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ORIGINAL ARTICLE

Anti-TNF therapies: a comprehensive analysis of adverse effects associated with immunosuppression

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Abstract Knowledge and understanding about the immunosuppressive properties of anti-TNF therapies and the adverse effects these causes have advanced over the last 10 years since the first of these drugs was approved. These drugs work by inhibiting tumour necrosis factor (TNF) in the body, which plays an essential role in the immune response to invading pathogens. Anti-TNF drugs have therapeutic value because high levels of TNF are thought to be part of the pathophysiology of many chronic inflammatory disorders such as rheumatoid arthritis and Crohn's disease. Anti-TNF drugs are usually well-tolerated, however, there have been reports of many potentially serious adverse effects. This article will comprehensively analyse these adverse effects; the incidence, symptoms and mechanisms will be discussed. In addition, the contraindications of this class of drugs will be explored and the detection and prevention methods that should be put in place by health care professionals who treat patients on these drugs will be described.

Keywords Anti-TNF · Biologics · Immunosuppresion · Adverse effects · Rheumatology

Introduction

Tumour necrosis factor (TNF) is a proinflammatory, multifunctional cytokine [1, 2] which is synthesised by various cells including activated monocytes, macrophages, and T-cells [2, 3]. TNF is initially produced as a transmembrane protein (tmTNF), which is cleaved to release the mature soluble cytokine sTNF [2, 4]. Finally it becomes biologically activated due to the aggregation of three TNF monomers to produce trimeric TNF, this then binds to one of the two cell-surface receptors which are expressed on many cells [2–4]:

1. Type 1 TNF receptors, p55
2. Type 2 TNF receptors, p75

In the normal body, TNF has an integral role in mounting the inflammatory response against invading pathogens [5]. Its functions are stated in Table 1.

Even though there is no invading pathogen, excessive amounts of TNF have been detected in patients with chronic inflammatory diseases. Therefore, it was concluded that TNF "plays an important role in the pathogenesis [7]" of these diseases. This led to the development of anti-TNF therapies as an alternative treatment.

Two types of anti-TNF therapies were created: monoclonal antibodies and soluble receptors. The Medicines and Healthcare products Regulatory Agency (MHRA) has approved three anti-TNF drugs, two are monoclonal antibodies namely infliximab and adalimumab, and one is a soluble receptor called etanercept [2], see Fig. 1.

Infliximab is a chimeric (human–mouse) monoclonal antibody, containing a constant region of the human IgG1 antibody and an antigen-binding region of a mouse antibody [3, 4, 8]. Adalimumab is a "humanised monoclonal antibody [4]", therefore it has both constant and variable regions of the human IgG1 antibody. Etanercept is a type 2 TNF receptor fusion protein, created from two extracellular domains of the type 2 TNF receptor (p75) fused with part of the human IgG1 antibody. See Table 2 for the method of

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Table 1 The function of TNF in the normal human body

TNF functions	1. Activation of neutrophils [6]
	2. Increasing activity of macrophages and natural killer cells [6]
	3. Increasing cell adhesion [1, 5]
	4. Inducing cytotoxicity against infected macrophages [1]

action of these anti-TNF agents and the inflammatory disorders which the National Institute of Clinical Excellence (NICE) has approved them for use.

This year is the tenth anniversary of the first anti-TNF agent, infliximab to be approved; whilst in many ways these drugs have revolutionised the treatment of inflammatory diseases. Their increased clinical use has resulted in a concomitant increase in the reporting of their adverse effects. In this article the adverse effects associated with the immunosuppression caused by anti-TNF agents will be comprehensively analysed.

Methods

The search strategy was designed to retrieve references relating to anti-TNF agents, their mode of action and how this relates to the adverse effects caused by these drugs. Database searches included Scopus, Amed, Cochrane library and Medline through both Ovid and Pubmed. Important articles were also obtained by using reference lists from key reviews, titles and abstracts of all articles were assessed for inclusion/exclusion.

Internet searches were also utilised for information, examples of sites used are google scholar, NICE website, MHRA website and national library of medicines. Search terms for both internet and database searches included "anti-TNF", "TNF antagonists" or the names of each of the anti-TNF agents plus one or more of the following words "adverse effects", "side effects", "complications", "immunity", "risks" and "infections". No date restrictions were placed on any searches, however, priority was given to the most up-to-date trials and reviews to ensure that the information used was as relevant as possible.

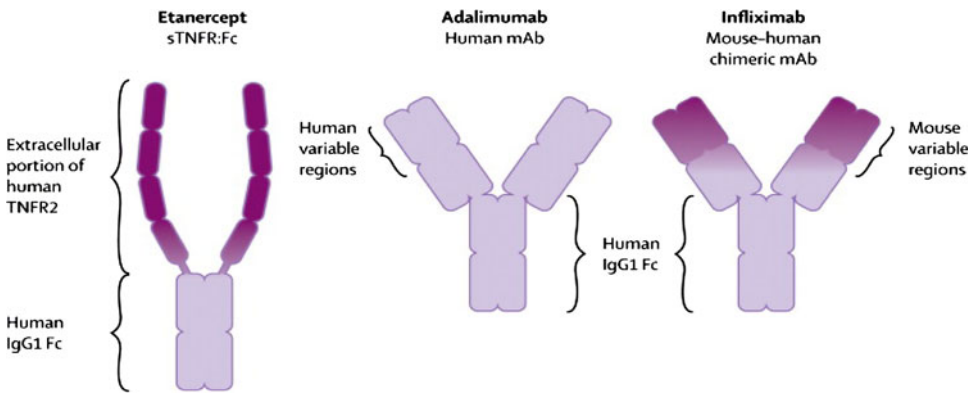

Fig. 1 Structures of the anti TNF agents [4]

Table 2 Anti TNF agents: their method of action and approved uses [8]

Agent	Presumed method of action	Approved uses
Etanercept	Binds to circulating TNF. May have effects that are mediated through neuro-endocrine pathways as well	Rheumatoid arthritis (RA) Psoriatic arthritis Moderate-to-severe plaque psoriasis Ankylosing spondylitis Juvenile inflammatory arthritis
Infliximab	Infliximab binds to soluble and membrane-bound forms of TNF-α and blocks the interaction of TNF-α with TNF-α receptors. Infliximab causes apoptosis of cells with cell-surface TNF	Moderate-to-severe plaque psoriasis Rheumatoid arthritis Fistulae in Crohn's disease Crohn's disease including children and adolescents Psoriatic arthritis Ankylosing spondylitis
Adalimumab	Adalimumab binds to soluble and membrane-bound TNF-α leading to a blockade of activity of TNF. Apoptosis of cells with membrane-bound TNF occurs	Rheumatoid arthritis Ankylosing spondylitis Psoriatic arthritis

Results and discussion

Due to the mechanism of action of all three anti-TNF drugs, immunosuppression is caused by blockage of the immune cascade TNF initiates. As a by-product of this, seven main types of adverse effects have been seen including:

1. Increased incidence of infections
2. Malignancies
3. Demyelinating syndromes
4. Worsening congestive cardiac failure (CCF)
5. Immunogenicity
6. Infusion/injection reactions and hypersensitivity
7. Hepatotoxicity
8. Haemological disorders

Reports of the above adverse effects have been associated with the use of all three anti-TNF therapies, however, there are slightly differing incidences for each drug, and the hypotheses for these differences are explained in Table 3 below.

Infections

It is not surprising that there is a high incidence of infections seen as an adverse effect of patients being treated with anti-TNF drugs when you consider the integral part TNF plays as a "central role in the initial host response to infection [4]". The incidence of infections is debatably the most important adverse effect of anti-TNF therapy. Many different types have been reported including, tuberculosis (TB), serious bacterial infections, listeriosis, atypical mycobacterial infections, histoplasmosis, coccidioldmycosis and pneumonia [9]. It is difficult to attribute these infections fully to the anti-TNF therapies because:

- Patients with chronic inflammatory diseases such as rheumatoid arthritis (RA) are know to have an approximately twofold predisposition to infections in comparison to the general public irrespective of treatment [3].
- Most patients who are candidates for anti-TNF treatment are usually already on corticosteroids and/or other immunosuppressive drugs which have already increased their infection risks.

However, due to the major role TNF plays in immunity against invading pathogens, it is biologically plausible that inhibition of TNF would cause an increase in infection incidence.

General bacterial infections are associated with all three anti-TNF agents; most of these are not serious and are resolved by antibiotic treatment and/or "temporarily stopping the drug [10]". The incidence of serious bacterial infections is a debated issue; there have been sporadic reports of fatal cases with infections such as severe pneumonia, meningitis and sepsis [9]. Yet other reviews state that there is "no increased incidence of serious infections [8]".

There is evidence that the risk of opportunistic infections is increased by the use of anti-TNF drugs. The major concern is the activation of latent TB [3]. It has been proven that TNF has a specific role in the defence against the TB pathogen causing the formation of granulomas and therefore containment of the disease. Therefore, screening for latent or active TB prior to treatment is highly recommended. In addition, on finding a positive test, the patient must undergo treatment for TB before initiation of any anti-TNF drugs.

Due to the essential role TNF has in granuloma formation; the reactivation of granulomatous fungal infections is another concern. There is no clear relationship between the formation of these infections and any one anti-TNF drug and their incidence is very low, therefore no guidelines have been produced to "screen and treat latent fungal infections [10]" before the start of anti-TNF drugs; however, clinicians still need to be vigilant.

Unfortunately, there is little data on the effects of anti-TNF agents on patients with existing viral infections [11]. However, the little data available suggest that their effect is dependant on the type of viral infection. Evidence suggests

Table 3 Hypotheses for the differences in risk of adverse effects anti-TNF drugs [6, 7]

Hypothesis	Explanation
Pharmacokinetics	Infliximab and adalimumab have longer half-lives and serum half-lives, greater volumes of distribution and have lower clearances than etanercept
Binding activities	Infliximab and adalimumab inhibit both type 1 and type 2 TNF receptors, however, etanercept will only inhibit type 1 receptors and therefore would leave type 2 inhibitors at least somewhat intact
Bioavailability	The intravenous form of infliximab has greater bioavailability due to its high association and low dissociation rates compared to etanercept and adalimumab, therefore they will have higher peak and more constant concentrations in the body
Induced apoptosis	There is evidence to suggest that infliximab can induce apoptosis of activated macrophages and T-cells therefore adversely affecting the immune response more than adalimumab and etanercept do

that patients with hepatitis c virus (HCV) have elevated levels of TNF in their bodies and this has been linked to the pathophysiology of the disease [12]. Small studies have shown that the anti-TNF drugs are safe and may even be beneficial to patients with HCV [12]. However, clinicians must be cautious when treating HCV patient with anti-TNF, monitoring of their serum aminotransferase and viral load is recommended [11, 12].

Conversely in patients with hepatitis B virus (HBV), the use of anti-TNF treatment is of greater concern as there have been reports of the reactivation of stable HBV [11, 12]. This may be due to the fact that TNF seems to "promote viral clearance [12]" and therefore controls the HBV; some studies recommend screening of patients for HBV before the initiation of anti-TNF therapy. In addition, the European Association for the Study of Liver Disease recommends that "antiviral treatment should be initiated 2–4 weeks before [8]" the start of the anti-TNF drugs and should continue throughout the patient's treatment [8].

Reports of the use of anti-TNF therapies in patients with existing human immunodeficiency virus (HIV) have suggested that they have been well-tolerated; however, the data are limited. It is important that HIV treatment is "well-established before initiation of therapy with a TNF inhibitor [11]". In addition, due to the immunocompromised nature of the disease, infection risk needs to be monitored closely whilst on anti-TNF therapy.

Malignancies

The oncogenic effect of all three anti-TNF drugs is of very real theoretical concern. The immune system, specifically TNF plays a large role in suppressing the development and spread of tumours by triggering apoptosis of tumour cells [9]. However, in reality the causal relationship between anti-TNF drugs and malignancies, specifically lymphoma, is a highly debated issue [3]. This is due to the fact that irrespective of medications used, the risk of lymphoma is known to be higher in patients with rheumatoid arthritis and Crohn's disease [3]. Therefore, when assessing study results it is difficult to attribute the estimated 2.3–6.4 times higher incidence of lymphomas in patients using anti-TNF drugs, compared to the general public, to the treatment rather than to the disease itself [3, 9].

However, information presented to the Food and Drug Administration (FDA) showed that there is an increased risk of lymphomas in patients on anti-TNF compared to patients with RA not on this treatment [13]. Is it debatable whether the incidence of other cancers is raised by the use of anti-TNF therapies, some reviews state that "Apart from lymphoma, the incidence of cancer is not significantly altered [3]", yet others talk about the increased risk of solid tumours and skin cancer [13]. Due to this uncertainty, continued vigilance is needed until the relationship is better understood [10].

Neurological

Since the approval of anti-TNF agents for treatment, there have been several reports of adverse effects on the neurological system, specifically reported are demyelinating syndromes and seizures. These adverse effects can be broadly placed into four main groups:

1. Exacerbation of Multiple Sclerosis(MS) [14]
2. New-onset MS [14]
3. Acute mental state changes for example encephalopathy
4. Cases of neurological disease excluding MS for example optic neuritis.

A wide variety of clinical symptoms have been attributed to these adverse effects, most commonly paresthesia, visual disturbances and confusion [3, 14]. Studies have proven that there is a "temporal relationship [15]" between neurological adverse effects and anti-TNF therapy; in addition it was found that all symptoms improved or disappeared completely when the therapy was discontinued [15]. The package leaflets of all three anti-TNF drugs state that nervous system disorders are an uncommon or rare side effect, see Appendices 1, 2 and 3; Table 4 for definitions.

The mechanism of action of these adverse effects is still largely unclear; however, one hypothesis is that anti-TNF drugs may cause exacerbation of autoimmunity by blocking the normal activity of TNF in the immune system and this will cause the effects stated in Table 5.

Table 4 Definitions of risk attributions used in package leaflets

	Seen in number of patients
Very common	More than 1 in 10
Common	Less than 1 in 10 but more than 1 in 100
Uncommon	Less than 1 in 100 but more than 1 in 1,000
Rare	Less than 1 in 1,000
Very rare	Less than 1 in 10,000

Table 5 The effects of TNF inhibition

Effects of inhibition of TNF	1. Decrease apoptosis of auto-reactive T-cells allowing them to continue to mount a response against the bodies own tissue and cells [14] 2. "Alter antigen-presenting cell function[14]" 3. "Increase T-cell receptor function[14]" 4. Inhibit the repair process TNF may play in helping remyelination of neurons [16] 5. Cause unidentified infections which attack the neurological system to become unmasked [16]

Due to the minor number of cases of seizures reported with the use of anti-TNF therapies a past history of seizure disorders does not seem to contraindicate the use of these drugs. In the case of patients with established demyelinating diseases such as MS, it is reasonable to avoid the use of these drugs, some clinicians will also be cautious when using them in patients with a family history of these diseases [8, 9, 15]. If any neurological symptoms are seen in patients on anti-TNF drugs they need to be discontinued immediately to avoid the progression of these symptoms [15].

Congestive cardiac failure

High levels of circulating TNF have been found in patients with congestive cardiac failure (CCF); it has been implicated in the pathogenesis of the disease and is thought to be the cause of the decreased cardiac contractility [3, 17]. Due to this finding, the therapeutic effects of anti-TNF drugs in patients with CCF were tested to see if the symptoms of the disease could be reduced. However, there was found to be no beneficial effects, and in some cases the anti-TNF drugs may even cause a worsening of the patient's CCF, see Table 6. Due to the serious adverse effects reported in the trials of etanercept and infliximab, adalimumab never underwent any treatment trials.

The mechanism of this adverse effect is still very uncertain and continues to be the subject of large studies. The issue is further complicated because patients with inflammatory disorders such as rheumatoid arthritis are know to be at higher risk for cardiovascular disease compared to the general public [17]. Therefore, a causal relationship between anti-TNF and CCF is hard to prove, nevertheless results of postmarking case reports and spontaneous reporting systems have shown the very real, albeit rare, adverse effect of CCF with patients on anti-TNF therapies developing CCF or experiencing worsening symptoms of their existing CCF. Although the mechanism of this adverse effect is still largely unknown, studies have hypothesised that using anti-TNF agents may "decrease TNF-alpha levels below physiological levels for repair [18]". In addition they have suggested that TNF may have beneficial effects on patients:

1. When the heart has acute ischemic injury, TNF may have a cytoprotective effect [18]
2. TNF may be able to "maintain peripheral blood flow in patients with heart failure [18]" by triggering the increased production of nitric oxide in the vascular system
3. TNF may have an "important role in tissue remodelling and repair" [18].

As anti-TNF drugs inhibit the majority of TNF in the body they will also halt of all these beneficial functions and therefore could lead to an exacerbation of the patients CCF. Given all this evidence, it is advisable to avoid using anti-TNF treatment in patients with symptomatic CCF. However, in patients with mild CCF, anti-TNF drugs can be utilised but care and strict vigilance are needed.

Immunogenicity

A number of studies have shown that anti-TNF drugs can lead to the formation of neutralising and non-neutralising antibodies [1]. Although there is evidence to suggest that these antibodies develop as a reaction to all three drugs, the risks vary slightly, see Table 7.

The formation of neutralising antibodies is of concern for patients on anti-TNF therapies as their production may

Table 6 Anti-TNF trials in patients with heart failure [18]

Trial	Year	Design	Patients	Results
RENAISSANCE	1999–2001	Large, randomized, phase2/3 placebo- controlled, double-blind trials of etanercept in patients with NYHA III–IV heart failure	925	Terminated and halted in 12.7 months due to poor clinical outcome. Trial resulted a dose-dependent trend toward increased all-cause mortality and hospitalizations in etanercept groups
RECOVER	1999–2001	Large, randomized, phase2/3 placebo- controlled, double-blind trials etanercept in patients with NYHA III-IV heart failure.	1,123	Terminated and halted in 5.7 months of due to poor clinical outcome like RENAISSANCE
RENEWAL	1999–2001	A combined analysis of medium and High dose of etanercept	NA	A trend toward increased mortality and chronic heart failure hospitalizations in etanercept-treated group
ATTACH	2000–2001	Randomized, double-blind, placebo-controlled, pilot trial of infliximab in patients of NYHA III–IV	150	TNF-a antagonism with infliximab did not improve and high doses adversely affected the clinical condition of patients with moderate to severe chronic heart failure

NYHA New York Heart Association, *NA* not spplicable, *RENAISSANCE* randomized etanercept North AmerIcan strategy to study antagonism of cytokines, *RECOVER* research into etanercept cytokine antagonism in ventricular dysfunction, *RENEWAL* randomized etanercept worldwide evaluation, *ATTACH* anti-TNF-α therapy against chronic heart failure

Table 7 Differing risks of formation of antibodies for the three anti-TNF drugs

Infliximab	Adalimumab	Etanercept
Infliximab is of most concern because of its chimeric structure, human antichimeric antibodies (HACA) can form against the variable mouse portion of the molecule [19]	Fewer patients on adaalimumab have been found with neutralising antibodies, this is probably due to its "fully humanized [19]" structure. However there have been reports of the formation of human antihuman antibodies (HAHA) [19]	There has been no reports of the formation of neutralising antibodies with patients on etanercept, yet there has been reports of non-neutralising antibody formation "in approximately 16% of patients [19]"

lead to allergic reactions to the drugs or change the efficiency of the agent.

The evidence of the development of autoantibodies in patients treated with anti-TNF drugs [19] is of greater concern; specifically there is evidence of the formation of antinuclear antibodies and anti-DNA antibodies. As with the risk of formation of neutralising antibodies, infliximab may be more likely to form these autoantibodies in comparison to adalimimab and etanercept [9, 19]. Even though this is a concern for health care professionals, the formation of these autoantibodies have been shown not to be a presage to autoimmune disorders [9].

Several studies have also found autoimmune diseases to be an adverse effect of anti-TNF agents. These studies have shown

1. There is a "temporal association [19]" between anti-TNF therapies and patients developing symptoms of an autoimmune disease [19]
2. After the anti-TNF drug is stopped, there is a regression of the autoimmune condition [19]
3. If the drug is re-given to a patient after being stopped due to formation of autoimmune symptoms, these symptoms will reappear and in some cases even become worse.

The most common autoimmune diseases seen with anti-TNF drugs are; drug induced lupus, vasculitis, interstitial lung disease, uveitis and psoriatic skin lesions.

Infusion/injection site reactions and hypersensitivity

Injection/infusion site reactions are the most common adverse reactions seen with anti-TNF drugs. The symptoms usually very mild and are therefore of "little clinical significance [8]", they include:

- minor itching and redness around the site
- headache
- dizziness
- nausea

These reactions are thought to be mediated by T-cells and are described as "delayed-time hypersensitivity reactions [9]". They would usually occur in the first month of treatment and decrease in severity over time, this is possibly due to an induced tolerance of the drug.

Injection site reactions are more common in etanercept and adalimumab. Infusion reactions on the other hand are more common with infliximab; these are also usually very mild and are remedied by slowing the infusion rate or prescribing either antihistamines or glucosteroids.

Hepatotoxicity

Anti-TNF agents have been associated with a small risk of hepatotoxicity; in 2004 the FDA issued a warning to healthcare professionals about the risks of hepatic disease [8, 15]. The warning was issued after FDA receiving approximately 35 case reports of hepatic disease from their MedWatch programme [8, 15]. Examples of the adverse effects reported were acute liver failure, hepatitis, and cholestasis; some of which were very severe leading to the need-to-need of transplantation or mortality. Infliximab seemed to be the cause in the majority of these cases, however, all three anti-TNF drugs have raised liver function tests as an uncommon or rare side effect on their package inserts, see Appendices 1, 2 and 3.

Haematological

There have been reports of haematological dyscrasias, such as aplastic anaemia and pancytopenia due to anti-TNF

Table 8 British Society for rheumatology guidelines for anti-TNF-α therapy [20]

Active disease	DAS > 5.1
Pretreatment	Failure of at least two DMARDs after adequate trial
Exclusion	Pregnancy or breast feeding
	Active infection
	High risk of infection (various identified)
	Malignancy or pre-malignancy
Withdrawal	Adverse events
	Lack of effect, DAS not improved by >1.2 at >3 months

DAS Disease activity score, *DMARDs* disease-modifying antirheumatic drugs

therapies, however, these adverse reactions are very rare. Nevertheless these disorders can be very serious, therefore, clinicians and patients both need to be aware of the symptoms for example "pallor, gum bleeding, easy brusibility, general bleeding and persistent fever or infection [12]". Due to the isolated nature of these cases, it is unnecessary to formally monitor patients for haematological dycrasias, however if symptoms are noticed patients should be taken off the anti-TNF drug and should be assessed for any underlying diseases [9].

Conclusion

The decision to start a patient on anti-TNF therapy is a very complicated one; these drugs cause immunosuppression which in turn leads to many potentially serious adverse effects. However, they are arguably "among the most effective treatments [3]" for chronic inflammatory diseases. Due to this, the risk-benefits analysis is complex, nevertheless when used correctly and when the adverse effects detection and prevention methods are put in place the benefits outweigh the risks, see Table 8.

There are many different adverse effects seen with anti-TNF drugs, all of which are still of great concern to clinicians prescribing these drugs. The incidence of infections has to be monitored closely to ensure that they do not become fatal. The lymphoma rate is also a serious concern; however, a causal relationship has yet to be found; more long-term studies are needed to clarify the importance of this relationship. In addition, the development of neurological disorders, CCF onset or worsening, immunogenicity, infusion/injection reactions, hepatotoxicity and haematological disorders are all very uncommon and seem to be easily reversed with discontinuation of treatment.

Finally, the most important thing to consider when using anti-TNF treatment is that all healthcare professionals and patients are aware of the adverse effects to ensue early detection, it is also important that the decision to start treatment should be individualised to the patient's circumstances and risk profile [17, 20].

Conflict of interest statement There are no conflicts of interest for this author.

Appendix 1

Package leaflet: information for the user 3799(53)

Humira

40 mg solution for injection in pre-filled syringe

Adalimumab

In this leaflet:

1. What Humira is and what it is used for
2. Before you use Humira
3. How to use Humira
4. Possible side effects
5. How to store Humira
6. Further information.

Possible side effects

Like all medicines, Humira can have side effects, although not everybody gets them. Most side effects are mild to moderate. However, some may be serious and require treatment. Side effects may occur at least up to 5 months after the last Humira injection.

Tell your doctor immediately if you notice any of the following:

- Severe rash hives or other signs of allergic reaction;
- Swollen face, hands, feet;
- Trouble breathing, swallowing;
- Shortness of breath with exertion or upon lying down or swelling of the feet;
- Signs and symptoms suggestive of blood disorders such as persistent fever, bruising, bleeding, paleness;

Tell your doctor as soon as possible if you notice any of the following:

- Signs of infection such as fever, feeling sick, wounds, dental problems, burning on urination;
- Feeling weak or tired;
- Coughing;
- Tinglings;
- Numbness;
- Double vision;
- Arm or leg weakness;
- A bump or open sore that doesn't heal.

The symptoms described above can be signs of the below listed side effects, which have been observed with Humira:

Very common (in more than 1 in 10 patients):

- injection site reactions (including pain, swelling, redness or itching).

Common (in more than 1 in 100 patients but less than 1 in 10 patients):

- Lower respiratory tract infections (such as bronchitis, pneumonia);

- Upper respiratory tract infections (including cold, runny nose, sinus infection);
- Viral infections (including influenza, cold blisters and shingles);
- Bacterial infections (including urinary tract infection);
- Fungal infection;
- Dizziness, including vertigo, headache sensation disorders;
- Cough, sore throat;
- Nausea, diarrhoea, abdominal pain, mouth inflammation and ulcers;
- Elevated liver enzymes;
- Rash, itching;
- Musculoskeletal pain;
- Fever, fatigue.

Uncommon (in more than 1 in 1,000 patients but less than 1 in 100 patients):

- Serious infections (including tuberculosis, histoplasmosis and sepsis [blood poisoning]), joint infection;
- Skin infections, skin warts, superficial fungal infections;
- Anaemia, low white blood cell and platelet counts, lymphopaenia (low immune cell counts);
- Swelling of the lymph nodes;
- Systemic lupus erythematosus;
- Allergic reactions (including seasonal and medicines allergy);
- Increased lipid and uric acid values, appetite disorders;
- Anxiety, depression, feeling sleepy and difficulty sleeping, shaking;
- Taste disturbances;
- Vision disturbances, eye inflammation or infection;
- Ear discomfort;
- Sensation of heart beating irregularly, high blood pressure, flushing;
- Asthma, shortness of breath, hoarseness;
- Abdominal symptoms (such as vomiting, constipation), rectal bleeding;
- Skin disorders (such as psoriasis, eczema or infections), itchy rash, and slow wound
- Healing, bruising, hair loss;
- Muscle weakness;
- Urinary disturbances (such as blood in urine, increased urinary frequency);
- Increased menstrual bleeding;
- Flu-like symptoms, chest pain, swelling of the feet;
- Accidental injury impaired healing.

Rare (in more than 1 in 10,000 patients but less than 1 in 1,000 patients)

- High pressure within the eyes, inflammation of the coloured part of the eye, extensive inflammation of the eye;
- Skin cancer; cancer, cancer that affects the lymph system, malignant melanoma;
- Thyroid disorders;
- Protein in urine;
- Reduction in blood platelets which increases risk of bleeding or bruising, reduction in blood cells which can cause weakness, bruising or make infections more likely;
- Chest pain, heart stops pumping, blockages in the arteries of the heart, fluid around the heart that can cause severe chest pain, heart problems that can cause shortness of breath or ankle swelling, sensation of heart beating rapidly;
- Hearing loss, buzzing;
- Inflammation of the pancreas which causes severe pain in the abdomen and back, inflammation that causes abdominal pain and diarrhoea, blockages of the intestine that cause nausea and vomiting, inflammation that causes pain on swallowing, indigestion, inflammation of the stomach which causes pain in the abdomen, nausea and vomiting;
- Extensive injury to the liver, abdominal symptoms (such as vomiting, indigestion, constipation), excess fat in the liver which can cause abdominal discomfort, fatigue and feeling unwell, stones in the gallbladder that can cause severe pain and fever, blood test shows changes in the way the liver is working;
- Inflammation that causes fever, skin rash, joint pain;
- Inflammation of the large intestine that causes fever, abdominal pain and cramping, constipation, skin and deep tissue destruction caused by infection;
- High blood level of calcium that is usually without symptoms but could cause abdominal pain, depression, weakness and kidney stones, low blood calcium that can cause tingling in the fingers and toes and muscle cramping;
- Abnormal muscle breakdown which can lead to kidney problems;
- Swelling in the back of the throat, fluid around the lungs that may cause shortness of breath, pain upon taking a deep breath;
- Inflammation of abdominal fat causing painful skin nodules;
- A sac in the wall of a major artery, blockage of a heart valve usually without symptoms but may cause shortness of breath with exercise, chest pain and fainting, inflammation and clot of a vein, blockage of a blood vessel, sensation of heart beating rapidly;
- Multiple sclerosis; facial muscle weakness or paralysis;
- Guillain-Barré syndrome, (muscle weakness, abnormal sensations, tingling in the arms and upper body);
- Intestinal perforation;
- Hepatosplenic T-cell lymphoma.

If any of the side effects gets serious, if you have any unusual effects, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

Full package leaflet is available at http://emc.medicines.org.uk/.

Appendix 2

Package leaflet: information for the user

Enbrel 25 mg powder and solvent for solution for injection
Etanercept

Read all (both sides) of this leaflet carefully before you start using this medicine

- Keep this leaflet. You may need to read it again.
- Your doctor will also give you a Patient Alert Card, which contains important safety information that you need to be aware of before and during treatment with Enbrel.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you or a child in your care. Do not pass it onto others. It may harm them, even if their symptoms are the same as yours or those of the child you are caring for.
- If you are concerned about any side effect, or if you notice any side effects that are not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:

Information in this leaflet is organised under the following 7 sections:

1. What Enbrel is and what it is used for
2. Before you use Enbrel
3. How to use Enbrel
4. Possible side effects
5. How to store Enbrel
6. Further information
7. Instructions for preparing and giving an injection of Enbrel (See overleaf).

Possible side effects

Like all medicines, Enbrel can cause side effects, although not everybody gets them. Other side effects that are not listed in this leaflet may occur. If you are concerned about any side effect, or if you notice any side effects that are not listed in this leaflet, please tell your doctor or pharmacist.

Allergic reactions

If any of the following happen, do not inject more Enbrel. Tell your doctor immediately, or go to the casualty department at your nearest hospital.

- Trouble swallowing or breathing.
- Swelling of the face, throat, hands, or feet.
- Feeling nervous or anxious, throbbing sensations, sudden reddening of the skin and/or a warm feeling.
- Severe rash, itching, or hives (elevated patches of red or pale skin that often itch).

Serious side effects

If you notice any of the following, you or the child may need urgent medical attention.

- Signs of *serious infections*, such as high fever that may be accompanied by cough, shortness of breath, chills, weakness, or a hot, red, tender, sore area on the skin or joints.
- Signs of *blood disorders*, such as bleeding, bruising, or paleness.
- Signs of *nerve disorders*, such as numbness or tingling, changes in vision, eye pain, or onset of weakness in an arm or leg.
- Signs of *worsening heart failure*, such as fatigue or shortness of breath with activity, swelling in the ankles, a feeling of fullness in the neck or abdomen, night-time shortness of breath or coughing, bluish colour of the nails or the lips.

These are rare or uncommon side effects, but are serious conditions (some of which may rarely be fatal). If these signs occur, tell your doctor immediately, or visit the casualty department at your nearest hospital.

Other side effects

The side effects and frequencies (likelihood of occurring) listed below are those that have been seen in adult patients. The side effects seen in children and adolescents are similar to those seen in adults.

Very common (may occur in more than 1 in 10 patients): Infections (including colds, sinusitis, bronchitis, urinary tract infections and skin infections); injection site reactions (including bleeding, bruising, redness, itching, pain, and swelling). Reactions at the injection site are very common, but do not occur as often after the first month of treatment. Some patients have developed a reaction at an injection site that was used before.

Common (may occur in less than 1 in 10, but more than 1 in 100 patients): allergic reactions; fever; itching;

antibodies directed against normal tissue (autoantibody formation).

Uncommon (may occur in less than 1 in 100, but more than 1 in 1,000 patients): serious infections (including pneumonia, deep skin infections, joint infections, blood infection, and infections at various sites); localised swelling of the skin (angioedema); low blood platelet count; hives (elevated patches of red or pale skin that often itch); psoriasis; rash; inflammation or scarring of the lungs.

Rare (may occur in less than 1 in 1,000 patients): serious allergic reactions (including severe localised swelling of the skin and wheezing); combined low platelet, red, and white blood cell count; nervous system disorders (with signs and symptoms similar to those of multiple sclerosis or inflammation of the nerves of the eyes or spinal cord); tuberculosis; worsening congestive heart failure; seizures; lupus or lupus-like syndrome (symptoms may include persistent rash, fever, joint pain, and tiredness); inflammation of the blood vessels; low red blood cell count, low white blood cell count, low neutrophil (a type of white blood cell) count; elevated liver blood tests; skin rash which may lead to severe blistering and peeling of the skin.

Very rare (may occur in less than 1 in 10,000 patients): failure of the bone marrow to produce crucial blood cells.

Not known Excessive activation of white blood cells associated with inflammation (macrophage activation syndrome).

Full package leaflet is available at http://emc.medicines.org.uk/.

Appendix 3

Package leaflet: Infliximab

Read all of this leaflet carefully before you start using this medicine

In addition to this leaflet, you will be given a patient alert card, which contains important safety information that you need to know before you are given Remicade and during treatment with Remicade.

- Keep this leaflet and the patient alert card. You may need to read them again.
- If you have further questions, please ask your doctor or your pharmacist.

This medicine has been prescribed for you personally and you should not pass it onto others. It may harm them, even if their symptoms are the same as yours.

In this leaflet

1. What Remicade is and what it is used for
2. Before you use Remicade
3. How to use Remicade
4. Possible side effects
5. Storing Remicade
6. Further information.

Possible side effects

Like all medicines, Remicade can have side effects. Most side effects are mild to moderate. However, some may be serious and may require treatment. Side effects may appear up to 6 months after the last infusion.

Tell your doctor immediately if you notice any of the following:

- pain or tenderness in chest, muscles, joints or jaw
- swelling of the hands, feet, ankles, face, lips, mouth or throat which may cause difficulty in swallowing or breathing
- hives or other signs of an allergic reaction
- fever
- rash
- itching
- shortness of breath with exertion or upon lying down or swelling of the feet.

Tell your doctor as soon as possible if you notice any of the following:

- signs of infection
- difficulty breathing and non-productive cough
- problems with urination
- changes in the way your heart beats, for example, if you notice it beating faster
- light-headedness
- tiredness
- hoarseness
- coughing
- headache
- tingling
- numbness
- double vision or other problems with your eyes
- arm or leg weakness
- signs of liver or spleen problems: eyes or skin turning yellow, dark-brown coloured urine, upper abdominal pain
- loss of weight
- night sweating.

The symptoms described above can be signs of the below listed side effects, which have been observed with Remicade.

Common: Headache, dizziness, nausea, abdominal symptoms, allergic reactions, rash, urticaria, viral infections (for example herpes), respiratory infections (cold, sinus infections, bronchitis, pneumonia).

Uncommon: Depression, agitation, sleep disturbances, impaired wound heeling, bacterial infections, (for example tuberculosis, urinary tract infections, deep skin infections, sepsis), fungal infections, asthma, abnormal liver function, low blood cell counts including anemia, worsening of demyelinating nerve disease, autoimmune disease activation (SLE, lupus), worsening of heart failure, hair loss, bleedings, allergic anaphylactic reactions, injection site reactions.

Rare: Gastrointestinal bleedings or perforation, circulatory failure, multiple sclerosis, lymphoma.

Your doctor may also do tests to examine your liver function and/or blood values. If you notice any side effects that are not mentioned in this leaflet, please tell your doctor.

Full package leaflet can be found at http://emc.medicines.org.uk/.

References

1. Atzeni F, Sarzi-Puttini P (2008) Autoantibody production in patients treated with anti-TNF-α. Expert Rev Clin Immunol 4(2):275–280
2. Deepe GS Jr, Wallis RS (2006) Tumor necrosis factor-α inhibitors and granulomatous infectious. Drug Discov Today Dis Mech 3(2):295–300
3. Olsen NJ, Stein CM (2004) New drugs for rheumatoid arthritis. N Engl J Med 350(21):2167–2179, 2226
4. Wallis RS (2008) Tumor necrosis factor antagonists: structure, function, and tuberculosis risks. Lancet Infect Dis 8(10):601–611
5. Kroesen S, Widmer AF, Tyndall A, Hasler P (2003) Serious bacterial infections in patients with rheumatoid arthritis under anti-TNF-α therapy. Rheumatology 42(5):617–621
6. Furst DE, Wallis R, Broder M, Beenhouwer DO (2006) Tumor necrosis factor antagonists: different kinetics and/or mechanisms of action may explain differences in the risk for developing granulomatous infection. Semin Arthritis Rheum 36(3):159–167
7. Wallis RS, Ehlers S (2005) Tumor necrosis factor and granuloma biology: explaining the differential infection risk of etanercept and infliximab. Semin Arthritis Rheum 34(5 SUPPL):34–38
8. Callen JP (2007) Complications and adverse reactions in the use of newer biologic agents. Semin Cutan Med Surg 26(1):6–14
9. Antoni C, Braun J (2002) Side effects of anti-TNF therapy: current knowledge. Clinl Exp Rheumatol 20(6 Suppl 28):S152–S157
10. Weinberg JM, Buchholz R (2006) TNF-alpha inhibitors, 1st edn. Birkh©Þuser Verlag, Basel
11. Stone JH (2008) Tumor necrosis factor-alpha inhibitors: risk of bacterial, viral, and fungal infections. http://www.uptodate.com/online/content/topic.do?topicKey=immuninf/8844. Accessed Oct 2008
12. Desai SB, Furst DE (2006) Problems encountered during anti-tumor necrosis factor therapy. Best Pract Res Clin Rheumatol 20(4):757–790
13. Stone JH (2008) Tumor necrosis factor-alpha inhibitors: risk of malignancy. http://www.uptodate.com/online/content/topic.do?topicKey=tx_rheum/14969. Accessed Oct 2008
14. Robinson WH, Genovese MC, Moreland LW (2001) Demyelinating and neurologic events reported in association with tumor necrosis factor α antagonism: by what mechanisms could tumor necrosis factor an antagonists improve rheumatoid arthritis but exacerbate multiple sclerosis? Arthritis Rheum 44(9):1977–1983
15. Stone JH (2008) Tumor necrosis factor-alpha inhibitors: an overview of adverse effects. http://www.uptodate.com/online/content/topic.do?topicKey=tx_rheum/12761&source=HISTORY. Accessed Oct 2008
16. Lee SJ, Kavanaugh A (2005) Adverse reactions to biologic agents: focus on autoimmune disease therapies. J Allergy Clin Immunol 116(4):900–905
17. Danila MI, Patkar NM, Curtis JR, Saag KG, Teng GG (2008) Biologics and heart failure in rheumatoid arthritis: are we any wiser? Curr Opin Rheumatol 20(3):327–333
18. Balakumar P, Singh M (2006) Anti-tumor necrosis factor-α therapy in heart failure: future directions. Basic Clin Pharmacol Toxicol 99(6):391–397
19. Stone JH (2008) Tumor necrosis factor-alpha inhibitors: induction of antibodies, autoantibodies, and autoimmune diseases. http://www.uptodate.com/online/content/topic.do?topicKey=tx_rheum/14677. Accessed Oct 2008
20. Moots RJ, Taggart A, Walker D (2003) Biologic therapy in clinical practice: enthusiasm must be tempered by caution. Rheumatology 42(5):614–616