Safety of Anti-Tumor Necrosis Factor Therapies in Arthritis Patients

Radu M. Nanau[1] and Manuela G. Neuman[1,2]

[1]*In Vitro* Drug Safety and Biotechnology and [2]Department of Pharmacology and Toxicology, Faculty of Medicine, University of Toronto, Toronto, Ontario, Canada

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ABSTRACT - Purpose. Inflammatory and rheumatic arthritis remain leading causes of disability worldwide. The arthritis therapeutic area commands the largest market for the prescription of biological and non-steroidal anti-inflammatory drugs (NSAID). Yet biotechnology and pharmaceutical companies conducting research and providing therapeutics in this area frequently face challenges in patient safety. The purpose of our study was to assess safety of anti-tumor necrosis factor therapies in arthritis patients. **Methods**: The present study systematically reviews adverse events of biologicals alone or in the presence of NSAIDs and other immunosuppressant therapeutics such as disease-modifying antirheumatic drugs (DMARD). We assessed the rheumatology literature that included clinical trials with anti-tumor necrosis factor (TNF) biologicals and case reports published between 2010 and 2014. **Results**: Currently approved anti-TNF biologicals in arthritis include the monoclonal antibodies infliximab, adalimumab, certolizumab pegol and golimumab, and the fusion protein etanercept. The most frequently-reported adverse event was infection. We grouped the adverse reactions as immune-mediated, hypersensitivity syndrome reactions including cutaneous and hepatic manifestation, neurological, hematological, and malignancy. **Discussion**: Most adverse events are due to the failure of host immunological control, which involves susceptibility to the drug itself, or *de novo* infection or reactivation of a latent bacterial or viral infection, often with a different expression of disease. Drug-induced liver injury associated with anti-TNF biologicals must be kept in mind when evaluating patients with increased liver enzymes. **Conclusion**: Risk assessment in individuals undergoing treatment with biologicals represents a step towards achieving a personalized medicine approach to identify those patients that will safely benefit from this therapeutic approach. Patients and physicians must be alert of anti-TNF agents as potential causes of drug-induced liver injury and monitor the therapies. Personalizing therapeutic pharmacovigilance promises to optimize benefits while minimizing side effects.

ABBREVIATIONS

ADA - anti-drug antibody
AE - adverse event
ADM - adalimumab
ALP - alkaline phosphatase
ALT - alanine aminotransferase
ANA - antinuclear antibody
anti-dsDNA - anti-double-stranded DNA antibody
AST - aspartate aminotransferase
AS - ankylosing spondylitis
CNS - central nervous system
CSF - cerebrospinal fluid
CZP - certolizumab pegol
DILI - drug-induced liver injury
DMARD - disease-modifying anti-rheumatic drug
ETN - etanercept
γ-GTP - γ-glutamyl transpeptidase
GLM - golimumab
HBV - hepatitis B virus
IFX - infliximab
ILD - interstitial lung disease
JIA - juvenile idiopathic arthritis
LFT - liver function test
MTX - methotrexate
NSAID - non-steroidal anti-inflammatory drug
PML - progressive multifocal leukoencephalopathy
RA - rheumatoid arthritis
RF - rheumatoid factor
TB - tuberculosis
Th - T helper
TNF - tumor necrosis factor

Correspondence Author: Manuela Neuman PhD, Asst. Professor of Pharmacology, Biophysics and Associated International Health, Department of Pharmacology and Toxicology, *In Vitro* Drug Safety and Biotechnology, Banting Institute, 100 College Street, Lab 217, Toronto, ON, CANADA, M5G 1L7 Tel: 416-398-4880
Email: manuela.neuman@utoronto.ca

INTRODUCTION

The intracellular destruction of pathogens by phagocytes provides the first line of defense against bacterial and viral infections. The apoptosis of phagocytic macrophages induces pro-inflammatory cytokines, leukotriene and prostaglandins that localize the infection at the site of entry. The attraction of leukocytes to tissues is essential for inflammation. The process is controlled by chemokines, which have an important role in the pathophysiology of inflammatory diseases. Tumor necrosis factor (TNF)-α is a pivotal cytokine that acts upon both the innate and the adaptive immune systems (1-3). At the same time, cytokines and chemokines represent potential targets for therapy. Cytokine technology uses human receptor elements linked to functional proteins to create potent soluble inhibitors of cytokine function.

There is a multitude of potential drug targets in the human autoimmune diseases field, which creates a great opportunity to reverse or prevent inflammation-induced tissue damage. Exposure to anti-TNF therapeutics impairs the production of T helper (Th) 1 cytokines. In patients with rheumatoid arthritis (RA), therapeutic intervention with anti-TNF biologicals restores the low proliferative responses of peripheral blood mononuclear to mitogens, thus suggesting reversibility of this process. Treatment with anti-TNF biologicals in RA led to accumulation of Th1 $CD4^+$ T cells in peripheral blood (4). Occasionally, treatment with anti-TNF biologicals in RA increased peripheral T cell reactivity to several microbial antigens with a significant increase in the production of interferon (5). In inflammatory rheumatic diseases, the pro-inflammatory effects of cytokines lead to inflammation, while the anti-inflammatory effects of biologicals at the level of the cartilage and osteocytes re-establish the balance between the pro- and anti-inflammatory messages. At the same time, there is a significant need for rapid target validation and post-market pharmacovigilance studies.

Clinically, TNF-α inhibitors have shown efficacy in inflammatory and autoimmune disorders. However, by increasing the reactivity of peripheral T cells to specific antigens, TNF-α also stimulates the antimicrobial defense mechanism (6). TNF-α is a key cytokine in the defense system against infectious diseases, and the efficacy of TNF-α inhibitors is paralleled by susceptibility to a variety of infections (7-9). Most reports to date have described increased susceptibility to intracellular pathogens in patients with underlying chronic infections. TNF-α-mediated pathways regulate the molecular interactions between cellular and viral factors within cells. Failure of host immunological control involves reactivation of latent infections. Nonetheless, TNF-α inhibitors have displayed a reasonable safety profile in the setting of some chronic viral infections, and in certain circumstances have demonstrated adjunctive activity in the treatment of these infections. Given the high prevalence of chronic viral infections in patients who are candidates for anti-TNF therapy and the potential for these agents in the treatment of chronic illness, additional studies are needed to assess the risks and benefits of such therapy in the individuals exposed to biologicals. While clinical trials of biologicals in RA note only slight infections, post-marketing analysis has clearly demonstrated an increased susceptibility to infections, especially those caused by *Mycobacterium tuberculosis* (8).

The aims of this review are to discuss adverse events (AE) in patients with RA, ankylosing spondylitis (AS) and juvenile idiopathic arthritis (JIA) treated with one of the four anti-TNF monoclonal antibodies infliximab (IFX, Remicade®, Janssen Biotech, Inc.), adalimumab (ADM, Humira®, AbbVie, Inc.), certolizumab pegol (CZP, Cimzia®, UCB, Inc.) golimumab (GLM, Simponi®, Janssen Biotech, Inc.), or the fusion protein etanercept (ETN, Enbrel®, Amgen, Inc.). AEs discussed include infections, infusion-related reactions, immune-mediated reactions, autoimmune AEs, hematological AEs, neurological AEs, as well as adverse drug reactions affecting the liver and the lungs. The association between cancer and anti-TNF biologicals in patients with immune-mediated inflammatory arthritis is also presented.

MATERIALS AND METHODS

The present study systematically reviews adverse events of biologicals alone or in the presence of NSAIDs and other immunosuppressant therapeutics such as DMARDs. We carried out a comprehensive search on Medline. We used Ovid and PubMed mesh database. Additionally, we assessed the rheumatology literature that included clinical trials with anti-TNF biologicals and case reports

published between 2010 and 2014.

Incidence rates of AEs are compiled from data reported in clinical trials of individuals with RA, AS or JIA using the terms "infliximab", "adalimumab", "etanercept", "certolizumab" or "golimumab," and "clinical trial". Further searches were performed for each section separately in order to get a more detailed picture of the AEs under investigation, using terms such as "infection," "hypersensitivity", "anaphylaxis", "cutaneous", "allergy", "lupus", "autoimmune," "rash," "neurological", "neuropathy", "demyelinating," "progressive multifocal leukoencephalopathy," "cytopenia", "anemia", "leukopenia", "neutropenia", "thrombocytopenia", "granulocytopenia," "pancytopenia," "lung", "respiratory", "interstitial," "pulmonary," "liver failure," "hepatotoxicity," "hepatitis," "cardiac failure," "malignancy," "cancer" or "neoplasm," along with the name of each drug. Inclusion criteria were studies performed in human patients with rheumatic conditions treated with anti-TNF agents published between 2010-present. Nevertheless, there are limitations in the interpretation, since data collection by various centers may introduce great variability in the outcomes. Moreover, there is patient heterogeneity depending on the inclusion/exclusion criteria of the study, as well as, the variants taken into analysis or the aim of the study. An additional source of variability is the statistical methods used especially in clinical trials. Thus, the data interpretation differs from one publication to the other.

Adverse Events

The rate of AEs in patients with inflammatory arthritis treated with anti-TNF biologicals in placebo-controlled clinical trials are shown in Table 1. Different treatment regimens included anti-TNF biologicals or the DMARD like methotrexate (MTX), in combination with placebo or with one another. The main AEs of IFX were infections, infusion reactions and abnormalities in hepatic enzymes levels, while the presence of anti-drug antibodies (ADA) and autoantibodies like antinuclear antibodies (ANA) and anti-double-stranded DNA (anti-dsDNA) antibodies was associated with a loss of efficacy and a higher risk of AEs. Incidence of AEs were similar between IFX and placebo in patients co-treated with MTX, with a trend towards higher incidences of infections and infusion reactions between IFX monotherapy and placebo (10-15). For ETN, the main AEs were infections, abnormalities in hepatic enzymes levels, neutropenia and infusion reactions. The rates of AEs were similar between patients treated with ETN or with MTX. Infusion reactions occurred more frequently during ETN injections compared to placebo injections (16-19). The main AEs of ADM were infections and infusion reactions. The incidence of infusion reactions was higher for ADM than placebo (20). Rates of serious AEs were low in CZP patients. A trend towards higher odds of developing serious AEs was noted for CZP compared to placebo, primarily due to higher odds of serious infections, regardless of MTX co-treatment (21-23). A dose-dependent trend towards higher rates of AEs was observed in patients treated with GLM, owing particularly to higher rates of infusion reactions and serious infections (24-26). These were consistent with the warnings included in the product information of the drugs (27-31).

Infections

Anti-TNF biologicals are recognized as risk factors for serious infections (27-31). Anti-TNF biologicals (especially IFX and ADM) are disproportionately associated with infections in the French research axed on tolerance of biotherapies registry and the Portuguese spontaneous reporting database (32, 33). In RA cohorts specifically, IFX use was a risk factor for opportunistic infections compared to ETN and MTX (32, 34). Concomitant immunosuppressant treatment, especially steroids, represents an additional risk factor for opportunistic infections among patient receiving anti-TNF treatment (32, 34).

While similar patterns were reported in these studies, the individual odds ratios of developing infections varied, as they included patients of different ethnic backgrounds from different areas of the world, patients with RA exclusively or patients with any condition treated by anti-TNF biologicals, as well as different treatment regimens depending on dose, frequency or physician preference. Adherence to several guidelines can help lead to a safer anti-TNF treatment course (35). These include screening for active or latent tuberculosis (TB), as well as vaccination against hepatitis B virus (HBV), varicella zoster virus, annual influenza, and human papilloma virus in young females. Opportunistic

bacterial and fungal infections have been documented, some with serious AEs (35).

Tuberculosis

Reactivation of latent TB or *de novo* TB infection is one of the most important infectious AEs in patients treated with anti-TNF biologicals. In patients, treatment with anti-TNF biologicals (IFX, ADM or ETN) increased the risk of developing TB compared to the general population (36-38). Rates of TB were also higher in RA patients not exposed to anti-TNF treatment compared to the general population (38). Among patients treated with anti-TNF biologicals, IFX and ADM carry risks similar to one another, while monoclonal antibodies are associated with higher odds of developing TB than ETN (39, 40).

As over one third of the world population may carry latent TB infection which can lead to active disease, especially under conditions of immunosuppression, it is important to detect and treat this infection prior to commencing anti-TNF treatment (41, 42). Guidelines for TB screening in future anti-TNF patients include detailed clinical history, physical examination, chest radiograph, and a tuberculin skin test (43). Exposure to anti-TNF biologicals increased the risk of developing active TB in a Taiwanese RA sample with a low incidence of TB screening (44). In contrast, screening excluded TB with a high degree of certainty (sensitivity 0.83, specificity 0.74, positive predictive value 0.29 and negative predictive value 0.97) in a small sample of patients with inflammatory rheumatic diseases treated with anti-TNF biologicals in an area with a high endemic rate (45). Among patients born in regions with low endemic TB rates, being a healthcare worker might be a risk factor of contacting the disease (46). *De novo* contamination was also observed in patients receiving anti-TNF treatment when coming into contact with infected individuals or traveling to regions with high endemic rates (47).

Non-tuberculosis Bacteria and Fungi

Non-TB bacterial infections include non-TB mycobacteriosis, listeriosis, legionellosis, staphylococcemia, salmonellosis, nocardiosis and pneumocystosis, with presentations including cutaneous manifestations, pulmonary presentation (predominantly pneumonia) and neurological manifestations (predominantly meningitis). Anti-TNF biologicals were risk factors for non-TB mycobacterial diseases compared to both RA patients not treated with these agents and to the general population. IFX and ADM were risk factors compared to ETN. RA was a risk factor among non-users of anti-TNF biologicals compared to the general population, while older age and RA were risk factors for non-TB mycobacterial disease among anti-TNF users (38). Treatment with anti-TNF biologicals is a risk factor for cutaneous infections. Skin infections generally only have cutaneous manifestations, but may also present systemic features such as fever (48).

The risks of developing *Legionella pneumophila* or *Listeria monocytogenes* infections were also higher among anti-TNF treated patients compared to the general population in European samples (36, 49, 50), while IFX or ADM use was a risk factor for legionellosis compared to ETN (50).

Fungal infections include pneumocystosis, histoplasmosis, aspergillosis, cryptococcosis, candidiasis, actinomycosis, blastomycosis and coccidioidosis, with predominantly pulmonary presentation. In a comprehensive review of the MEDLINE and PubMed databases, invasive fungal infections associated with IFX occurred after a median 55 days and a median 3 infusions after initiating treatment, while occurring after a median 144 days in ETN patients. Invasive fungal infections in anti-TNF patients were lethal in 32.2% of the cases in which outcome was available (51).

Pneumocystis jirovecii colonization was detected in 25.6% of RA, AS and psoriatic arthritis patients treated with anti-TNF biologicals, of which half occurred with IFX. Risk factors include corticosteroids use, MTX use and IFX duration of >3 years (52). The onset of *Pneumocystis* pneumonia in the Food and Drug Administration Adverse Event Reporting System database occurred after a mean 21 ± 18 days since starting IFX, and after a mean 2.1 ± 1.3 IFX infusions. *Pneumocystis* pneumonia resulted in death in 27.4% of these cases (53). IFX was also a risk factor for coccidioidomycosis in a sample of inflammatory arthritis patients. The cumulative incidence of coccidioidomycosis in this sample was 1.1% (2.8% among IFX patients and 0.5% among patients receiving other medications) (54).

Viruses

Viral infections include HBV, cytomegalivirus,

varicella zoster virus, herpes simplex virus, Epstein-Barr virus, and John Cunningham virus. In these cases, the affected organs are those in which the virus proliferates predominantly. Viruses are the predominant infections in pediatric and adolescent JIA patients, suggesting likely childhood diseases such as infections by members of the herpes virus family (55).

The main concern regarding viral infections in anti-TNF patients is infections and reactivation of HBV. As such, anti-TNF biologicals should be avoided in chronic HBV infection, classified as positive by the presence of HBV surface antigen, and in resolved HBV infection, classified as positive by the presence of anti-HBV core and/or anti-HBV surface antibodies (56). Treatment with anti-TNF was a risk factor for HBV seroconversion in a sample of RA patients (57). ADM was associated with a low HBV risk in an RA population, which could mean either that ADM suppresses HBV reactivation, or that ADM is not used out of concern in individuals with a high risk of HBV infection (58). While a diagnosis of RA was a risk factor for slightly elevated aspartate aminotransferase (AST) and alanine aminotransferase (ALT) in an RA sample with pre-existing HBV infection, these did not exceed the upper limit of normal (59). Viral reactivation was not observed in small samples of RA patients with resolved HBV infection treated with anti-TNF agents (60, 61).

Monoclonal antibodies were risk factors for varicella zoster virus infections compared to ETN (62). IFX or ETN were not risk factors for Epstein-Barr viremia in peripheral blood mononuclear cells in RA patients. Instead, a positive correlation was observed between Epstein-Barr viral load and disease activity in RA patients (63).

Parasites

The main parasitic infection is leishmaniasis (*Leishmania sp.*), which generally includes visceral or cutaneous presentation. Also infection with *Strongyloides stercoralis* with pulmonary and gastrointestinal symptoms are described (32).

Infusion Reactions

Anti-TNF biologicals are disproportionately associated with general disorders and administration site conditions in the Portuguese spontaneous reporting database (33). Infusion reactions accounted for 257 of 920 (27.9%) cutaneous AEs reported in a large sample of patients with chronic inflammatory rheumatic conditions treated with IFX, ADM or ETN, including erythema, urticaria, eczema or rash, which can be accompanied by pain and swelling. Such reactions occur with all anti-TNF biologicals, primarily in the first month of treatment (48, 64).

Monoclonal antibodies are structurally immunonegenic as they contain sections that can be recognized by the immune system as non-self epitopes, leading to the production of specific ADAs (65). The presence of IgE ADAs was associated with acute infusion reactions in IFX patients (66). Anaphylaxis is an example of acute infusion reaction. The most commonly accepted mechanism of anaphylaxis reaction involves IgE-mediated type I acute hypersensitivity. This hypersensitivity reaction is characterized by the release of mediators from mast cells, basophils and recruited inflammatory cells. Symptoms of anaphylaxis can occur between a few minutes to a few hours after exposure to the drug, and can include any combination of cutaneous, cardiovascular, respiratory distress, laryngeal edema and severe bronchospasm, gastrointestinal and neurologic/muscular symptoms, and severe hypotension (65, 67, 68).

IgE ADAs were also significantly associated with positive skin tests results in patients with previous immediate hypersensitivity reaction to IFX. In turn, skin tests positivity was also associated with early and severe reactions. These results support the hypothesis that infusion reactions to IFX are IgE-mediated, while skin tests with IFX preparations provide a predictive tool for these AEs (69, 70). This was demonstrated in a study in which positive skin tests were reported in all cases of urticaria and in 5 of 8 cases of anaphylaxis. The remaining 3 of 8 cases of anaphylaxis occurred at the first dose, suggesting non-IgE anaphylaxis (69). These are also known as anaphylactoid reactions. Anaphylactoid reactions have symptoms similar to anaphylaxis reactions, but occur in an IgE-independent manner (65, 67).

An overall rate of acute infusion reactions of 5.8% was observed in a retrospective analysis of 135 RA patients treated with IFX over a 9 years period (71). In this study, most infusion reactions were mild or moderate in intensity, and most

occurred early during IFX treatment. The areas most commonly affected by acute infusion reactions were the neck and the head, followed by the skin. The most common of these were pruritis, headache, facial flushing and chest tightness (71). The most common delayed infusion reactions, occurring 1-14 days post-infusion, were moderate in severity, and included chest/respiratory symptoms, general manifestations and skin manifestations. These occurred after a mean 7.2 days. Most delayed infusion reactions also occurred during the early phases of treatment (71).

Risk factors for acute hypersensitivity reactions in patients treated with anti-TNF monoclonal antibodies include patient-specific factors such as disease, atopic phenotype and concomitant use of immunosuppressants, as well as drug-specific factors such as dose, duration, number of infusions and route of administration. The highest rate of IFX infusion reactions was found in RA patients, suggesting that infusion reactions may be, at least in part, mediated by the same mechanisms as the disease itself. While immunosuppressants may help limit the development of ADAs and thus of infusion reactions, the role of prophylaxis with acetaminophen and antihistamines is less clear. The dose and frequency of IFX administration are closely related to ADAs formation, and thus with infusion reactions, as ADAs develop primarily in patients receiving lower doses or intermittent treatment (65, 67).

Infusion reactions are detailed in Table 2. Drug intolerance with cutaneous manifestations and swelling, and occasionally dyspnea and tachycardia, are reported in several patients with infusion reactions (72-81). Cardiopulmonary arrest accompanied a case of severe IFX anaphylaxis (82). Allergic hypereosinophilia is described elsewhere (83).

Desensitization was performed in a series of patients with clinically-observed hypersensitivity reactions to anti-TNF biologicals and positive skin tests. A standard 12-step protocol was used for desensitization, involving the administration of increasing doses at 15 min intervals. Manifestations occurring during desensitization were less frequent and less severe in nature. In cases in which hypersensitivity occurred during desensitization, patient-specific modifications were made to the protocol, usually involving the administration of antihistamines, and the protocol was repeated (68). ADM desensitization was performed using gradually increasing doses ranging from 5 to 15 mg at a time. Dose escalations occurred every 30 min, for a cumulative dose of 40 mg. The 40 mg were administered quicker using larger doses during subsequent infusions, and ADM was accompanied by antihistamines and antileukotrienes during the first 4 treatment sessions (79).

Immune System Disorders

Immune system disorders encompass AEs in which the immune system overreacts to non-threatening foreign substances or against the body's own tissues. Anti-TNF biologicals are disproportionately associated with immune system disorders (33). Anti-TNF biologicals are associated with autoimmune disorders, particularly cutaneous disorders, drug-induced psoriasis, inflammatory bowel disease and autoimmune hepatitis (64, 84, 85). Immune system disorders described in recent case reports are detailed in Table 3.

Immune-mediated Reactions

Immune-mediated reactions include lichenoid eruptions, in which infiltration between the epidermis and dermis was shown by biopsy (86-88), vasculitis (87, 89-93), a case of recurrent subacute prurigo with eosinophilia is also described (94), a case of Stevens-Johnson syndrome characterized by abdominal desquamation (95), a case of pustular dermatitis (96), dermatomyositis (97, 98), and a case of morphea (99).

Autoimmune Adverse Events

Lupus-like syndrome is a common autoimmune AE. The incidence of lupus-like syndrome was 1.75% in a small sample of spondyloarthritis patients treated with IFX, ADM or ETN (100). Specifically, the incidence of IFX-induced systemic lupus erythematosus was 1.3% in a recent systematic review (101). A high incidence of autoantibodies including ANAs, anti-dsDNA antibodies, anticardiolipin antibodies, anti-histone antibodies, anti-nucleosome antibodies and anti-neutrophil cytoplasmic antibodies positivity was noted in these patients (100, 101). Several recent case reports describe drug-induced lupus in patients treated with anti-TNF biologicals (102-112). While manifestations were varied, a common feature was

the presence of autoantibodies. Levels of autoantibodies decreased after discontinuation of anti-TNF biologicals in most patients, and even returned to normal in some (102). Autoantibodies were negative in a patient diagnosed with discoid lupus erythematosus (112).

The first step in the treatment of drug-induced systemic lupus erythematosus is the discontinuation of the offending drug, while treatment with corticosteroids and immunosuppressive agents may be required to achieve full symptoms resolution (113). The pathogenesis of systemic lupus erythematosus is believed to involve a shift from Th1 cytokines towards Th2 cytokines, brought about by TNF-α inhibition with anti-TNF biologicals. This cytokines shift is then thought to bring about the production of autoantibodies and the development of systemic lupus erythematosus. Alternatively, TNF-α inhibition prevents apoptosis through decreased CD44 production, preventing the clearance of nuclear debris and apoptotic neutrophils, and thus promoting the production of antibodies against DNA and nuclear components (113).

Another common autoimmune AE of anti-TNF biologicals is drug-induced psoriasis. This was recently described in a review of the literature and of the French pharmacovigilance database. The majority of cases involved pustular lesions. The most commonly affected sites were the palms and/or soles. All of IFX, ADM and ETN were involved, with IFX accounting for more cases than the other two drugs. Recurrence of psoriasis can occur at the same location as the initial reaction or at a different site. It can further occur with a different anti-TNF biological (114).

Ten cases of psoriasiform eruptions are described in patients with inflammatory arthritis (RA and spondylo-arthropathy) treated with ETN or ADM. The condition presented pustular, plaque or guttate morphology. Plantar plaques or pustules are described in 4 of 10 (40.0%) cases. Nail involvement was not observed. Topical treatment was provided in 4 of 10 (40.0%) cases. The initial anti-TNF biological was interrupted in 8 of 10 (80.0%) cases. Among these, switching to a different anti-TNF biological led to either no improvement or only partial improvement. Further stopping anti-TNF biologicals led to complete symptoms resolution, or at least partial improvement of psoriasiform eruptions. Partial improvement was obtained with topical ointments without modifying treatment in the remaining 2 of 10 (20.0%) cases (115). Psoriasis lesions are also described in several recent case reports (87, 107, 116-121).

Autoimmune AEs with cutaneous manifestations also included intermediate bullous and cicatricial pemphigoid (122) and granuloma annulare (123). Other autoimmune AEs in patients treated with anti-TNF biologicals included *de novo* or exacerbation of autoimmune hepatitis (124-128) and antiphospholipid syndrome (129, 130). IFX is believed to lead to the unmasking of autoimmune hepatitis by binding to transmembrane TNF on the cell surface, thus inducing apoptosis and leading to the release of nucleosomes (131).

Neurological Adverse Events

The majority of neurological AEs reported in relation to IFX, ADM, CZP or ETN in the Food and Drug Administration Adverse Event Reporting System occurred in RA patients, with 393 of 772 (50.9%) events over a 10 years period. ETN and IFX were associated with the majority of these events (132). In RA patients specifically, the most common neurological AEs were central nervous system (CNS)/spinal demyelination, optic neuritis, peripheral neuropathy and facial palsy, with low incidences of transverse myelitis, leukoencephalopathy, other demyelinating disease, cerebrovascular disease, encephalopathy and CNS infections (132). Neurological adverse events are described in Table 4.

Among 33 reports of demyelinating disorders in French patients with rheumatic diseases treated with anti-TNF biologicals over a 3 years period, IFX was used in 15 (45.4%) patients, ETN in 12 (36.4%) and ADM in 6 (18.2%). Two thirds of these cases involved the CNS (encephalic involvement, transverse myelitis, optic neuritis) and one third the peripheral nervous system (chronic inflammatory demyelinating poly-radiculo-neuropathy, Guillain-Barré syndrome). Cerebrospinal fluid analysis revealed raised protein levels in 4 patients, immunoglobulin oligoclonal bands in 11 and/or pleiocytosis in 4, while it was normal in 6 patients with CNS involvement. Cerebrospinal fluid analysis showed raised protein levels in 9 of 10 (90.0%) of patients with peripheral nervous system involvement in which analysis was

performed (133). White matter lesions were common findings on magnetic resonance imaging in patients with CNS involvement. Anti-TNF biologicals were discontinued in all patients with CNS involvement and in 10 (90.9%) patients with peripheral nervous system involvement. Treatment with glucocorticoids was initiated in 15 (68.2%) and complete resolution was noted in 12 (54.5%), with partial resolution in 8 (36.4%) and no changes in the remaining 2 patients (9.1%) with CNS involvement. Intravenous immunoglobulins were administered in 8 patients, with 2 (25.0%) complete and 6 (75.0%) partial recoveries in patients with peripheral nervous system involvement. The remaining 2 patients did not receive any treatment, with neurological symptoms remaining either stable or improving. The anti-TNF treatment was continued in one patient, with neurological symptoms remaining stable. Two (25.0%) of the patients treated with intravenous immunoglobulins relapsed, one upon introduction of ADM and one without any subsequent anti-TNF treatment (133). Demyelination events occurred in 3 patients treated with GLM 100 mg for rheumatological indications in a large clinical trial. The incidence of demyelination events in GLM was 0.12 per 100 patient-years (134).

Demyelinating diseases are detailed in a few patients (135-137). CNS demyelination evolved to multiple sclerosis in two patients (138), with new-onset multiple sclerosis in another patient (139). Neuropathy with various presentations (140-143), myelitis (142, 144) and neuritis (142, 145, 146) are described elsewhere. A case of tumefactive demyelinating lesions is also presented (147). Encephalopathy is described in several patients (142, 148-150).

Progressive multifocal leuko-encephalopathy (PML) is a subacute CNS infection associated with the destruction of oligo-dendrocytes by John Cunningham virus. John Cunningham virus reactivation occurs under conditions of immunosuppression. Symptoms include confusion, motor impairment, impaired coordination, speech disorders and visual disturbances, while seizures are uncommon. Demyelinated areas are visible in the parietal and occipital regions. Diagnostic confirmation is usually obtained by identification of John Cunningham virus in cerebrospinal fluid or by brain biopsy (151, 152). The incidence of PML is low, and it is comparable between the general population and RA patients (152). A total of 34 PML cases were confirmed among autoimmune rheumatic diseases patients in the Food and Drug Administration Adverse Event Reporting System database. Among these, 15 patients were exposed to biological agents and 19 patients were exposed to other anti-inflammatory agents such as azathioprine, cyclosporin A and prednisone equivalents. One case is reported in an RA patient treated with IFX (153). IFX and ADM have been associated with PML in a recent review of the Canada Vigilance and World Health Organization adverse event databases (154). Two recent cases of PML are described (155, 156). A case of encephalitis associated with Epstein-Barr virus infection is also reported (129).

Hematological Adverse Events

Hematological AEs are important safety considerations of anti-TNF biologicals. Cytopenia describes a condition marked by a reduction in the number of blood cells, and it can include anemia, leukopenia, neutropenia, thrombocytopenia, granulocytopenia or pancytopenia. Transient neutropenia (neutrophil count $<1.50\times10^9$/L) is the predominant non-malignant hematological complication in patients treated with anti-TNF biologicals. Risk factors include a history of neutropenia on other medications or a low baseline neutrophil count. However, neutropenia can develop without co-medication as well. ETN was the biological most often associated with this hematological complication, and consequently most cases were reported in RA patients (157). Hematological adverse events in recent case reports are detailed in Table 5.

Neutropenia is described in 5 RA patients treated with ETN (158). In two patients, neutrophil counts dropped from baseline until they reached a low but stable level during treatment. ETN was continued and the patients are being monitored. A third patient experienced a significant drop in the neutrophil count while on ETN. A rebound in the neutrophil count to a low but stable level was observed upon ETN discontinuation and a switch to ADM. Mild neutropenia is described in a patient treated with ETN plus MTX. ETN was well tolerated after gradual MTX discontinuation. Neutropenia occurred in a fifth ETN patient, and any attempt to re-introduce ETN failed due to

recurrent neutropenia (158). Neutropenia is also detailed in several case reports in which neutrophil counts improved following discontinuation of anti-TNF biologicals (159-161). Two patients had a history of neutropenia while receiving DMARDs, therefore the influence of co-medication such as MTX cannot be discounted (159). Another patient had no history of abnormal hematological parameters during MTX treatment (161).

Leukopenia is described in two patients treated with ETN and DMARDs. No improvement in the leukocytes count was achieved when the DMARDs were discontinued, but leukocyte levels normalized when ETN was discontinued (162, 163).

In a recent review, thrombocytopenia (platelet count $<150\times10^9$/L) was observed predominantly in anti-TNF patients without co-medication, thus suggesting that this hematological complication is likely a consequence of these biologicals. IFX and ETN were associated with thrombocytopenia (157). Thrombocytopenia is described in two patients. Platelet counts rebounded soon after discontinuation of anti-TNF biologicals (164).

Lymphocytosis followed by neutropenia is described in a patient treated with ADM plus MTX. Discontinuation of MTX led to resolution of lymphocytosis, while neutropenia also resolved soon after ADM discontinuation. Therefore, ADM was only responsible for neutropenia in this patient (165).

Anti-TNF biologicals such as IFX, ADM and GLM improve anemia in RA and AS patients. On the other hand, ETN has no significant effects on hemoglobin levels (166, 167).

Pancytopenia is described in two patients treated with ETN plus MTX (168, 169). One of the patients developed severe multilobar pneumonia, although a pathogenic organism could not be definitively identified, likely due to prophylactic antibiotic treatment. The patient died of multi-organ failure resulting from septic shock of respiratory (169). Pancytopenia associated with hemophagocytic syndrome complicated a case of drug-induced lupus (170).

Adverse Events Affecting Other Organs

Adverse events affecting other organs in recent case reports are detailed in Table 6.

Lung Disease

Anti-TNF biologicals are further associated with respiratory, thoracic and mediastinal disorders (33). Interstitial lung disease (ILD) describes a large group of pulmonary conditions associated with inflammation and fibrosis. Non-infective respiratory, thoracic and mediastinal disorders are reported in 8 of 201 (4.0%) patients with long-standing RA treated with ADM (171). The incidence of ILD was 0.6% in a large post-marketing surveillance sample of RA patients treated with ETN (172). Treatment with anti-TNF biologicals (IFX, ADM and ETN) is thus a risk for the development of ILD in RA patients. RA itself and MTX co-treatment represent additional risk factors for ILD, while age ≥65 years, a history of ILD, and concomitant immunosuppressants are risk factors for fatal ILD in RA patients (173-175). Cases of ILD in CZP-treated patients have also been recently described, while serious non-infectious pulmonary AEs are reported in clinical trials in RA patients receiving GLM in the presence of MTX only (176). Lung biopsies are often needed to confirm ILD (175). The most common classifications of ILD were interstitial pneumonia, nonspecific interstitial pneumonia, organizing pneumonia, diffuse alveolar damage and lymphoid interstitial pneumonia (175).

ILD is described in 3 patients (177-179). Progressive resolution of symptoms occurred in a patient treated with prednisone (179), while little recovery was observed in two patients upon treatment with methylprednisolone (177, 178). Differences could be explained by more extensive affected areas in the latter two patients, who were also older (177, 178). In another study, exposure to ETN led to exacerbation of the condition in a patient with a history of ILD (180).

Upon CZP exposure, a patient with a previous episode of pneumonitis while on MTX treatment developed fatal fibrosing alveolitis with respiratory failure (181). Diffuse alveolar hemorrhage is described in two patients (182, 183). Interstitial pneumonia (184-187) and acute pneumonitis (188, 189) were diagnosed elsewhere. Interstitial pneumonia was fatal in an elderly patient with a history of ILD treated with ETN (187). Lupus occurred in the presence of organizing pneumonia in another patient (190).

Hepatitis

Hepatic AEs in patients treated with anti-TNF biologicals are usually classified as infectious AEs, as they result from reactivation of viral hepatitis B. Alternatively, anti-TNF biologicals may also uncover autoimmune hepatitis, while instance of symptomatic, severe acute hepatitis are rare (191). Ghabril et al. (192) identified a total of 34 cases of drug-induced liver injury (DILI) associated with the use of TNF-α antagonists between 2003 and 2011 (26 IFX, 4 ETN and 4 ADM).

The incidence of elevations in ALT and AST over the upper limit of normal occurred in 5.9% of RA patients in a large sample treated with IFX, ADM or ETN (193). IFX, ADM and to a certain degree ETN were risk factors for ALT and AST elevations >2 times over the upper limit of normal compared with DMARDs (193, 194). Asymptomatic AST and ALT elevations >10 times over the upper limit of normal were observed in a patient treated with ETN plus MTX. Liver function test results normalized after ETN interruption, but recurred with ADM. IFX was well tolerated despite persistently positive ANA (195).

Acute hepatitis with positive ANA and anti-dsDNA antibodies is reported in two patients. DILI was diagnosed in both patients as features of autoimmune hepatitis or sclerosing cholangitis were absent in biopsy, despite persistently high autoantibodies (196, 197).

Sarcoidosis

Sarcoidosis is a granulomatous disorder that can affect multiple organs. Neurosarcoidosis is described in an RA patient treated with ETN (198). The mechanism of neurosarcoidosis is believed to involve the expansion of inflammatory meningitis into the brain parenchyma or into the spinal cord (199). Manifestations of neurosarcoidosis depend on the affected neuroaxis. For example, infiltration of granulomas into leptomeningeal and intraparenchymal structures can lead to cranial nerve palsies, basal meningitis or endocrine dysfunction, the consequences of which may be peripheral neuropathies and sensorimotor polyneuropathy (200). Cases of thoracic and pulmonary sarcoidosis are described elsewhere (201, 202). Additional cases of granulomatous hepatitis and granulomatous interstitial nephritis are also presented (203, 204).

Cardiovascular Effects of anti-TNF Biologicals

Based on data from Medicare and drug benefit programs (1994-2004), the use of anti-TNF biologicals (ETN and IFX) was associated with an increased risk of heart failure compared to MTX in elderly (≥65 years) RA patients (205). Both ETN and IFX were risk factors for heart failure in a sample of 2121 younger (<50 years of age) RA patients. The risk with anti-TNF biologicals was comparable to that of DMARDs, which can be attributed in part to a relatively low overall incidence in this younger population (206). Based on this evidence, older age is a risk factor for heart failure in RA patients treated with anti-TNF biologicals. Furthermore, elderly anti-TNF patients were found to have a 4.2-fold higher risk of death from heart failure compared to MTX patients (205). Elsewhere, RA disease activity was the main risk factor for the 3 years incidence of heart failure, and overall anti-TNF biologicals generally shows more beneficial than detrimental effects with respect to the risk of heart failure, owing primarily to the reduction in the inflammatory activity of RA (207, 208). The incidences of tachyarrhythmias and bradyarrhythmias were not different between IFX and placebo in a sample of 75 spondyloarthritis or RA patients (209). Furthermore, anti-TNF biologicals have positive effects on cardiovascular health by improving metabolic parameters, at least in the short term (210).

Cardiovascular AEs are described in a few RA patients treated with IFX and ETN (211-214). Supraventricular tachycardia occurred within 3 hours of the 8th IFX infusion in the first of these patients (211). A significant decrease in cardiac output (7.04 ± 2.3 to 6.12 ± 2.1 L/min) and in stroke volume (91 ± 29.0 to 83 ± 28.8 mL/beat), with non-significant increases in systolic blood pressure, diastolic blood pressure and total peripheral vascular resistance, also occurred as an infusion reaction in an IFX patient (212). Dilated cardiomyopathy was induced by IFX after 6 months of treatment in the third patient (213). Severe heart failure, reversible upon ETN discontinuation, developed in an AS patient (214).

Relationship between Anti-TNF Biologicals and Cancer

The relationship between anti-TNF biologicals and cancer is controversial. The following section

provides a brief analysis of the current knowledge.

Anti-TNF biologicals were disproportionately associated with benign, malignant or unspecified neoplasms (33). However, inflammation is a known risk factor for cancer, such that the increased risk of cancer observed in RA cohorts treated with anti-TNF agents could be a result of the underlying disease (215).

Overall, the risk of cancer is similar in RA patients treated with anti-TNF biologicals and the general population. Using data from randomized controlled clinical trials, IFX and ADM were associated with an increased risk of malignancies compared to placebo, particularly a non-significant trend towards a higher incidence of lymphomas (216, 217). While the risk of lymphoma, particularly Hodgkin's lymphoma, appears increased in RA patients treated with anti-TNF biologicals, patients with RA carry a 2-3-fold higher risk of lymphomas compared to the general population. Risk factors for lymphoma include RA, predominantly in individuals with positive rheumatoid factor (218, 219). When adding biologicals to the equation, no increased risk of cancers is usually found between patients exposed to anti-TNF agents or placebo. It is interesting to note that while anti-TNF monoclonal antibodies may be risk factors, no significant differences exist between anti-TNF agents and placebo when IFX, ADM and ETN are considered together. Looking at individual cancers separately and individuals biologicals separately would thus likely offer a more appropriate means to compare anti-TNF and placebo, yet no significant differences are apparent due to the relatively low incidence of these AEs (215).

Using data from 33 placebo-controlled trials, treatment with anti-TNF agents was not associated with an increased risk of cancer compared to placebo in RA patients treated for up to 2 years. A trend towards an increased risk of non-melanoma skin cancers was however observed (220). As such, treatment with anti-TNF biologicals is a risk factor for cutaneous malignancies (64). Skin neoplasms include melanoma, and non-melanoma cancers such as basal cell carcinoma (48). IFX and ETN are associated with non-melanoma skin cancer and with melanoma based on data from the US National Data Bank for Rheumatic Diseases (221). Anti-TNF biologicals were associated with non-melanoma skin cancer in a recent meta-analysis, but not with other types of cancer (222). Overall, these reports suggest that RA patients may be predisposed to higher rates of malignancies than the general population, especially lymphomas, while long-term exposure to biologicals appears safe. An alternative explanation could be that anti-TNF biologicals may cause cancer on their own but may also decrease the risk of cancer associated with the chronic inflammatory environment. Based on current knowledge, no definitive conclusions could be drawn with regards to the risk of cancer in anti-TNF patients, and studies with longer follow-up times may help elucidate the relationship, if any.

DISCUSSION

The present review discussed AEs in which anti-TNF biologicals were incriminated. However, additional factors such as co-medication should be considered when analyzing the causes of AEs. The majority of RA patients that are treated with anti-TNF biologicals are also taking NSAIDs as painkillers or as additional therapies.

Several NSAIDs play a prominent role in the history of idiosyncratic hepatotoxicity. For example, diclofenac was shown to produce hepatic injury since the 1980s. In 15-20% of patients taking the drug, aminotransferase levels are markedly increased (223- 230). Clinically, acute disease resembles acute viral hepatitis and chronic injury is similar to chronic hepatitis (227, 231). At the histological level, the main lesion has been hepatic necrosis. The necrosis is non-zonal although it tends to be more marked in zone 3. Female gender is a risk factor for hepatotoxicity susceptibility. In addition, patients with osteoarthritis have a significantly higher incidence of hepatic injury than RA patients (230). Most cases have presented with the syndrome of acute hepatitis characterized by jaundice and to a varying degree by fatigue, anorexia, nausea and vomiting. Fever, rash and eosinophilia are uncommon, but were recorded in one report (232). As with other drug-induced hepatocellular injury, massive necrosis with fulminant hepatic failure and death were noted (230, 233). Chronic active hepatitis was also described with diclofenac. The mechanism of this reaction was delayed-onset hypersensitivity (234). Rostom et al. (235) reviewed NSAIDs hepatoxicity in randomized controlled trials in arthritis patients. Laine et al. (236) further studied liver injury

associated with diclofenac in a large sample of arthritis patients in a long-term prospective clinical trial, and concluded that this is not an uncommon AE. Moreover, Pilotto et al. (237) reported NSAIDs-related gastrointestinal bleeding. Diclofenac was associated with hospitalization in a case-crossover study, including peptic ulcer, bleeding and perforation (238).

The major side effects of NSAIDs which are the gastrointestinal complications, renal disturbances and cardiovascular events are presented in the seminal review by Harirfoorosh et al., (239). Arthritis patients using pain killers and NSAIDs are prone to cardiovascular disease (240) and renal damage (241). However, the population treated for RA presents a heterogeneity in patient population in terms of specific disease involvement, and ethnic diversity of the patients. Moreover, age group is an important parameter. The majority of patients are elderly individuals that, in addition to RA, may present another underlying disease (diabetes, hypertension, obesity) that may direct them to ADRs. Also, the type and small number of ADRs, when compared to the general population taking the same medication, make any conclusion regarding the risk of NSAIDs incrimination in interaction with biologicals almost impossible to judge. In many of these studies, the inflammation and inflammatory activators that exist continuously in RA is ignored. The target of both biologicals and NSAIDs is inflammation. This phenomenon is important since inflammation is by itself a risk factor of cardiovascular events. Biologicals and NSAIDs thereby, both should reduce the cause for increase cardiovascular ADRs. However, no study can identify the impact of separate component in an adverse event.

Gastrointestinal complications are frequent during the NSAIDs therapy for RA (239). Several factors including a history of gastric mucosa damage, age over 60 years, previous exposure and ADR to NSAIDs, and/or drug interactions with corticosteroids or anticoagulants increase the risk of developing gastrointestinal side effects. These factors may also influence the interaction between biologicals and NSAID.

Ibuprofen is a widely-used NSAID with antipyretic and analgesic properties that can produce an unpredictable hypersensitivity syndrome reaction likely caused by a combination of metabolic and immunologic factors. Immune-mediated components, such as T cell cytokines and chemokines, can exacerbate cellular responses and create complex pathways that lead to a variety of clinical manifestations including severe cutaneous reaction and of drug-induced liver injury (242-244).

Treatment of RA and related conditions with low doses of MTX may lead to steatosis. MTX-induced fibrosis can appear during treatment. Rarely, cirrhosis was reported (245, 246). A case of MTX anaphylaxis allowed ETN to be continued in a patient co-treated with these two agents (247).

One of the most worrisome conditions is DILI. The clinical syndrome of acute liver damage relates, at least in part, to the apparent mechanism of injury. Hepatic injury induced by large single overdose of intrinsically toxic drugs, (e.g., acetaminophen) develops within 24 to 72 hours of intake and usually, is accompanied by renal failure. Regular intake of some toxic drugs (e.g., methotrexate) leads to slowly evolving chronic disease. Liver damage due to hypersensitivity-type of idiosyncrasy to NSAIDs, it is not dose-dependent. Usually appears after one to five weeks of taking the drug unless there has been previous exposure and is preceded or accompanied by systemic features that are hallmarks of hypersensitivity (243). Hepatic injury attributable to metabolic idiosyncrasy may appear after weeks to months of taking the drug in the normally prescribed dose and usually presents without the systemic features. Organs other than the liver may be involved in the syndrome of DILI as the result of selective injury or as part of hypersensitivity reaction (244). Regardless of underlying disease, hepatotoxicity of NSAIDs was described in many cases (248).

However, RA per se may be responsible for susceptibility to certain NSAIDs. Patients with JIA and RA appear to be more vulnerable than others, and there is a positive correlation between activity of the underlying disease and susceptibility to the hepatic injury. Hepatic damage induced by aspirin occurs in 50% or more of patients with high but normal blood levels of the drug (> 15 mg/dl). This level can be achieved by the dose given in active RA. The injury is intrinsic. Bilirubin levels are normal or slightly elevated and jaundice is noted in less than 5% of cases. Values of aminotransferases are elevated, 5-40-fold. Biopsy has shown focal necrosis with mild inflammatory response in the portal areas and sinusoids and ultrastructural

changes (249-253). The abnormality disappears promptly on stopping the drug. Overdoses of aspirin lead to microvesicular steatosis (249, 254).

In a study reported by the Acute Liver Failure Study Group, prolonged administration of high doses of NSAIDs for RA resulted in irreversible acute liver failure that led to liver transplant or death (255).

Other cytotoxic drugs have been employed in the treatment of RA, although not as widely used (251). The effects of DMARDs on the liver, especially those of MTX, are important to consider as possible triggers for hepatotoxicity. Glycogen inclusions in the nuclei are described as prominent in DILI. These features are common findings in the liver of diabetics but can be also seen in non-diabetic individuals. Particular attention has been paid to the association with prolonged MTX-exposure. Thus, the steatosis produced by MTX leads primarily to hepatomegaly as a clinical manifestation (256).

The diagnosis of drug-induced injury can often be difficult. The relationship between drug-ingestion and toxicity is not always clear. Patients may be taking multiple medications making identification of the offending agent difficult, and they may have concomitant diseases, which can produce similar clinical and laboratory features. Characteristics suggesting drug toxicity include good health prior to ingesting the drug, clinical illness or biochemical abnormalities developing after beginning the drug, and after the drug is withdrawn. If an immunologic reaction is suspected, the illness will generally recur upon reintroduction of the offending substance. However, rechallenge is not advised.

Dose and frequency related adverse events have not been reported in the clinical trials with anti-TNF medication. Infections generally tend to occur during the first 1-2 years of treatment with anti-TNF (32). Therefore after a prolonged immune suppression the initial infection is reactivated. However, the majority of non-viral opportunistic infections occurred in the first 6 months of treatment with anti-TNF (33). Regarding cutaneous AEs primarily appear in first few months of treatment (64). Specific infusion-related severe anaphylactic reactions related to the presence of anti-IFX ADAs; scheduled dosing is thus preferred over episodic dosing in order to avoid ADAs (66). Autoimmune AEs are also associated with the presence of autoantibodies (101).

Neurological AEs occurred between a few months to a few years of anti-TNF treatment (same wide range of treatment duration for all of IFX, ADM and ETN) (133). Haematologic effects such as thrombocytopenia, neutropenia, thrombosis occurred between a few weeks to several months of anti-TNF treatment (157).

We conclude that the number and severity of the ADRs have no relationship with dose or length of anti-TTNF treatment. The only exception is immune-mediated AEs, which tend to occur more frequently in the presence of ADAs or autoantibodies. The presence of ADA occur more frequently when treatment is not administered continuously.

As a result of the frequent co-treatment with anti-TNF biologicals and DMARDs or NSAIDs, the effects of all therapeutics need to be considered, and thus the superimposed effects of drug-drug interactions cannot be discounted for both immune-mediated mechanisms and those resulting from abnormal drug metabolism and clearance. Pharmacovigilance practice is vital for the successful development, marketing and defence of pharmaceutical products.

The scope of the search for safe anti-TNF therapeutics should be broadened to the molecular level and cover various receptors involved in the side effects and also to explore interaction with other therapeutics that might be given concomitantly. In addition, to predict various side effects of anti-TNFs, identification of readily measured biomarkers is of therapeutic interest. We recommend laboratory monitoring of TNF levels in blood and the ADA to different anti-TNF therapeutics. To avoid possible NSAID hypersensitivity we recommend the use of lymphocyte toxicity assay to the specific NSAID.

CONCLUSION

Adverse drug reactions remain a persistent concern in the prescription of many commonly-used therapeutic agents in clinical practice. Anti-TNF biologicals are efficient and generally safe in the treatment of patients with RA. Increased experience resulting from their extensive use has verified their overall safety profile with favorable risk-benefit ratio. However, caution is strongly advised in the administration of biological therapies. The use of

anti-TNF therapies in combination with NSAIDs by individuals with chronic liver disease can provoke development of hepatotoxicity. Physicians should monitor patients for infections. Moreover, anti-TNF agents *per se* and in combination with other medication administered are potential causes of drug-induced, cardiovascular, gastrointestinal and liver injury. Monitoring remains the cornerstone of early diagnosis and effective management. From the point of view of pharmaceutical companies and health authorities, post-marketing surveillance continues to be paramount with every newly introduced agent. From the perspective of physicians and their patients, pharmacovigilance and personalized medicine provide the necessary tools for optimizing therapy while minimizing side effects.

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Table 1. Incidence of adverse events in clinical trials

Trials and Patients	Regimens		
ATTRACT (10) Active RA patients treated with MTX for ≥3 months	MTX plus placebo injection, through week 30 Serious AEs: 14 of 86 (16.3%)	MTX plus IFX 3 mg/kg every 8 weeks, through week 30 Serious AEs: 8 of 89 (9.0%) MTX plus IFX 3 mg/kg every 4 weeks, through week 30 Serious AEs: 11 of 86 (12.8%)	MTX plus IFX 10 mg/kg every 8 weeks, through week 30 Serious AEs: 8 of 87 (9.2%) MTX plus IFX 10 mg/kg every 4 weeks, through week 30 Serious AEs: 10 of 80 (12.5%)
ATTRACT (11) Active RA patients treated with MTX for ≥3 months	MTX plus placebo injection, through week 54 Serious AEs: 18 of 86 (20.9%)	MTX plus IFX 3 mg/kg every 8 weeks, through week 54 Serious AEs: 10 of 88 (11.4%) MTX plus IFX 3 mg/kg every 4 weeks, through week 54 Serious AEs: 14 of 86 (16.3%)	MTX plus IFX 10 mg/kg every 8 weeks, through week 54 Serious AEs: 17 of 87 (19.5%) MTX plus IFX 10 mg/kg every 4 weeks, through week 54 Serious AEs: 16 of 81 (19.8%)
Active-Controlled Study of Patients Receiving Infliximab for the Treatment of Rheumatoid Arthritis of Early Onset Study (12) Active RA ≤3 years duration	MTX plus placebo injection, through week 54 Infusion reactions: 20 of 291 (6.9%) Serious AEs: 32 of 291 (11.0%) ANA: 29 of 256 (11.3%)	MTX plus IFX 3 mg/kg every 8 weeks, through week 54 Infusion reactions: 279 of 372 (21.2%) Serious AEs: 52 of 372 (14.0%) ANA: 118 of 298 (39.6%)	MTX plus IFX 6 mg/kg every 8 weeks, through week 54 Infusion reactions: 56 of 377 (14.8%) Serious AEs: 51 of 377 (13.5%) ANA: 106 of 309 (34.3%)
START (13) Active RA patients treated with MTX for ≥3 months	MTX plus placebo injection, through week 22 (n=361) AEs: 239 (66.2%) Serious AEs: 27 (7.5%) Serious infections: 6 (1.7%)	MTX plus IFX 3 mg/kg every 8 weeks, through week 22 (n=360) AEs: 251 (69.7%) Serious AEs: 28 (7.8%) Serious infections: 6 (1.7%)	MTX plus IFX 10 mg/kg every 8 weeks, through week 22 (n=361) AEs: 261 (72.3%) Serious AEs: 27 (7.5%) Serious infections: 19 (5.3%)
Ruperto et al. (14) Active juvenile rheumatoid arthritis patients treated with MTX for ≥3 months	MTX plus placebo, through week 14 (n=60) Infusion reactions: 5 (8.3%) AEs: 49 (81.7%) AEs leading to discontinuation of study agent: 1 (1.7%) Serious AEs: 3 (5.0%) Infections: 28 (46.7%) Serious infections: 2 (3.3%)	MTX plus IFX 3 mg/kg every 8 weeks, through week 52 (n=60) Infusion reactions: 21 (35.0%) AEs: 58 (96.7%) AEs leading to discontinuation of study agent: 2 (3.3%) Serious AEs: 19 (31.7%) Infections: 41 (68.3%) Serious infections: 5 (8.3%) Presence of ADAs: 20 of 53 (37.7%) ALT ≥90 IU/liter and elevations of ≥100% from baseline: 3.3% Decreases in the neutrophil count (<1.5 × 10^3 cells/μl and decrease ≥33%): 1.7% ANA positivity (titer ≥1:320): 8 of 54 (14.8%) Presence of anti-dsDNA antibodies: 7 of 54 (13.0%)	MTX plus IFX 6 mg/kg every 8 weeks, through week 52 (n=60) Infusion reactions: 10 (17.5%) AEs: 54 (94.7%) AEs leading to discontinuation of study agent: 5 (8.8%) Serious AEs: 5 (8.8%) Infections: 37 (64.9%) Serious infections: 1 (1.8%) Presence of ADAs: 6 of 49 (12.2%) ALT ≥90 IU/liter and elevations of ≥100% from baseline: 8.8% Decreases in the neutrophil count (<1.5 × 10^3 cells/μl and decrease ≥33%): 8.8% ANA positivity (titer ≥1:320): 1 of 46 patients (2.2%) Presence of anti-dsDNA antibodies: 0 of 46 (0.0%)
ASSERT (15)	Placebo, through week 24 (n=75) AEs: 54 (72.0%) Serious AEs: 2 (2.7%) Infusion reactions: 7 (9.3%) Infections: 27 (36.0%) Serious infections: 0 (0.0%) Increases in ALT: 3 (4.0%) Increases in AST: 2 (2.7%)		IFX 5 mg/kg, through week 24 (n=202) AEs: 166 (82.2%) Serious AEs: 7 (3.5%) Infusion reactions: 22 (10.9%) Infections: 86 (42.6%) Serious infections: 2 (1.0%) Increases in ALT: 19 (9.4%) Increases in AST: 11 (5.4%)

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Table 1 Cont'd.

Trials and Patients	Regimens		
Enbrel ERA (16) Early RA patients	MTX plus placebo, through 12 months (n=217) Injection site reactions: 16 (7.4%) Elevated AST: 32% Elevated ALT: 44% Neutropenia: 8%	ETN 10 mg twice/week plus placebo, through 12 months (n=208) Injection site reactions: 63 (30.3%) (p<0.05 vs. MTX)	ETN 25 mg twice/week plus placebo, through 12 months (n=207) Injection site reactions: 77 (37.2%) (p<0.05 vs. MTX) Elevated AST: 16% Elevated ALT: 24% Neutropenia: 16%
TEMPO (17) Active RA patients	MTX plus placebo, through 12 months (n=228) AE: 185 (81.1%) Injection site reaction: 4 (1.8%) Nausea: 73 (32.0%) Rash: 21 (9.2%) Vomiting: 26 (11.4%) Infections: 146 (64.0%) Serious infections: 10 (4.4%) Grade 3-4 abnormalities in hepatic enzymes levels: 5 (2.2%)	ETN 25 mg twice/week plus placebo, through 12 months (n=223) AE: 192 (86.1%) Injection site reaction: 46 (20.7%) (p<0.0001 vs. MTX) Nausea: 22 (9.9%) (p<0.0001 vs. MTX) Rash: 16 (7.2%) Vomiting: 7 (3.1%) (p<0.0001 vs. MTX) Infections: 131 (58.7%) Serious infections: 10 (4.5%) Grade 3-4 abnormalities in hepatic enzymes levels: 2 (0.9%)	MTX plus ETN25 mg twice/week, through 12 months (n=231) AE: 1187 (81.0%) Injection site reaction: 23 (10.0%) (p<0.0002 vs. MTX, p=0.0017 vs. ETN) Nausea: 55 (23.8%) (p<0.0001 vs. ETN) Rash: 23 (10.0%) Vomiting: 12 (5.2%) (p=0.0177 vs. MTX) Infections: 154 (66.7%) Serious infections: 10 (4.3%) Grade 3-4 abnormalities in hepatic enzymes levels: 2 (0.9%)
ADORE (18) Active RA despite ≥3 months of MTX	ETN 25 mg twice/week, through week 16 (n = 159) AEs: 100 (62.9%) AEs causing treatment withdrawal: 13 (8.2%) Serious AEs: 8 (5.0%) Infections: 39 (24.5%)	MTX plus ETN25 mg twice/week, through week 16 (n = 155) AEs: 109 (70.3%) AEs causing treatment withdrawal: 9 (5.8%) Serious AEs: 7 (4.5%) Infections: 50 (32.3%)	
COMET (19) Moderate to severe MTX-naïve RA	MTX plus placebo, through 12 months (n=268) AEs: 246 (91.8%) Serious AEs: 34 (12.7%) Serious infections: 8 (3.0%) Incidence of malignancies: 4 (1.5%)	MTX plus ETN25 mg twice/week, through 12 months (n = 274) AEs: 247 (90.1%) Serious AEs: 33 (12.0%) Serious infections: 5 (1.8%)	
ARMADA (20) Active RA patients receiving MTX at stable dose for ≥6 months	MTX plus placebo, though week 24 (n=62) Treatment discontinuation as a result of AEs: 2 Presence of ADAs: 1	ADM 20 mg every other week plus placebo, though week 24 (n=69) Treatment discontinuation as a result of AEs: 4 Presence of ADAs: 1	ADM 40 mg every other week plus placebo, though week 24 (n=67) Treatment discontinuation as a result of AEs: 0 Presence of ADAs: 0	ADM 80 mg every other week plus placebo, though week 24 (n=73) Treatment discontinuation as a result of AEs: 1 Presence of ADAs: 1
RAPID 1 (21) Active RA patients receiving MTX at stable dose for ≥6 months	MTX plus placebo injection, through week 24 (events per 100 patient-years, n=199) AEs: 125.9 AEs related to study drug: 54.7 Serious AEs: 12.0	MTX plus CZP 200 mg, through week 24 (events per 100 patient-years, n=392) AEs: 96.6 AEs related to study drug: 55.1 Serious AEs: 14.8	MTX plus CZP 400 mg, through week 24 (events per 100 patient-years, n=389) AEs: 94.5 AEs related to study drug: 52.7 Serious AEs: 15.2
RAPID 2 (22) Active RA patients receiving MTX at stable dose for ≥6 months	MTX plus placebo injection, through week 24 (n=125) Treatment-emergent AEs: 66 (52.8%) Infections: 26 (20.8%) Serious AEs: 4 (3.2%) Serious infections: 0 (0.0%) AEs leading to withdrawal of treatment: 2 (1.6%)	MTX plus placebo injection, through week 24 (n=248) Treatment-emergent AEs: 139 (56.0%) Infections: 69 (27.8%) Serious AEs: 18 (7.3%) Serious infections: 8 (3.2%) AEs leading to withdrawal of treatment: 12 (4.8%)	MTX plus placebo injection, through week 24 (n=246) Treatment-emergent AEs: 125 (50.8%) Infections: 53 (21.5%) Serious AEs: 18 (7.3%) Serious infections: 6 (2.4%) AEs leading to withdrawal of treatment: 7 (2.8%)
FAST4WARD (23) Active RA patients who have failed ≥1 DMARDs	Placebo, through week 24 (n=109) AEs: 63 (57.8%) Serious AEs: 3 (2.8%) Serious infections: 0 (0.0%) AEs leading to withdrawal: 2 (1.8%)	CZP 400 mg, through week 24 (n=111) AEs: 84 (75.7%) Serious AEs: 8 (7.2%) Serious infections: 2 (1.8%) AEs leading to withdrawal: 5 (4.5%)	

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Table 1 Cont'd.

Trials and Patients	Regimens			
GO-BEFORE (24) MTX-naïve active RA patients	MTX plus placebo, through week 24 (n=160) AEs: 116 (72.5%) Serious AEs: 11 (6.9%) Infections: 52 (32.5%) Serious infections: 3 (1.9%) Injection-site reactions: 3 (1.9%)	GLM 100 mg plus placebo, through week 24 (n=157) AEs: 107 (68.2%) Serious AEs: 5 (3.2%) Infections: 55 (35.0%) Serious infections: 2 (1.3%) Injection-site reactions: 17 (10.8%)	GLM 50 mg plus MTX, through week 24 (n=158) AEs: 129 (81.6%) Serious AEs: 10 (6.3%) Infections: 54 (34.2%) Serious infections: 2 (1.3%) Injection-site reactions: 7 (4.4%)	GLM 100 mg plus MTX, through week 24 (n=159) AEs: 121 (76.1%) Serious AEs: 10 (6.3%) Infections: 50 (31.4%) Serious infections: 7 (4.4%) Injection-site reactions: 14 (8.8%)
GO-FORWARD (25) Active RA patients treated with MTX for ≥3 months	MTX plus placebo, through week 24 (n=134) AEs: 89 (66.4%) Serious AEs: 5 (3.7%) Infections: 37 (27.6%) Serious infections: 1 (0.7%) Injection-site reactions: 4 (3.0%)	GLM 100 mg plus placebo, through week 24 (n=133) AEs: 98 (73.7%) Serious AEs: 8 (6.0%) Infections: 50 (37.6%) Serious infections: 4 (3.0%) Injection-site reactions: 10 (7.5%)	GLM 50 mg plus MTX, through week 24 (n=212) AEs: 87 (41.0%) Serious AEs: 9 (4.2%) Infections: 34 (16.0%) Serious infections: 2 (0.9%) Injection-site reactions: 5 (2.4%)	GLM 100 mg plus MTX, through week 24 (n=105) AEs: 78 (74.3%) Serious AEs: 13 (12.4%) Infections: 39 (37.1%) Serious infections: 5 (4.8%) Injection-site reactions: 5 (4.8%)
GO-AFTER (26) Active RA patients MTX treatment in 66% of sample	Placebo, through week 16 (n=155) AEs: 108 (69.7%) Serious AEs: 11 (7.1%) Infections: 51 (32.9%) Serious infections: 5 (3.2%) Injection-site reactions: 6 (3.9%)	GLM 50 mg, through week 16 (n=152) AEs: 93 (61.2%) Serious AEs: 8 (5.3%) Infections: 53 (34.9%) Serious infections: 5 (3.3%) Injection-site reactions: 9 (5.9%)	GLM 100 mg, through week 16 (n=152) AEs: 111 (73.0%) by week 16 Serious AEs: 4 (2.6%) Infections: 55 (36.2%) Serious infections: 1 (0.7%) Injection-site reactions: 16 (10.5%)	

Table 2. Infusion reactions

Reference	Patient Conditions	Treatment	Course of Reaction	Presentation of Symptoms	Diagnosis	Techniques to Validate Diagnosis	Management of Symptoms
(72)	RA	IFX	Cutaneous	Symptoms recurrent while on IFX	Atopic dermatitis	Physical examination	Hydrocortisone and tacrolimus IFX not discontinued
(73)	RA	IFX	Cutaneous	Symptoms after 17 months of IFX	Recurrent atopic dermatitis	Physical examination	Triamcinolone IFX not discontinued
(74)	Long-standing RA with multiple drug intolerances	IFX + MTX + prednisone	Cutaneous	Within 30 min of each infusion	IFX intolerance	Physical examination	Diphenhydramine IFX discontinued
(75)	RA	ETN	Cutaneous, swelling and tachycardia	After 4 months of ETN	Angioedema	Physical examination	Adrenaline, antihistaminic and methylprednisolone ETN discontinued
(76)	AS	ETN	Cutaneous and swelling	After 22nd infusion of ETN Previous symptoms on ADM	Injection-site reaction	Intradermal testing supporting IgE-mediated reaction	ETN desensitization
(77)	AS	ETN	Cutaneous	After 6 months of ETN	Urticaria pigmentosa	Histology	No treatment ETN discontinued
(78)	RA	ETN + DMARDs	Cutaneous and swelling	After several months of ETN	Allergy and anaphylaxis	Physical examination	Diphenhydramine, epinephrine and corticosteroids ETN discontinued
(79)	RA	ADM	Cutaneous, swelling, asthma and hypotension	After 11th infusion of ADM Previous symptoms on ETN and after 10th infusion of ADM	Anaphylactic reaction	Physical examination	Corticosteroids and antihistamines ADM discontinued
(80)	RF-positive RA	IFX + prednisolone	Cutaneous and eosinophilia	After 9 years of IFX	Intermittent pruritic rash (Wells' syndrome)	Punch biopsy Histology	Prednisolone IFX not discontinued
(81)	Long-standing ANA-positive JIA	ETN + MTX	Cutaneous and swelling	After 5th weekly ETN injection	Anaphylaxis	Physical examination	ETN discontinued
(81)	ANA-positive, HLA-B27-positive enthesitis-related JIA	ETN	Cutaneous, swelling and dyspnea	Within minutes of 3rd ETN injection	Anaphylaxis	Physical examination	Antihistamines and prednisone ETN discontinued
(82)	AS	IFX	Cutaneous and dyspnea Cardiopulmo n-ary arrest	After 2nd infusion of IFX	Severe anaphylaxis	Electrocardio-gram	Treated for anaphylaxis Discontinued
(83)	RF-negative RA	ADM + MTX	Cutaneous, swelling and eosinophilia	After 2 years of ADM	Lymphocytic hypereosinophilia	Skin biopsy	Prednisone and imatinib mesylate ADM and MTX discontinued

Table 3. Immune-mediated and autoimmune adverse events

Reference	Patient Conditions	Treatment	Course of Reaction	Presentation of Symptoms	Diagnosis	Techniques to Validate Diagnosis	Management of Symptoms
(86)	RF-positive severe RA	ETN + DMARDs	Cutaneous	After 2 months of ETN	Lichenoid eruption	Skin biopsy	Mometasone fuorate ETN not discontinued
(87)	JIA and Crohn's disease	IFX	Cutaneous	After 4 years of IFX	Lichenoid dermatitis	Skin biopsy	corticosteroids and emollients, IFX discontinued
(88)	RA	ETN + MTX	Cutaneous	After 1 year of ETN	Lichen planus	Punch biopsy	Ciprofloxacin and steroids ETN discontinued
(89)	RA and secondary amyloidosis	ETN + DMARDs	Cutaneous and leukocytosis	After 1 week of ETN (3 infusions)	Cutaneous vasculitis	Skin biopsy	Prednisolone IFX discontinued
(89)	RA and secondary amyloidosis	IFX + MTX and bucillamine	Cutaneous and leukocytosis	After 6 weeks of IFX (3 infusions)	Leukocytoclastic vasculitis	Skin biopsy	No treatment IFX discontinued
(89)	RA	IFX + MTX	Cutaneous and leukocytosis	After 3 weeks of IFX (2 infusions)	Leukocytoclastic vasculitis	Clinical Skin biopsy not performed	Dexamethasone ETN discontinued
(87)	Long-standing JIA	IFX	Cutaneous	After 4 years of IFX	Cutaneous leukocytoclastic vasculitis	Punch biopsy	Systemic corticosteroids IFX discontinued
(90)	HLA-B27-positive AS	GLM	Cutaneous	After 2nd infusion of GLM Previous exposure to ADM and ETN	Leukocytoclastic vasculitis	Skin biopsy	Glucocorticoids GLM discontinued
(91)	RA	ETN	Cutaneous	After 12 months of ETN	Cutaneous small-vessel vasculitis	Skin biopsy	Prednisone ETN discontinued
(91)	RA	IFX	Cutaneous	After 6 years of IFX	Cutaneous small-vessel vasculitis	Skin biopsy	Prednisone IFX discontinued
(91)	RA	IFX	Cutaneous	After 5 years of IFX	Cutaneous small-vessel vasculitis	Skin biopsy	Prednisone IFX discontinued
(91)	RA	ETN	Peripheral nerves	After 3 years of ETN	Peripheral nerve vasculitis with neuropathy	Neuromuscular biopsy	Prednisone and cyclophosphamide ETN discontinued
(92)	RF-negative erosive RA	GLM	Pulmonary and haemoptysis	After 3 years of GLM	Wegener's granulomatosis	Chest X-rays CT scan Bronchoscopy	Prednisone GLM discontinued
(93)	HLA-B27-negative AS	ETN	Cutaneous, joint pain and acute renal failure	After 6 months of ETN	Henoch-Schönlein purpura	Skin biopsy Urinalysis Renal biopsy Immuno-fluorescence	Methylprednisone, prednisone, then corticosteroids ETN discontinued
(94)	RA	IFX + prednisone	Cutaneous and eosinophilia	After 4 months of IFX	Subacute prurigo with eosinophilia	Skin biopsy	Systemic corticosteroids IFX discontinued
(95)	Long-standing RA	ADM + MTX + prednisone	Cutaneous	After 5th ADM injection	Stevens-Johnson syndrome	Clinical Biopsy was refused	Hydrocortisone then prednisone ADM discontinued
(96)	RA	ETN	Cutaneous	Symptoms after 2nd infusion of ETN	Pustular dermatitis	Skin biopsy	Corticosteroids ETN discontinued

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Table 3 Cont'd.

Reference	Patient Conditions	Treatment	Course of Reaction	Presentation of Symptoms	Diagnosis	Techniques to Validate Diagnosis	Management of Symptoms
(97)	RF-positive RA	ETN	Cutaneous and dyspnea	After 5 months of sequential ADM followed by ETN	Dermatomyositis	Punch biopsy	Mycophenolate mofetil, methylprednisolone and corticosteroids ETN discontinued
(97)	RF-positive RA	ETN	Cutaneous	After 2 years of ETN	Dermatomyositis	Punch biopsy Autoantibodies	Cobetasol and prednisone ETN discontinued
(97)	RF-negative inflammatory arthritis	ADM + MTX	Cutaneous, muscle edema and photosensitivity	After 4 months of ADM	Dermatomyositis	Punch biopsy Electromyo-graphy Autoantibodies	Prednisone and mepacrine ADM discontinued
(97)	RF-positive RA and history of dermatomyositis	ADM	Cutaneous and pulmonary	After 2 months of ADM	Dermatomyositis	Pulmonary function tests	Prednisone and cyclophosphamide ADM discontinued
(98)	Long-standing JIA	ETN + prednisone	Cutaneous and photosensitivity	After 2 months of weekly ETN Previous 10 years of sporadic ETN	Dermatomyositis Recurrence on ADM	Punch biopsy	Prednisone ETN discontinued
(99)	HLA-B27-positive AS	ADM	Cutaneous	Symptoms after 12 months of ADM	Morphea	Skin biopsy	Clobetasol proprionate ADM discontinued
(102)	ANA-positive, andi-dsDNA antibodies-positive RA	IFX	Photosensitivity, arthritis and serositis	After 10 days of IFX	IFX systemic lupus erythematosus	Autoantibodies	IFX discontinued
(102)	ANA-positive, andi-dsDNA antibodies-positive RA	IFX	Arthritis and leukopenia	After 33 months of IFX	IFX systemic lupus erythematosus	Autoantibodies	IFX discontinued
(102)	RA	IFX	Arthritis, serositis and hemolytic, anemia with reticulocytosis	After 12 months of IFX	IFX systemic lupus erythematosus	Autoantibodies	IFX discontinued
(102)	RA	IFX	Serositis	After 12 months of IFX	IFX systemic lupus erythematosus	Autoantibodies	IFX discontinued
(103)	ANA-positive anti-cyclic citrullinated peptide antibodies-positive RF-negative RA	ADM + MTX	Cutaneous	After 2nd ADM infusion after a 3 months gap following 2 years of ADM	Drug-induced cutaneous lupus erythematosus	Skin biopsy Autoantibodies	ADM discontinued and MTX maintained
(104)	RA	ETN	Cutaneous	After 2 months of ETN Previous 3 years of ADM	Drug-induced subacute cutaneous lupus-like syndrome	Skin biopsy Autoantibodies	Prednisone, hydroxychloroquine sulfate and corticosteroids ETN discontinued
(105)	RF-positive severe erosive RA	ETN	Joint pain, vasculitis and lymphopenia	After 7 months of ETN	Drug-induced lupus	Autoantibodies	Steroids ETN discontinued
(105)	RF-positive RA	ETN	Joint pain	After 3 years of ETN	Drug-induced lupus	Autoantibodies	Methylprednisolone ETN discontinued

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Table 3 Cont'd.

Reference	Patient Conditions	Treatment	Course of Reaction	Presentation of Symptoms	Diagnosis	Techniques to Validate Diagnosis	Management of Symptoms
(105)	ANA-positive RF-positive RA	ADM	Joint pain, vasculitis and lymphopenia	After 1 year of ADM	Drug-induced lupus	Autoantibodies	Prednisolone ADM discontinued
(106)	ANA-positive RF-negative destructive RA	ADM	Cutaneous, muscle pain	After 8 months of ADM with previous 3 years of ETN	Drug-induced lupus erythematosus	Skin biopsy Autoantibodies	Corticosteroids ADM discontinued
(107)	RA and autoimmune hepatitis	IFX + AZA + prednisone	Cutaneous	After 4 months of IFX	Drug-induced lupus-like syndrome	Skin biopsy Colloidal iron stain Autoantibodies	No treatment IFX discontinued
(108)	ANA-positive RF-negative HLA-B27-positive AS	IFX + DMARDs + cortico-steroids	Cutaneous	After 4 years of IFX	Drug-induced chilblain lupus erythematosus	Skin biopsy Autoantibodies	Corticosteroids IFX discontinued
(109)	Active AS	IFX	Thoracic pain and dyspnea	After 8 months of IFX	Drug-induced lupus-like syndrome	Autoantibodies	Methylprednisolone IFX discontinued
(110)	Axial AS	IFX	Joint pain and swelling, and leukocytosis	After 6th IFX infusion	Drug-induced lupus erythematosus	Autoantibodies	Prednisolone IFX discontinued
(111)	Severe RF-negative RA	GLM	Cutaneous	After 16 months of GLM Previous 12 weeks of ETN and 10 months of IFX	Drug-induced subacute cutaneous lupus erythematosus aggravated by sun exposure	Skin biopsy Autoantibodies	Mometasone furoate GLM discontinued
(112)	Active RA	IFX + lefluno-mide	Cutaneous	After 6th IFX infusion	Drug-induced discoid lupus erythematos	Skin biopsy Autoantibodies	Hydroxy-chloroquine and methylprednisolone IFX discontinued
(116)	RA	IFX	Cutaneous and leukocytosis	After 5 weeks of IFX	Generalized psoriasiform and pustular eruption	Skin biopsy	Prednisolone IFX discontinued
(117)	Long-standing HLA-B27-positive AS and CD	ADM	Cutaneous	After 15 months of ADM	New-onset psoriasis	Punch biopsy	Triamcinolone and cetirizine ADM discontinued
(117)	RF-positive RA	ADM	Cutaneous	After 3 years of ADM	New-onset psoriasis	Punch biopsy	Fluocinonide and cetirizine ADM discontinued
(118)	JIA and uveitis	ADM	Cutaneous	After 9 months of ADM	Psoriasis with severe scalp involvement	Skin biopsy	Multi-drug dermatologic therapy ADM discontinued
(119)	HLA-B27-negative spondylo-arthropathy	GLM + leflunomid e	Cutaneous	After 2 months of GLM Previous exposure to IFX and GLM	Bullae and psoriasiform hyperkeratosis	Skin biopsy	No treatment GLM discontinued
(107)	RA	ETN	Cutaneous	After 4 months of ETN	Palmoplantar pustular psoriasis	Histology	Phototherapy and halobetasol ETN discontinued
(87)	JIA	ADM + leflunomid e	Cutaneous	After 10 months of ADM	Palmoplantar pustular psoriasis	Skin biopsy	Steroids and vitamin D ADM discontinued

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Table 3 Cont'd.

Refer-ence	Patient Conditions	Treatment	Course of Reaction	Presentation of Symptoms	Diagnosis	Techniques to Validate Diagnosis	Management of Symptoms
(87)	Long-standing JIA and chronic iridociclitis	ETN + MTX	Cutaneous	After 1 year of ETN	Palmoplantar pustular psoriasis	Clinical Biopsy was refused	Steroids and vitamin D derivatives ETN discontinued
(120)	Long-standing RA	CZP	Cutaneous	After 2nd infusion of CZP	Palmoplantar psoriasis	Skin biopsy	Steroids CZP discontinued
(121)	RA	ADM + MTX	Cutaneous	After 4 months of ADM	Palmoplantar subcorneal pustular dermatosis	Skin biopsy Histology	Clobetasol propionate ADM discontinued
(122)	Erosive RA	ADM + DMARDs	Cutaneous	After 3 years of ADM	Intermediate bullous pemphigoid and cicatricial pemphigoi	Gingival and skin biopsies	Corticosteroids ADM discontinued
(122)	RA	IFX + AZA	Cutaneous	After 7th IFX infusion	Pemphigus foliaceus	Histology Serology	Corticosteroids IFX discontinued
(123)	RF-positive erosive RA and hepatitis C virus infection	ADM + HQ	Cutaneous	Symptoms after 22 months of ADM	Granuloma annulare Relapse on ETN	Skin biopsy	Prednisone and fexofenadine ADM discontinued
(124)	AS Normal baseline LFT results Negative baseline ANA	IFX	Epigastric discomfort and jaundice LFT: bilirubin 97 pmol/L, ALP 521 U/L, γ-GTP 614 U/L, ALT 621 U/L and AST 821 U/L	After 3 months of IFX	*De novo* autoimmune hepatitis with a mixed hepatitis and cholestatic presentation	CT scan of the abdomen Liver biopsy Autoantibodies Abnormal LFT results	Prednisone IFX discontinued
(125)	RA Asymptomatic cirrhosis Normal baseline LFT results Negative baseline ANA	IFX	Scleral icterus and moderate jaundice LFT: ALP 840 U/L, AST 1690 U/L, ALT 2250 U/L, total bilirubin 15.14 mg/dL and direct bilirubin 12.2 mg/dL	After 1 year of IFX	*De novo* autoimmune hepatitis with cholestatic presentation	Liver MRI Liver biopsy Autoantibodies Abnormal LFT results	Methylprednisolone IFX discontinued
(126)	RA Negative baseline ANA	IFX + MTX and prednisolone	LFT: ALT 1061 U/L, AST 2019 U/L and ALP 244 U/L	After 3 years of IFX	Autoimmune hepatitis	Liver biopsy Autoantibodies Abnormal LFT results	Prednisolone IFX discontinued

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Table 3 Cont'd.

Reference	Patient Conditions	Treatment	Course of Reaction	Presentation of Symptoms	Diagnosis	Techniques to Validate Diagnosis	Management of Symptoms
(127)	RA Mild baseline abnormal LFT results attributed to NSAIDs	ETN + MTX and NSAIDs	Tender hepatomegaly LFL: total bilirubin 1.2 mg/dl, direct bilirubin 0.6 mg/dL, AST 237 IU/L, ALT 300 IU/L, ALP 488 IU/L and γ-GTP 126 IU/L	After 2 weeks of ETN	Acute exacerbation of autoimmune hepatitis	Liver biopsy Autoantibodies Abnormal LFT results	Glucocorticoids ETN discontinued
(128)	RA Normal baseline LFT results Negative baseline ANA	ADM	Mild hepatomegaly with steatosis LFT: ALT 266 UI/L and AST 555 UI/L, normal bilirubin, ALP and γ-GTP	After 5th infusion of ADM	Autoimmune hepatitis	Liver biopsy Autoantibodies Abnormal LFT results	Prednisone ADM discontinued
(129)	Erosive RA	ETN	Neurological	After 37 months of ETN	Antiphospho-lipid syndrome/ central nervous system lupus	Cranial MRI Autoantibodies	Corticosteroids, warfarin and azathioprine ETN discontinued
(130)	Spondylo-arthropathy	ADM + MTX	Gastrointestinal, leukocytosis and neutrophilia	After 3rd infusion of ADM	Antiphospho-lipid syndrome	Autoantibodies	Heparin, tinzaparin, clopidogrel and steroids ADM discontinued

Table 4. Neurological adverse events

Reference	Patient Character-istics	Treatment for Conditions	Course of Reaction	Presentation of Symptoms	Diagnosis	Technique to Validate Diagnosis	Treatment for Symptoms
(135)	AS	ETN	Paresthesia and urinary incontinence	After 30 months of ETN	Demyelinating disease	Neurological examination Brain MRI	ETN discontinued
(136)	AS and acute anterior HLA-B27-positive uveitis	IFX	Blurred vision and scotoma Myopic chorioretinal atrophy	After 10 months of IFX	Occipital demyelination	Brain MRI	IFX discontinued
(137)	AS + psoriasis	IFX	Paresthesia	After 4 years of ETN, ADM and IFX	Multifocal sensory motor demyelinating neuropathy with conduction block	CSF analysis Electromyography Nerve biopsy	Intravenous immunoglobulin IFX discontinued

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Table 4 Cont'd.

Reference	Patient Characteristics	Treatment for Conditions	Course of Reaction	Presentation of Symptoms	Diagnosis	Technique to Validate Diagnosis	Treatment for Symptoms
(137)	AS + Crohn's disease	IFX	Sensory motor deficit	After 6 months of IFX	Multifocal sensory motor demyelinating neuropathy with conduction block	CSF analysis Electromyography Nerve biopsy	Intravenous immunoglobulin ETN discontinued
(137)	RA	ADM	Tingling and burning sensations	After 2 years of ADM	Multifocal sensory demyelinating neuropathy	CSF analysis Electromyography Nerve biopsy	No treatment ADM dose reduced
(138)	HLA-B27-negative AS	ADM	Reduced hearing acuity and urinary incontinence	After 3 years of ADM	CNS demyelination evolving to multiple sclerosis	CSF analysis Brain MRI	Intravenous methylprednisolone ADM discontinued
(138)	AS	ETN	Ptosis and peripheral paresis	After 6 years of ETN	CNS demyelination evolving to multiple sclerosis	CSF analysis Brain MRI Cervical MRI	Intravenous methylprednisolone ETN discontinued
(139)	RF-positive RA	ADM	Diplopia, ataxic gait, oculomotorius palsy and abducens palsy	After 22 months of ADM	New-onset multiple sclerosis	Brain MRI	Sodium bicarbonate and metoclopramide ADM discontinued
(140)	RA	ETN	Pain, swelling, loss of balance, muscle weakness and ataxia Loss of sensory perception	After 2nd infusion of ETN	Chronic inflammatory demyelinating polyneuropathy	CSF analysis Electrodiagnostic findings	Intravenous immunoglobulin ETN discontinued
(140)	RA	IFX + MTX, HQ and prednisone	Numbness	After 1 year of IFX	Chronic inflammatory demyelinating polyneuropathy	Electrodiagnostic findings	Intravenous immunoglobulin IFX discontinued
(141)	RA	ADM	Progressive weakness	After 8 months of ADM	Immune-mediated monofocal motor neuropathy	Clinical Arm MRI	Endovenous immunoglobulin ADM discontinued
(142)	RA, Crohn's disease, interstitial lung disease, Reynaud's syndrome, bullous dermatosis and livedo reticularis	ADM	Spinothalamic sensory loss	After 2.5 years of IFX and 4 months of ADM	Small fiber polyneuropathy	Skin biopsy Nerve conduction study and electro-myography	No treatment ADM discontinued
(142)	RA	ADM	Numbness, weakness and decreased reflexes	After 2.5 years of ADM	Chronic inflammatory axonal polyradiculo-neuropathy	CSF analysis Spinal MRI	Intravenous immunoglobulin, azathioprine and prednisone ADM discontinued
(143)	RA	ADM + MTX	Tetraparesis, facial paralysis, ophthalmoparesis and respiratory failure	After 14 months of ADM	Guillain-Barré syndrome with acute motor axonal neuropathy	CSF analysis Neurophysiological examination	Intravenous immune-globulins ADM and MTX discontinued
(142)	AS and Grave's disease	IFX	Leg weakness and paraparesis	After 1.5 years of IFX	Longitudinally extensive transverse myelitis	Neurological exam Nerve conduction study and electromyography Brain and spinal MRI	Intravenous methylprednisolone IFX discontinued

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Table 4 Cont'd.

Reference	Patient Characteristics	Treatment for Conditions	Course of Reaction	Presentation of Symptoms	Diagnosis	Technique to Validate Diagnosis	Treatment for Symptoms
(144)	RA	ETN	Paresthesia and bowel incontinence	After 42 months of ETN	Cervical myelitis	Spinal MRI	Folate supplements and methylprednisolone ETN discontinued
(145)	RF-positive RA	ADM	Pain and parasthesias	After 4 weeks of ADM	Mononeuritis multiplex	Electromyography Sural nerve biopsy	Methylprednisolone and cyclosporine ADM discontinued
(142)	RA	ETN	Visual loss and scotoma	After 4 years of ETN	Acute optic neuritis	Brain MRI	No treatment ETN discontinued
(146)	RA and osteoporosis	IFX	Amaurosis	Symptoms after 4th infusion of IFX	Optic neuritis	MRI of the orbits	Methylprednisolone IFX discontinued
(147)	HLA-B27-positive AS	ETN	Aphasia and hemiparesis Generalized seizures	After 11 months of ETN	Tumefactive demyelinating lesions	CSF analysis Brain MRI Brain biopsy	Intravenous methylprednisolone ETN discontinued
(142)	Juvenile RA	ETN	Spastic quadraparesis and leukopenia	After 2 months of ETN	Autoimmune leukoencephalopathy	CSF analysis: anti-brain antibodies Brain MRI	Intravenous methylprednisolone, intravenous immunoglobulin, cyclophosphamide, azathiprine and prednisone ETN discontinued
(148)	RF-negative pediatric systemic idiopathic arthritis	ETN	Generalized seizures and sustained clonus	After 3rd infusion of ETN	Encephalopathy	CSF analysis Electroencephalogram Brain MRI	No treatment ETN discontinued
(149)	RF-positive erosive RA	IFX + MTX, HQ and prednisone	Generalized tonic-clonic seizures, coma and orofacial myoclonus	After 3 years of IFX	Global encephalopathy	Brain MRI Electroencephalogram	Pulse methylprednisolone IFX discontinued
(150)	RA	ADM + MTX	Cognitive slowing and bradykinesia Prechiasmatic conduction delay	After 3 months of ADM	Demyelinating leukoencephalopathy with negative JCV	CSF analysis Brain MRI	Treatment not specified ADM discontinued
(155)	RF-positive erosive RA	IFX + MTX and prednisone	Progressive confusion, poor coordination and weakness	After 5 years of IFX	Progressive multifocal leukoencephalopathy with positive polyomavirus	CSF analysis Brain MRI Solochromeeosin staining Polyomavirus immunostaining	Supportive therapy IFX and MTX discontinued
(156)	Erosive polyarthritis and systemic lupus erythematosus	ETN and prednisone	Hemiparesis and hemiataxia Facial numbness and dysarthria	After 4 years of ETN	Progressive multifocal leukoencephalopathy with positive JCV	CSF analysis Brain MRI Neurological examination Serological evaluation	No treatment ETN discontinued
(129)	RA	ETN	Neurological illness	After 1 month of ETN	Epstein-Barr virus encephalitis	CSF analysis Brain MRI Polymerase chain reaction	Valganciclovir ETN discontinued

Table 5. Hematological adverse events

Reference	Patient Characteristics	Treatment for Conditions	Course of Reaction	Presentation of Symptoms	Diagnosis	Technique to Validate Diagnosis	Treatment for Symptoms
(159)	RA	ETN + MTX and predni-solone	Asymptomatic	After 7th ETN injection	Neutropenia (0.84×109/L)	Bone marrow examination Laboratory evaluation	Increase prednisolone dose ETN discontinued
(159)	RA	ETN + MTX	Sore throat, mouth ulcers and pyrexia	After 1st ETN injection	Severe neutropenia (0.17×109/L)	Bone marrow examination Laboratory evaluation	Prednisolone ETN discontinued
(160)	RA	ADM + MTX and prednisone	Asymptomatic	After 1st ADM injection	Neutropenia (lowest 0.90×109/L)	Laboratory evaluation	No treatment ADM discontinued
(161)	RA	ETN + prednisolone	Gingival abscess	After 1 month of ETN	Severe neutropenia (total leukocyte count 1.25×109/L and the absolute neutrophil count 0.15×109/L)	Bone marrow examination Cytogenetic analysis Laboratory evaluation	Granulocyte stimulating factor ETN discontinued
(162)	Sacroiliitis	ETN + MTX and SSZ	Presentations not detailed	After 6 months of ETN	Leukopenia (leukocytes 3.1×1012/L and polymorphonuclear leukocytes 1.16×1012/L)	Laboratory evaluation	ETN discontinued
(163)	RA	ETN + MTX and leflunomide	Petechia	After 3 months of ETN	Leukopenia (white blood cells 2.4×109/L vs. 5.9×109/L at baseline) Thrombocytopenia (platelet count 60×109/L vs. 187×109/L at baseline)	Laboratory evaluation	ETN discontinued
(164)	RA	ETN	Asymptomatic	After 3rd ETN injection	Thrombocytopenia (platelet count 38×109/L)	Laboratory evaluation	No treatment ETN discontinued
(164)	RA	IFX + MTX	Chest infection treated with amoxycillin	After 2 years of IFX	Sudden thrombocytopenia (platelet count 26×109/L)	Laboratory evaluation	No treatment ETN and MTX discontinued
(165)	RA	ADM + MTX	Asymptomatic	After 8 months of ADM	Lymphocytosis (white blood cells 7.8×109/L, neutrophils 2.8×109/L and lymphocytes 4.0×109/L)	Laboratory evaluation	No treatment MTX and ADM discontinued
(168)	RA	ETN + MTX	Fever (38.5-C), buccal ulcerations and pancytopenia	After 3 weeks of ETN	Pancytopenia (white blood cells 2.88×109/L, absolute neutrophils 1.09×109/L, platelets 30×109/L)		Acyclovir and ciprofloxacin ETN and MTX discontinued
(169)	RA	ETN + MTX and prednisone	Severe multilobar pneumonia	After 1 year of ETN	Severe pancytopenia (platelets 122×109/L, erythrocytes 2.81×1012/L, hematocrit 26.2%, hemoglobin 8.4 g/dL, neutrophils 0.95×109/L, lymphocytes 0.29×109/L and leukocytes 1.41×109/L)	Laboratory evaluation	Piperacillin-tazobactam and targocid ETN discontinued
(170)	RF-positive RA	ETN + MTX and predni-solone	Cutaneous, disseminated intravascular coagulation, respiratory failure, leukocytoclastic vasculitis, pancytopenia with white blood cell count 2000/μL, hemoglobin 8.5 g/dL, platelet count 84000/μL	After 3 years of ETN	Drug-induced lupus accompanied by hemophagocytic syndrome	Laboratory evaluation Skin biopsy Bone marrow biopsy Chest and abdomen CT scan Cytokine profile analysis Autoantibodies	IV methylprednisolone

Table 6. Adverse events in other organs

Reference	Patient Characteristics	Treatment for Conditions	Course of Reaction	Presentation of Symptoms	Diagnosis	Technique to Validate Diagnosis	Treatment for Symptoms
(177)	RF-positive anti-CCP-positive RA	CZP + MTX	Dyspnea and cough Inspiratory crepitations, ground-glass opacities Respiratory function impairment	After 8 weeks of CZP	Non-infectious ILD	High-resolution CT scan Bronchoscopy	Methylprednisolone CZP discontinued
(178)	Erosive RA	CZP + MTX	Dyspnea and cough Basal crackles, ground-glass opacities Respiratory function impairment	After 4 months of CZP	Non-infectious ILD with features of organizing pneumonia	Chest CT Lung biopsy	Methylprednisolone CZP discontinued
(179)	RA	ADM + MTX	Dyspnea and cough Ground-glass opacities	After 2nd dose of ADM	Acute ILD	High-resolution CT scan	Prednisone ADM discontinued
(181)	RF-positive RA	CZP + leflunomide and prednisone	Dyspnea and cough Severe interstitial lung fibrosis Pulmonary eosinophilia	After 3 months of CZP	Fibrosing alveolitis	Chest X-ray	Methylprednisolone CZP discontinued Died of respiratory failure
(182)	AS	IFX + piroxicam	Dyspnea and cough Hemoptysis	After 2nd dose of IFX	Diffuse alveolar hemorrhage	CT scan Fiberoptic bronchoscopy	No treatment IFX discontinued
(183)	RA and psoriatic arthritis	ETN	Dyspnea and cough Severe tachypnea and fine rales	After 1 month of ETN	Diffuse alveolar hemorrhage and severe acute respiratory distress syndrome	Chest CT scan Bronchoalveolar lavage Lung biopsy Tracheotomy	Steroids ETN discontinued
(184)	RA	IFX + AZA	Dyspnea and cough	After 2nd dose of IFX	Interstitial pneumonitis	Chest x-rays High-resolution CT scan Transbronchial biopsy	Methylprednisolone IFX discontinued
(185)	RA	ADM + prednisolone	Cough Rales, ground-glass opacities	After 5 months of ADM	Interstitial pneumonia	Chest x-rays High-resolution CT scan	Prednisolone ADM discontinued
(186)	RA	ADM + NSAIDs and DMARDs	Cough Fine crackles, , ground-glass opacities	After 1 month of ADM	Interstitial pneumonia	High-resolution CT scan	Methylprednisolone ADM discontinued
(187)	RA and history of ILD	ETN + prednisolone	Cough Fine crackles, ground-glass opacities	After 2 months of ETN	Interstitial pneumonia with fatal respiratory failure	CT scan	Steroids ETN discontinued
(188)	RF-positive anti-CCP-positive RA	ADM without DMARDs	Dyspnea and cough	After 42 months of ADM	Acute pneumonitis	High-resolution CT scan Pulmonary function tests Lung biopsy	Corticosteroids ADM discontinued
(189)	RA	CZP + MTX	Dyspnea and cough Ground-glass opacities Acute respiratory distress	After 4th dose of IFX	Severe acute pneumonitis	Positron emission tomography/CT scan High-resolution CT scan	Prednisolone CZP discontinued
(190)	RA	ETN monotherapy	Dyspnea and cough Transient skin rash, leukopenia	After 16 months of ETN	Organizing pneumonia with concomitant lupus	Chest radiography High-resolution CT scan Thoracoscopic lung biopsy Autoantibodies	Prednisolone ETN discontinued

Cont'd…

Table 6 Cont'd.

Reference	Patient Characteristics	Treatment for Conditions	Course of Reaction	Presentation of Symptoms	Diagnosis	Technique to Validate Diagnosis	Treatment for Symptoms
(196)	RF-positive RA	IFX + NSAIDs and prednisone	Jaundice with ALT 448 U/L, AST 1100 U/L and total bilirubin 16.6 mg/dL	After 3rd dose of IFX	Acute drug-induced liver injury with positive serum ANA, and IgG, IgM and IgA anti-dsDNA antibodies	Core liver biopsy	Methyl-prednisolone IFX discontinued
(197)	HLA-B27-positive AS	IFX with previous MTX and NSAIDs	Persistently elevated aminotransferase levels with AST 177 IU/L and ALT 412 IU/L	After 3rd dose of IFX	Acute drug-induced liver injury with positive serum ANA and anti-dsDNA antibodies	Percutaneous liver biopsy Abnormal LFT results	No treatment IFX discontinued
(198)	Erosie RF-positive anti-CCP-positive RA	ETN mono-therapy	Dyspnea Facial palsy, eyesight deficiency	After 4 years of ETN	Neurosarcoidosis	Cerebral MRI Cerebral fluid 18F-fluoride PET-CT scan Elevated angiotensin-converting enzyme in serum	IV steroids ETN discontinued
(201)	AS	IFX + NSAIDs	Progressive dyspnea Hilar adenopathy Ground-glass opacities	After 27 months of IFX	Stage II thoracic sarcoidosis	Chest radiography CT scan Histology	No treatment IFX discontinued
(202)	Erosive RF-positive RA	ETN mono-therapy	Progressive dyspnea and asthenia Hilar adenopathy Diffuse nodular pattern	After 49 months of ETN	Pulmonary granulomatosis compatible with sarcoidosis	Chest radiography High-resolution CT scan Bronchoscopy Transbronchial biopsy	Prednisone ETN discontinued
(203)	Erosive RA Positive ANA	ETN + MTX and prednisone	Slightly elevated ALP, γ-GTP, ALT and AST Normal bilirubin and LDH	After 4 months	Granulomatous hepatitis	Abnormal LFT results Liver biopsy	Ursodiol ETN discontinued
(204)	AS	ADM + ibuprofen	Elevated serum creatinine level Low estimated glomerular filtration Hilar adenopathy	After 18 months of ADM	Granulomatous interstitial nephritis	Chest radiograph Kidney biopsy Immunohistochemistry	Prednisone ADM and ibuprofen discontinued