, randomized, double-blind clinical trial of combination therapy with adalimumab plus methotrexate versus methotrexate alone or adalimumab alone in patients with early, aggressive rheumatoid arthritis who had not had previous methotrexate treatment. *Arthritis Rheum,* 54(1), 26-37.

Carmona, L., Gomez-Reino, J. J., Rodriguez-Valverde, V., Montero, D., Pascual-Gomez, E., Mola, E. M., Carreno , L., & Figueroa, M. (2005). Effectiveness of recommendations

to prevent reactivation of latent tuberculosis infection in patients treated with tumor necrosis factor antagonists. *Arthritis Rheum*, 52(6), 1766-1772.

Cepeda, E. J., Williams, F. M., Ishimori, M. L., Weisman, M. H., & Reveille, J. D. (2008). The use of anti-tumour necrosis factor therapy in HIV-positive individuals with rheumatic disease. *Ann Rheum Dis*, 67(5), 710-712.

Charpin, C., Guis, S., Colson, P., Borentain, P., Mattei, J. P., Alcaraz, P., Balandraud, N., Thomachot, B., Roudier J., & Gerolami, R. (2009). Safety of TNF-blocking agents in rheumatic patients with serology suggesting past hepatitis B state: results from a cohort of 21 patients. *Arthritis Res Ther*, 11(6), R179.

Choi, H. J., Kim, M. Y., Kim, H. O., & Park, Y. M. (2006). An atypical varicella exanthem associated with the use of infliximab. *Int J Dermatol*, 45(8), 999-1000.

Cohen, C. D., Horster, S., Sander, C. A., & Bogner, J. R. (2003). Kaposi's sarcoma associated with tumour necrosis factor alpha neutralising therapy. *Ann Rheum Dis*, 62(7), 684.

den Broeder, A. A., Creemers, M. C., Fransen, J., de Jong, E., de Rooij, D. J., Wymenga, A., de Waal-Malefijt. M., & van den Hoogen, F. H. (2007). Risk factors for surgical site infections and other complications in elective surgery in patients with rheumatoid arthritis with special attention for anti-tumor necrosis factor: a large retrospective study. *J Rheumatol*, 34(4), 689-695.

Dixon, W. G., Watson, K., Lunt, M., Hyrich, K. L., Silman, A. J., & Symmons, D. P. (2006). Rates of serious infection, including site-specific and bacterial intracellular infection, in rheumatoid arthritis patients receiving anti-tumor necrosis factor therapy: results from the British Society for Rheumatology Biologics Register. *Arthritis Rheum*, 54(8), 2368-2376.

Dobloug, J. H., Forre, O., Kvien, T. K., Egeland, T., & Degre, M. (1982). Natural killer (NK) cell activity of peripheral blood, synovial fluid, and synovial tissue lymphocytes from patients with rheumatoid arthritis and juvenile rheumatoid arthritis. *Ann Rheum Dis*, 41(5), 490-494.

Fomin, I., Caspi, D., Levy, V., Varsano, N., Shalev, Y., Paran, D., Levartovsky, D., Litinsky, I., Kaufman, I., Wigler, I., Mendelson E., & Elkayam, O. (2006). Vaccination against influenza in rheumatoid arthritis: the effect of disease modifying drugs, including TNF alpha blockers. *Ann Rheum Dis*, 65(2), 191-194.

Fox, R. I., Fong, S., Tsoukas, C., & Vaughan, J. H. (1984). Characterization of recirculating lymphocytes in rheumatoid arthritis patients: selective deficiency of natural killer cells in thoracic duct lymph. *J Immunol*, 132(6), 2883-2887.

Furst, D. E. (2010). The risk of infections with biologic therapies for rheumatoid arthritis. *Semin Arthritis Rheum*, 39(5), 327-346.

Furst, D. E., Breedveld, F. C., Kalden, J. R., Smolen, J. S., Burmester, G. R., Dougados, M., Emery, P., Gibofsky, A., Kavanaugh, A. F., Keystone, E. C., Klareskog, L., Russell, A. S., van de Putte, L. B., & Weisman, M. H. (2003). Updated consensus statement on biological agents for the treatment of rheumatoid arthritis and other immune mediated inflammatory diseases (May 2003). *Ann Rheum Dis*, 62 Suppl 2, ii2-9.

Furst, D. E., Schiff, M. H., Fleischmann, R. M., Strand, V., Birbara, C. A., Compagnone, D., Fischkoff, S. A., & Chartash, E. K. (2003). Adalimumab, a fully human anti tumor necrosis factor-alpha monoclonal antibody, and concomitant standard antirheumatic therapy for the treatment of rheumatoid arthritis: results of STAR (Safety Trial of Adalimumab in Rheumatoid Arthritis). *J Rheumatol*, 30(12), 2563-2571.

Furst, D. E., Wallis, R., Broder, M., & Beenhouwer, D. O. (2006). Tumor necrosis factor antagonists: different kinetics and/or mechanisms of action may explain differences in the risk for developing granulomatous infection. *Semin Arthritis Rheum*, 36(3), 159-167.

Galloway, J. B., Hyrich, K. L., Mercer, L. K., Dixon, W. G., Fu, B., Ustianowski, A. P., Watson, K. D., Lunt, M., & Symmons, D. P. (2011). Anti-TNF therapy is associated with an increased risk of serious infections in patients with rheumatoid arthritis especially in the first 6 months of treatment: updated results from the British Society for Rheumatology Biologics Register with special emphasis on risks in the elderly. *Rheumatology (Oxford)*, 50(1), 124-131.

Gardam, M. A., Keystone, E. C., Menzies, R., Manners, S., Skamene, E., Long, R., & Vinh, D. C. (2003). Anti-tumour necrosis factor agents and tuberculosis risk: mechanisms of action and clinical management. *Lancet Infect Dis*, 3(3), 148-155.

Genovese, M. C., Bathon, J. M., Martin, R. W., Fleischmann, R. M., Tesser, J. R., Schiff, M. H., Keystone, E. C., Wasko, M. C., Moreland, L. W., Weaver, A. L., Markenson, J., Cannon, G. W., Spencer-Green, G., & Finck, B. K. (2002). Etanercept versus methotrexate in patients with early rheumatoid arthritis: two-year radiographic and clinical outcomes. *Arthritis Rheum*, 46(6), 1443-1450.

Gerster, J. C., & Dudler, J. (2004). Cellulitis caused by Capnocytophaga cynodegmi associated with etanercept treatment in a patient with rheumatoid arthritis. *Clin Rheumatol*, 23(6), 570-571.

Haerter, G., Manfras, B. J., de Jong-Hesse, Y., Wilts, H., Mertens, T., Kern, P., & Schmitt, M. (2004). Cytomegalovirus retinitis in a patient treated with anti-tumor necrosis factor alpha antibody therapy for rheumatoid arthritis. *Clin Infect Dis*, 39(9), e88-94.

Harris, J., & Keane, J. (2010). How tumour necrosis factor blockers interfere with tuberculosis immunity. *Clin Exp Immunol*, 161(1), 1-9.

Hughes, L. B., Criswell, L. A., Beasley, T. M., Edberg, J. C., Kimberly, R. P., Moreland, L. W., Seldin, M. F., & Bridges, S. L. (2004). Genetic risk factors for infection in patients with early rheumatoid arthritis. *Genes Immun*, 5(8), 641-647.

Jansen, T. L. (2010). When rheumatology meets hepatology: are anti-TNFs safe in hepatitis B virus carriers? *Arthritis Res Ther*, 12(1), 103.

Jimenez, F. G., Colmenero, J. D., & Irigoyen, M. V. (2005). Reactivation of brucellosis after treatment with infliximab in a patient with rheumatoid arthritis. *J Infect*, 50(4), 370-371.

Kaine, J. L., Kivitz, A. J., Birbara, C., & Luo, A. Y. (2007). Immune responses following administration of influenza and pneumococcal vaccines to patients with rheumatoid arthritis receiving adalimumab. *J Rheumatol*, 34(2), 272-279.

Kapetanovic, M. C., Saxne, T., Nilsson, J. A., & Geborek, P. (2007). Influenza vaccination as model for testing immune modulation induced by anti-TNF and methotrexate therapy in rheumatoid arthritis patients. *Rheumatology (Oxford)*, 46(4), 608-611.

Kapetanovic, M. C., Saxne, T., Sjoholm, A., Truedsson, L., Jonsson, G., & Geborek, P. (2006). Influence of methotrexate, TNF blockers and prednisolone on antibody responses to pneumococcal polysaccharide vaccine in patients with rheumatoid arthritis. *Rheumatology (Oxford)*, 45(1), 106-111.

Kaur, P. P., Chan, V. C., & Berney, S. N. (2007). Successful etanercept use in an HIV-positive patient with rheumatoid arthritis. *J Clin Rheumatol*, 13(2), 79-80.

Keane, J., Gershon, S., Wise, R. P., Mirabile-Levens, E., Kasznica, J., Schwieterman, W. D., Siegel, J. N., & Braun, M. M. (2001). Tuberculosis associated with infliximab, a tumor necrosis factor alpha-neutralizing agent. *N Engl J Med*, 345(15), 1098-1104.

Keystone, E. C., Kavanaugh, A. F., Sharp, J. T., Tannenbaum, H., Hua, Y., Teoh, L. S., Fischkoff, S. A., & Chartash, E. K. (2004). Radiographic, clinical, and functional outcomes of treatment with adalimumab (a human anti-tumor necrosis factor monoclonal antibody) in patients with active rheumatoid arthritis receiving concomitant methotrexate therapy: a randomized, placebo-controlled, 52-week trial. *Arthritis Rheum*, 50(5), 1400-1411.

Klareskog, L., van der Heijde, D., de Jager, J. P., Gough, A., Kalden, J., Malaise, M., Martin Mola, E., Pavelka, K., Sany, J., Settas, L., Wajdula, J., Pedersen, R., Fatenejad, S., & Sanda, M. (2004). Therapeutic effect of the combination of etanercept and methotrexate compared with each treatment alone in patients with rheumatoid arthritis: double-blind randomised controlled trial. *Lancet*, 363(9410), 675-681.

Lee, J. H., Slifman, N. R., Gershon, S. K., Edwards, E. T., Schwieterman, W. D., Siegel, J. N., Wise, R. P., Brown, S. L., Udall, Jr J. N., & Braun, M. M. (2002). Life-threatening histoplasmosis complicating immunotherapy with tumor necrosis factor alpha antagonists infliximab and etanercept. *Arthritis Rheum*, 46(10), 2565-2570.

Lipsky, P. E., van der Heijde, D. M., St Clair, E. W., Furst, D. E., Breedveld, F. C., Kalden, J. R., Smolen, J. S., Weisman, M., Emery, P., Feldmann, M., Harriman, G. R., & Maini, R. N. (2000). Infliximab and methotrexate in the treatment of rheumatoid arthritis. Anti-Tumor Necrosis Factor Trial in Rheumatoid Arthritis with Concomitant Therapy Study Group. *N Engl J Med*, 343(22), 1594-1602.

Listing, J., Strangfeld, A., Kary, S., Rau, R., von Hinueber, U., Stoyanova-Scholz, M., Gromnica-Ihle, E., Antoni, C., Herzer, P., Kekow, J., Schneider, M., & Zink, A. (2005). Infections in patients with rheumatoid arthritis treated with biologic agents. *Arthritis Rheum*, 52(11), 3403-3412.

Maini, R., St Clair, E. W., Breedveld, F., Furst, D., Kalden, J., Weisman, M., Smolen, J., Emery, P., Harriman, G., Feldmann, M., & Lipsky, P. (1999). Infliximab (chimeric anti-tumour necrosis factor alpha monoclonal antibody) versus placebo in rheumatoid arthritis patients receiving concomitant methotrexate: a randomised phase III trial. ATTRACT Study Group. *Lancet*, 354(9194), 1932-1939.

Maini, R. N., Breedveld, F. C., Kalden, J. R., Smolen, J. S., Furst, D., Weisman, M. H., St Clair, E. W., Keenan, G. F., van der Heijde, D., Marsters, P. A., & Lipsky, P. E. (2004). Sustained improvement over two years in physical function, structural damage, and signs and symptoms among patients with rheumatoid arthritis treated with infliximab and methotrexate. *Arthritis Rheum*, 50(4), 1051-1065.

Marotte, H., Fontanges, E., Bailly, F., Zoulim, F., Trepo, C., & Miossec, P. (2007). Etanercept treatment for three months is safe in patients with rheumatological manifestations associated with hepatitis C virus. *Rheumatology* (Oxford), 46(1), 97-99.

Mitchell, D. M., Spitz, P. W., Young, D. Y., Bloch, D. A., McShane, D. J., & Fries, J. F. (1986). Survival, prognosis, and causes of death in rheumatoid arthritis. *Arthritis Rheum*, 29(6), 706-714.

Mohan, V. P., Scanga, C. A., Yu, K., Scott, H. M., Tanaka, K. E., Tsang, E., Tsai, M. M., Flynn, J. L., & Chan, J. (2001). Effects of tumor necrosis factor alpha on host immune

response in chronic persistent tuberculosis: possible role for limiting pathology. *Infect Immun*, 69(3), 1847-1855.

Montero, J. A., Ruiz-Moreno, J. M., Rodriguez, A. E., Ferrer, C., Sanchis, E., & Alio, J. L. (2006). Endogenous endophthalmitis by Propionibacterium acnes associated with leflunomide and adalimumab therapy. *Eur J Ophthalmol*, 16(2), 343-345.

Parke, F. A., & Reveille, J. D. (2004). Anti-tumor necrosis factor agents for rheumatoid arthritis in the setting of chronic hepatitis C infection. *Arthritis Rheum*, 51(5), 800-804.

Salliot, C., Dougados, M., & Gossec, L. (2009). Risk of serious infections during rituximab, abatacept and anakinra treatments for rheumatoid arthritis: meta-analyses of randomised placebo-controlled trials. *Ann Rheum Dis*, 68(1), 25-32.

Schiff, M. H., Burmester, G. R., Kent, J. D., Pangan, A. L., Kupper, H., Fitzpatrick, S. B., & Donovan, C. (2006). Safety analyses of adalimumab (HUMIRA) in global clinical trials and US postmarketing surveillance of patients with rheumatoid arthritis. *Ann Rheum Dis*, 65(7), 889-894.

Shale, M. J., Seow, C. H., Coffin, C. S., Kaplan, G. G., Panaccione, R., & Ghosh, S. (2010). Review article: chronic viral infection in the anti-tumour necrosis factor therapy era in inflammatory bowel disease. *Aliment Pharmacol Ther*, 31(1), 20-34.

Sipsas, N. V., Papaparaskevas, J., Stefanou, I., Kalatzis, K., Vlachoyiannopoulos, P., & Avlamis, A. (2006). Septic arthritis due to Roseomonas mucosa in a rheumatoid arthritis patient receiving infliximab therapy. *Diagn Microbiol Infect Dis*, 55(4), 343-345.

Smitten, A. L., Choi, H. K., Hochberg, M. C., Suissa, S., Simon, T. A., Testa, M. A., & Chan, K. A. (2007). The risk of herpes zoster in patients with rheumatoid arthritis in the United States and the United Kingdom. *Arthritis Rheum*, 57(8), 1431-1438.

St Clair, E. W., van der Heijde, D. M., Smolen, J. S., Maini, R. N., Bathon, J. M., Emery, P., Keystone, E., Schiff, M., Kalden, J. R., Wang, B., Dewoody, K., Weiss, R., & Baker, D. (2004). Combination of infliximab and methotrexate therapy for early rheumatoid arthritis: a randomized, controlled trial. *Arthritis Rheum*, 50(11), 3432-3443.

Strangfeld, A., Listing, J., Herzer, P., Liebhaber, A., Rockwitz, K., Richter, C., & Zink, A. (2009). Risk of herpes zoster in patients with rheumatoid arthritis treated with anti-TNF-alpha agents. *JAMA*, 301(7), 737-744.

Symmons, D. P., Jones, M. A., Scott, D. L., & Prior, P. (1998). Longterm mortality outcome in patients with rheumatoid arthritis: early presenters continue to do well. *J Rheumatol*, 25(6), 1072-1077.

Torre-Cisneros, J., Del Castillo, M., Caston, J. J., Castro, M. C., Perez, V., & Collantes, E. (2005). Infliximab does not activate replication of lymphotropic herpesviruses in patients with refractory rheumatoid arthritis. *Rheumatology* (Oxford), 44(9), 1132-1135.

Tubach, F., Ravaud, P., Salmon-Ceron, D., Petitpain, N., Brocq, O., Grados, F., Guillaume, J. C., Leport, J., Roudaut, A., Solau-Gervais, E., Lemann, M., Mariette, X., & Lortholary, O. (2006). Emergence of Legionella pneumophila pneumonia in patients receiving tumor necrosis factor-alpha antagonists. *Clin Infect Dis*, 43(10), e95-100.

van de Putte, L. B., Atkins, C., Malaise, M., Sany, J., Russell, A. S., van Riel, P. L., Settas, L., Bijlsma, J. W., Todesco, S., Dougados, M., Nash, P., Emery, P., Walter, N., Kaul, M., Fischkoff, S., & Kupper, H. (2004). Efficacy and safety of adalimumab as monotherapy in patients with rheumatoid arthritis for whom previous disease modifying antirheumatic drug treatment has failed. *Ann Rheum Dis*, 63(5), 508-516.

van der Heijde, D., Klareskog, L., Rodriguez-Valverde, V., Codreanu, C., Bolosiu, H., Melo-Gomes, J., Tornero-Molina, J., Wajdula, J., Pedersen, R., & Fatenejad, S. (2006). Comparison of etanercept and methotrexate, alone and combined, in the treatment of rheumatoid arthritis: two-year clinical and radiographic results from the TEMPO study, a double-blind, randomized trial. *Arthritis Rheum*, 54(4), 1063-1074.

van Riel, P. L., Taggart, A. J., Sany, J., Gaubitz, M., Nab, H. W., Pedersen, R., Freundlich, B., & MacPeek, D. (2006). Efficacy and safety of combination etanercept and methotrexate versus etanercept alone in patients with rheumatoid arthritis with an inadequate response to methotrexate: the ADORE study. *Ann Rheum Dis*, 65(11), 1478-1483. 10.1136/ard.2005.043299

Vassilopoulos, D., Apostolopoulou, A., Hadziyannis, E., Papatheodoridis, G. V., Manolakopoulos, S., Koskinas, J., Manesis, E. K., & Archimandritis, A. I. (2010). Long-term safety of anti-TNF treatment in patients with rheumatic diseases and chronic or resolved hepatitis B virus infection. *Ann Rheum Dis*, 69(7), 1352-1355.

Vonkeman, H., ten Napel, C., Rasker, H., & van de Laar, M. (2004). Disseminated primary varicella infection during infliximab treatment. *J Rheumatol*, 31(12), 2517-2518.

Wallis, R. S., Broder, M. S., Wong, J. Y., Hanson, M. E., & Beenhouwer, D. O. (2004). Granulomatous infectious diseases associated with tumor necrosis factor antagonists. *Clin Infect Dis*, 38(9), 1261-1265.

Weinblatt, M. E., Keystone, E. C., Furst, D. E., Kavanaugh, A. F., Chartash, E. K., & Segurado, O. G. (2006). Long term efficacy and safety of adalimumab plus methotrexate in patients with rheumatoid arthritis: ARMADA 4 year extended study. *Ann Rheum Dis*, 65(6), 753-759.

Weinblatt, M. E., Keystone, E. C., Furst, D. E., Moreland, L. W., Weisman, M. H., Birbara, C. A., Teoh, L. A., Fischkoff, S. A., & Chartash, E. K. (2003). Adalimumab, a fully human anti-tumor necrosis factor alpha monoclonal antibody, for the treatment of rheumatoid arthritis in patients taking concomitant methotrexate: the ARMADA trial. *Arthritis Rheum*, 48(1), 35-45.

Wendling, D., Streit, G., Toussirot, E., & Prati, C. (2008). Herpes zoster in patients taking TNFalpha antagonists for chronic inflammatory joint disease. *Joint Bone Spine*, 75(5), 540-543.

Winthrop, K. L., & Chiller, T. (2009). Preventing and treating biologic-associated opportunistic infections. *Nat Rev Rheumatol*, 5(7), 405-410.

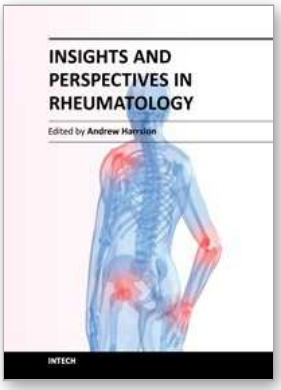
Wolfe, F., Michaud, K., & Chakravarty, E. F. (2006). Rates and predictors of herpes zoster in patients with rheumatoid arthritis and non-inflammatory musculoskeletal disorders. *Rheumatology (Oxford)*, 45(11), 1370-1375. 10.1093/rheumatology/kel328

Xynos, I. D., Tektonidou, M. G., Pikazis, D., & Sipsas, N. V. (2009). Leishmaniasis, autoimmune rheumatic disease, and anti-tumor necrosis factor therapy, Europe. *Emerg Infect Dis*, 15(6), 956-959.

Young, C. L., Adamson, T. C., 3rd, Vaughan, J. H., & Fox, R. I. (1984). Immunohistologic characterization of synovial membrane lymphocytes in rheumatoid arthritis. *Arthritis Rheum*, 27(1), 32-39.

Zein, N. N. (2005). Etanercept as an adjuvant to interferon and ribavirin in treatment-naive patients with chronic hepatitis C virus infection: a phase 2 randomized, double-blind, placebo-controlled study. *J Hepatol*, 42(3), 315-322.

Zingarelli, S., Frassi, M., Bazzani, C., Scarsi, M., Puoti, M., & Airo, P. (2009). Use of tumor necrosis factor-alpha-blocking agents in hepatitis B virus-positive patients: reports of 3 cases and review of the literature. *J Rheumatol*, 36(6), 1188-1194.



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This book offers a range of perspectives on pathogenesis, clinical features and treatment of different rheumatic diseases, with a particular focus on some of the interesting aspects of Sjögren's syndrome. It contains detailed and thorough reviews by international experts, with a diverse range of academic backgrounds. It will also serve as a useful source of information for anyone with a passive interest in rheumatology, from the genetic and molecular level, through to the psychological impact of pain and disability.

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