Investigating the potential side effects of anti-TNF therapy for rheumatoid arthritis: cause for concern?

ARTICLE *in* IMMUNOTHERAPY · APRIL 2015

Impact Factor: 2.44 · DOI: 10.2217/imt.15.4 · Source: PubMed

7 AUTHORS, INCLUDING:

Luigi Gianturco
Istituto Ortopedico Galeazzi
25 PUBLICATIONS **91** CITATIONS
SEE PROFILE

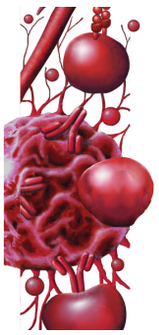
Rossella Talotta
Ospedale Luigi Sacco
15 PUBLICATIONS **38** CITATIONS
SEE PROFILE

Maurizio Turiel
University of Milan
111 PUBLICATIONS **1,779** CITATIONS
SEE PROFILE

Piercarlo Sarzi-Puttini
University of Milan
268 PUBLICATIONS **4,478** CITATIONS
SEE PROFILE

Perspective

Immunotherapy



Investigating the potential side effects of anti-TNF therapy for rheumatoid arthritis: cause for concern?

Fabiola Atzeni*[,1], Luigi Gianturco[2], Rossella Talotta[3], Valentina Varisco[3], Maria Chiara Ditto[3], Maurizio Turiel[2] & Piercarlo Sarzi-Puttini[3]

[1]IRCCS Galeazzi Orthopedic Institute, Milan, Italy

[2]Cardiology Unit, Department of Biomedical Sciences for Health, IRCCS Galeazzi Orthopedic Institute, University of Milan, Milan, Italy

[3]Rheumatology Unit, L. Sacco University Hospital, Milan, 20127, Italy

*Author for correspondence: atzenifabiola@hotmail.com

There are now five anti-TNF drugs available for clinical use, and it will not be long before they are joined by biosimilar drugs. Some patients treated with selective TNF drugs may develop adverse events such as infections, malignancies, acute infusion and injection reactions, autoimmunity and cardiovascular effects. Registry data consistently show that, particularly during the first 6 months, anti-TNF drugs slightly increase the risk of serious infections of the skin, soft tissues and joints, but it does not seem to increase the risk of cancer other than nonmelanoma skin cancers. A number of studies have shown that the administration of biological agents can lead to the formation of neutralizing and nonneutralizing antibodies. Lipid levels increase, but the atherogenic index remains stable and qualitative changes to lipid particles may reduce the risk of cardiovascular diseases. Patients treated with anti-TNF drugs therefore need to be monitored regularly.

Keywords: anti-TNF therapy • autoimmunity • cancer • infections • lipid profiles

Background

TNF-α, a key cytokine in the pathogenesis of rheumatoid arthritis (RA) [1], is mainly produced by activated macrophages, T lymphocytes and NK cells, but is also expressed at lower levels by fibroblasts, and smooth muscle and tumor cells. Its complex immune functions include the stimulation of inflammation, cytotoxicity, the regulation of cell adhesion and the induction of cachexia [2].

Clarifying the role of TNF-α in the pathogenesis of RA has been important for the development of drugs capable of controlling the clinical signs and symptoms of the disease, and halting its radiographic progression. The five anti-TNF drugs currently approved in Europe for treating RA patients are the three monoclonal antibodies (infliximab [INF], adalimumab [ADA] and golimumab [GLM]), the recombinant TNF receptor etanercept (ETN) and pegylated certolizumab (CTZ) [3], which all have different structures, morphology, pharmacokinetic properties and activity. However, although they have revolutionized the therapeutic approach to patients with active RA who fail to respond to conventional therapy, they may also cause adverse events such as infections, malignancies, acute infusion and injection reactions, autoimmunity and cardiovascular (CV) effects.

The aim of this review is to consider the clinical significance of adverse events developing during anti-TNF inhibitors.

Search strategy

In order to be included in this review, the studies had to be systematic reviews or observational studies (i.e., cross-sectional, noninterventional case–control or cohort studies) evaluating the risk of complications such as infections, CV involvement, malignancies, etc. in patients exposed to biological disease modifying antirheumatic drugs (DMARDs). A search was made of the PubMed databases from 1998 to December 2014 using the keywords: 'rheumatoid arthritis' or 'arthritis', and 'anti-TNF drugs' and adverse events.

Future Medicine part of fsg

Infections

Registries have greatly improved our understanding of the risk profiles of anti-TNF drugs since they were first introduced more than 10 years ago [4] not only because they contain data relating to thousands of patients with 'real world' disabilities and co-morbidities, but also because they include those who would not be considered eligible for randomized controlled trials (RCTs). Patients with RA are at risk of infections because of their underlying disease and the use of immunosuppressants, and registry data have consistently shown a slightly increased risk of severe opportunistic infections during the first months of anti-TNF drugs, although this is more true of the monoclonal antibodies than ETN [4].

Mycobacterium infections

By binding its transmembrane receptors TNFRI and TNFRII, TNF-α (a crucial cytokine involved the pathogenesis of inflammatory autoimmune diseases) contributes to immunity against various infective agents including *Mycobacterium tuberculosis*. *In vitro* and *in vivo* studies have shown that the presence of TNF-α is needed to overcome infections due to mycobacteria by means of phagocytosis or granuloma formation. The interaction between TNF-α and its receptors leads to various intracellular molecular pathways ranging from proliferation and inflammation (via NF-κB) to apoptosis (via FADD or caspase-8). TNF-α may have a soluble or transmembranous form (tm TNF-α), of which the latter plays an important role in maintaining granulomatous inflammatory diseases because, in addition to acting as a TNFRI and TNFRII ligand, it may act as a receptor and generate an intracellular cascade in carrying cells. This outside-to-inside or reverse signal mechanism has been demonstrated in the case of NK lymphocytes, monocytes-macrophages and T cells, and seems to amplify or tune the immune response [5]. INF and ADA have greater affinity for tm TNF-α, but also form stable complexes with soluble TNF-α in a 2:2 ratio. ENT has greater aviditity for soluble TNF-α but dissociates from it more quickly than monoclonal antibodies. Their increased ability to bind TNF-α molecules makes monoclonal antibodies more effective in clearing them from the bloodstream, but simultaneously favors antibody- or complement-mediated cytolysis. By binding tm TNF-α, INF and ADA have a greater effect on granulomatous diseases such as Crohn's disease but, by inhibiting or killing cells expressing tm TNF-α, they may increase the risk of disseminating pathogens that generate granulomatous infections such as tuberculosis (Figure 1). Moreover, it has been demonstrated that ADA and INF play a major inhibitory role in interferon-gamma (IFN-γ)-driven phagosome maturation containing Mycobacterium species, another mechanism involved in defense against this bacteria [6]. IFN and ADA also have a more pronounced effect on CD4+ cell activation against mycobacteria than ETN [7]. Given the above, the opportunistic infection most frequently associated with anti-TNF drugs is tuberculosis (TB), which is highly likely to lead to complicated, widespread extrapulmonary infection [8], and is mainly caused by the reactivation of latent tuberculous foci as a result of a destabilized balance between host immunity and pathogen virulence [9].

A recent meta-analysis of RCTs and long-term extension studies has shown that there have been 31 cases of TB during anti-TNF drugs with an odds ratio of 1.92 (95% CI: 0.91–4.03, p = 0.085). The incidence was higher in RA patients treated with anti-TNF monoclonal antibodies (307.71, 95% CI: 184.79–454.93) than in those treated with ETN (67.58, 95% CI: 12.1–163.94), and in areas in which TB is more frequent [10]. All candidates for anti-TNF drugs should therefore be screened for TB by means of a history, physical examination, purified protein derivative skin test and chest radiography, and it is strongly recommended that any latent TB be treated before starting anti-TNF therapy [11], particularly in endemic areas. Immunosuppressed patients (especially those receiving anti-TNF drugs) are at high risk of progressing from latent TB infection to TB disease. The diagnosis of latent TB infection is mainly based on the patient's medical history and a physical examination, a tuberculin skin test (TST) or interferon-gamma release assays (IGRAs), and chest radiographs. According to the CDC guidelines, the main disadvantages of TSTs are the need for training in interpreting the results, the time required for the reaction and the influence of Kock Bacillus vaccination on the findings [12]. These problems have been partially overcome by the use of IGRAs although there are still limited data concerning the use in some populations, such as patients recently exposed to TB, children aged <5 years and immunocompromised subjects. The guidelines suggest preferring the use of IGRAs in patients who have poor rates of return on TSTs and those who have undergone BCG vaccination, and preferring TSTs in children aged <5 years; however, there are no clear indications concerning which test is more appropriate in patients receiving immunosuppressive therapy [13].

Bacterial, viral & fungal infections

The other most frequently encountered viral and bacterial infections in patients treated with anti-TNF drugs are respiratory infections (including pneumonia), infections of the skin and soft tissue, and urinary tract infec-

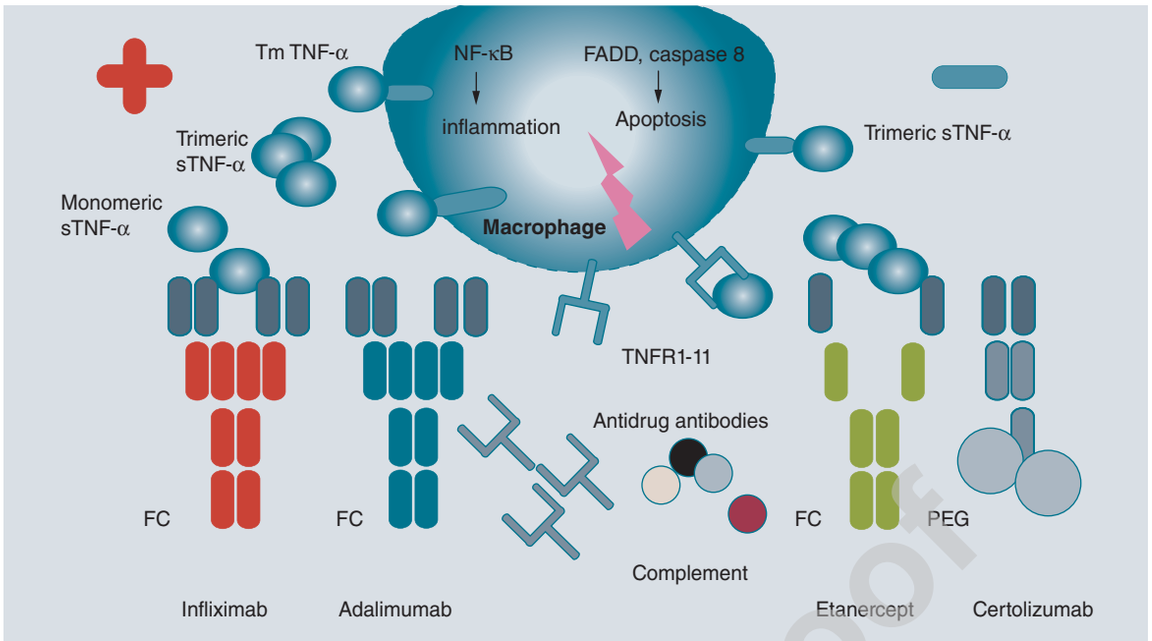


Figure 1. Different immunological properties of anti-TNF drugs. Monoclonal antibodies (infliximab and adalimumab) bind both trimeric and monomeric sTNF-α and Tm TNF-α with a higher avidity than etanercept. The molecular structure of monoclonal antibodies also induces a major activation of the immune system via antibodies or complement-mediated cytotoxicity.
FC: Fragment crystallizable; PEG: Polyethylene glycol; sTNF-α: Soluble TNF-α; Tm TNF-α: Transmembrane TNF-α.

tions [14]. Dixon *et al.* [15] found that patients undergoing anti-TNF drugs have a fourfold increased risk of skin and soft tissue infections, which suggests that TNF plays a greater physiological role in host defenses of the skin and soft tissue than in those of other tissues. Cryptococcosis, histoplasmosis and coccidioidomycosis have all been associated with anti-TNF drugs in endemic areas [16], which indicates that anti-TNF drugs should be started with caution in patients who live in or visit regions with endemic mycoses. Patients receiving anti-TNF drugs may also be at increased risk of *Pneumocystis jiroveci* and *Nocardia* infectious diseases [16].

The incidence of septic arthritis is also increased by anti-TNF drugs, and this could delay the healing of surgical wounds [17]. Many reports have also suggested an increased risk of *Listeria* infection due to foods made using unpasteurized milk and *Salmonella* infection due to undercooked eggs or meat [15], and a study by the British Society for Rheumatology Biologics Register has shown that advising patients to avoid high-risk foods when starting anti-TNF drugs may reduce the risk [18].

Herpes zoster (HZ), a neurocutaneous disease characterized by a painful vesicular dermatomal rash due to the reactivation of varicella zoster virus, is one of the most frequently observed adverse events in clinical trials of anti-TNF drugs, and this has been confirmed by the German Rheumatoid Arthritis Observation of Biologic Therapy (RABBIT) register [19]. A recent meta-analysis of seven registries found that the pooled risk ratio for HZ was 1.61 (95% CI: 1.16–2.23; p = 0.004), and that severe HZ occurred in 4.9–20.9% patients treated with anti-TNF drugs as against 2.0–5.5% of those treated with conventional DMARDs [20]. The same meta-analysis revealed a significantly increased risk of HZ in up to 61% of patients with systemic inflammatory diseases receiving anti-TNF drugs, thus raising the question as to whether systematic prophylactic treatment should be given to those with a known history of HZ and whether previously unaffected patients should be vaccinated [20].

A relative lack of TNF or decreased T-cell activation and IFN production may reactivate hepatitis B virus (HBV), and a number of reports indicate that INF may be associated with the reactivation of stable HBV infection [21]. We studied a cohort of 72 anti-HBc carriers and found no evidence of HBV reactivation, but such patients should always be carefully monitored [22]. These data have been confirmed by a recent systematic review and meta-analysis based on 10 eligible studies showing that the prevalence of HBV reactivation was 3.9% (95% CI: 1.1–8.4%, I (2): 51.1%) for patients treated with ETN and 4.6% (95% CI: 0.5–12.5%, I (2): 28.7%) for these treated with ADA [23]. Furthermore, for patients without any antiviral prophylaxis the pooled reactivation was 4.0% (95% CI: 1.2–8.3%, I (2): 75.6%).

In conclusion, HBV reactivation rate is relatively low in patients treated with anti-TNF drugs for rheumatic conditions; however, the antiviral prophylaxis would be recommended in patients with overt chronic HBV infection [23,24]. There are limited data concerning the use of anti-TNF drugs in chronic carriers of hepatitis C virus (HCV) infections, but all patients should be screened for HCV before starting anti-TNF drugs [23]. Preliminary data suggest that anti-TNF drugs are safe in patients with chronic hepatitis C [24], but should be administered together with antiviral therapy in those with hepatitis B.

Malignancies

RA patients are at increased risk of developing hematological and solid neoplasias (lung cancer and nonmelanoma skin cancer), and a large Swedish study has shown that the prognosis of non-Hodgkin lymphoma and cancer in general is worse in RA patients [25,26]. Given the role of T and B cells in the pathogenesis of systemic rheumatic diseases and lymphoproliferative disorders, the risk of lymphoma is greater in RA patients, particularly those with overlapping RA and Sjögren's syndrome (pSS), because of persistent antigenic stimulation [27]. Their risk of developing lymphoproliferative disorders (particularly non-Hodgkin lymphoma) is two- to three-times higher than that of the general population, and there is some evidence that anti-TNF drugs increase the risk of skin cancers, including melanoma [28]. For example, a study of 18,572 RA patients found that standardized incidence ratio of neoplasia 2.9 in those treated with anti-TNF drugs as against 1.7 in those treated with methotrexate, although this difference was probably due to the more active disease of the former [29].

Various observational studies have found a similar incidence of hematological malignancies or solid neoplasias in patients treated with biological therapy or DMARDs [30–32], but a meta-analysis found differences in the risk of lymphoproliferative disorders in RA patients depending on their treatment and the type of immunosuppressant: the standardized incidence ratio was 5.1 (95% CI: 0.9–28.6) in those receiving DMARDs and 11.5 (95% CI: 3.7–26.9) in those treated with biological agents [33]. Although a recent meta-analysis did not find any evidence of an excess cancer risk among adult RA patients receiving anti-TNF drugs, but it did not rule out the possibility that prolonged treatment might lead to such a risk emerging as there was a trend toward an increased rate of nonmelanoma skin cancer [34].

In conclusion, although the data are controversial, they suggest that patients treated with anti-TNF drugs should be monitored carefully in order to prevent the development of neoplasia or ensure that it is treated early.

Infusion- or injection-related skin reactions & immunogenicity

It has been shown that the administration of biological agents can lead to the formation of neutralizing and nonneutralizing antibodies [35,36]. The structure of monoclonal antibodies, which contain domains such as the complementarity determining regions, raise the risk of immunogenicity by involving the idiotype-anti-idiotype network [37]. It has been shown that, although ETN has a fragment constant (Fc) domain, it is less likely to induce complement-mediated cytotoxicity than monoclonal drugs, perhaps because of its more rigid region and the lack of a heavy chain (CH)1 domain. These immunological features lead to a risk of anti-drug antibody formation that may cause ADCC or complement-dependent cytotoxicity. The novel CTZ pegol anti-TNF drug has a pegylated Fab' fragment and, as it lacks an Fc domain, does not seem to induce ADCC or complement-dependent cytotoxicity; however, the recognition of tmTNF or sTNF-alpha may induce cytolysis or apoptosis through alternative pathways involving, for example, the FADD-caspase8 cascade (Figure 1).

However, the immunogenicity of INF and ETN is better characterized than that of the other anti-TNF agents because they have been used for longer, and it is known that the immunogenicity of INF is increased by its chimeric structure, dose, administration route and frequency of administration.

The human anti-chimeric antibodies (HACAs) produced during INF therapy favor the formation of immune complexes that give rise to adverse events such as acute infusion reactions, which occur within 1–2 h of administration and include fever, nausea, breathlessness and headache [36,38], but no association has been found between antibodies against anti-TNF drugs and delayed hypersensitivity reactions, which occur 3–12 days after infusion and are characterized by myalgia, arthralgia, pruritus, facial or peripheral edema, sore throat and headache [38]. The effect of ADA immunogenicity on infusion reactions is still unclear, but we have recently demonstrated that the correlation between the presence of anti-drug antibodies and infusion reactions depends on the type of antibody (IgG, IgM or IgA) [38]. The rates of injection site reactions are 36% for ETN, 15% for ADA, 6.4% for CTZ and 5.8% for GLM, and it is well known that their incidence is higher among the patients who develop HACAs [36].

Autoimmunity

It has been reported that RA patients treated with selective anti-TNF drugs develop various autoantibodies: antinuclear antibodies, anti-double-

stranded DNA (anti-dsDNA) antibodies [35,36] and anti-phospholipid antibodies. Autoantibodies have been anecdotally associated with clinical manifestations suggesting drug-induced systemic lupus erythematosus [39], and it was originally thought that this may be due to the occurrence of low-affinity anti-dsDNA IgM or IgA antibodies rather than the anti-dsDNA IgG antibodies more typically associated with systemic lupus erythematosus (SLE) [39].

However, during the course of the BIOGEAS project, the Autoimmune Diseases Study Group of the Spanish Society of Internal Medicine identified 233 cases of autoimmune disease following the administration of anti-TNF drugs, including 92 cases of lupus (mainly in RA patients receiving INF or ETN) [40]. The most frequent manifestations were cutaneous lesions, arthromyalgia and general symptoms (fever, malaise, asthenia), but most of the patients did not fulfil ≥4 SLE criteria. Serositis was more frequent in patients receiving INF, whereas cutaneous involvement occurred more frequently in those treated with ETN [40]. In a recent study, Moulis *et al.* [41] analyzed data coming from the French registries for anti-TNF drugs from 2000 to 2012 and found a significant trend for IFN and ADA in the induction of lupus or lupus-like syndromes, confirming on the other hand a safer profile for ETN.

Cardiovascular disease

INF, ETN and ADA have greatly improved the outcomes of severe RA, and reduced the burden of CV disease, which is the leading cause of death in patients with severe RA [42]. Jacobsson *et al.* [43] found that the age/gender-adjusted incidence of a first CV event was 14.0/1000 person-years at risk (95% CI: 5.7–22.4) in patients treated with anti-TNF drugs, but 35.4/1000 person-years (95% CI: 16.5–54.4) in those not treated, possibly because of the effects of anti-TNF drugs on inflammation. A systematic review of 16 publications and a meta-analysis of 11 showed that anti-TNF drugs were associated with a reduced risk of all CV events (pooled adjusted RR: 0.46, 95% CI: 0.28–0.77), myocardial infarction (MI; pooled adjusted RR: 0.81, 95% CI: 0.68–0.96) and cerebrovascular accident (pooled adjusted RR: 0.69; 95% CI: 0.53–0.89) in cohort studies, and the meta-analysis of RCTs also produced a point estimate indicating a lower risk of CV events, although this was not statistically significant (pooled RR: 0.85, 95% CI: 0.28–2.59) [44]. A British Society for Rheumatology Biologics Register study found that RA patients treated with anti-TNF drugs do not have a lower incidence of MI than those treated with traditional DMARDs [45], but the risk of MI was markedly reduced in those who respond to anti-TNF drugs within 6 months, thus supporting the idea that inflammation plays a pivotal role in MI [45]. It has been shown in a recent systematic review and meta-analysis of cohort studies that anti-TNF drugs are associated with a reduced risk for all CV events (pooled adjusted RR: 0.46, 95% CI: 0.28–0.77), MI (pooled adjusted RR: 0.81, 95% CI: 0.68–0.96) and cerebrovascular accidents (pooled adjusted RR: 0.69, 95% CI: 0.53–0.89). Furthermore, a meta-analysis of RCTs led to a point estimate indicating an albeit not statistically significant lower CV risk (pooled RR: 0.85, 95% CI: 0.28–2.59) [46]. This suggests that the difference in the findings of observational studies and RCTs relates to outcomes but not the overall trend, and this supported by the fact that recent American studies have confirmed that the use of anti-TNF-α drugs is associated with a lower risk of CV events in RA patients than the use of DMARDs [47].

Taken together, the published findings suggest that anti-TNF drugs have favorable effects on the risk of CV disease. However, despite the findings of the meta-analysis, the lack of any suitable placebo-controlled studies makes it impossible to draw any definite conclusions. On the basis of the similarities in the underlying inflammatory processes of RA and atherosclerosis, the potentially favorable effect of anti-TNF drugs on CV risk may be due to attenuated intima media thickness (IMT) progression (or even a reduction in IMT). The few studies that have investigated the effect of a TNF blockade on IMT in RA patients indicate no progression or even the regression of IMT, but these involved small numbers of patients and had sub-optimal methodological designs. Furthermore, we have demonstrated the efficacy of long-term DMARD treatment (with methotrexate and anti-TNF drugs) in reducing disease activity, and delaying or even reversing the progression of endothelial dysfunction and atherosclerosis as a result of an increase in coronary flow reserve, with no changes in IMT [48]. However, it is interesting to note that a cross-sectional study has suggested that blocking TNF reduces the number of unstable plaques in comparison with treatment with DMARDs alone. In their review of the effect of anti-TNF drugs on arterial stiffness as evaluated by means of pulse wave velocity and the augmentation index, Dulai *et al.* [49] found that, despite the limitations of the studies themselves, the evidence suggests that anti-TNF drugs may have a beneficial effect on arterial stiffness and therefore CV risk. However, although patients with severe chronic heart failure (CHF) have higher circulating levels of TNF than healthy subjects, it has been found that ETN has no effect on CHF, and that high-dose INF has detrimental effects on patients with moderate to severe CHF: consequently, severe heart failure contra-

indicates the use of anti-TNF drugs in patients with RA [50].

In conclusion, the CV effects of anti-TNF drugs are both protective and negative. Furthermore, a systematic review and meta-analysis of 32 articles (including 13 prospective before/after studies) showed that long-term anti-TNF treatment is associated with increased levels of high-density lipoprotein, total cholesterol and triglycerides, whereas low-density lipoprotein levels and the atherogenic index remain unchanged, and the levels of apolipoprotein B/A decrease [51]. The presumed cardioprotective effects of anti-TNF drugs in RA therefore do not seem to be explained by quantitative lipid changes: the increased high-density lipoprotein levels may have some benefit, but this needs to be confirmed by prospective studies with long-term follow-up. Moreover, most of the studies found that the variation in lipid profiles was associated with a reduction in disease activity.

Finally, although recent observational studies do not indicate that anti-TNF-drugs have a detrimental effect on cardiac function, some investigators recommend echocardiography before starting anti-TNF therapy.

Conclusion

Despite their efficacy, the immunomodulatory properties anti-TNF drugs have raised many safety concerns, and prompted careful evaluations in clinical trials and intensive postmarketing surveillance. It seems that INF is the most immunogenic of the anti-TNF drugs and ETN the least immunogenic [52]. It also seems that the immunogenicity of INF may explain a significant proportion of the associated infusion reactions, but the lack of standardized antiglobulin assays has limited detailed research that would lead to more rational prescribing [52]. Registry data have consistently shown that anti-TNF drugs are associated with a slightly increased risk of serious infections of the skin, soft tissues and joints, particularly during the first 6 months [14,52], and that this risk increases with age and the concomitant use of corticosteroids. Severe opportunistic infections, particularly granulomatous infections, occasionally occur in patients treated with the monoclonal antibodies (again more frequently in patients who are also receiving corticosteroids), but are less often encountered in those treated with ETN [52,53] and so, although the shorter dosing interval of the latter might be considered less convenient by some patients, it is potentially safer.

Registry data indicate that anti-TNF therapy does not seem to increase the risk of cancers other than nonmelanoma skin cancer [52,53]. The potential advantage of registries over RCTs when evaluating safety is due to the fact that they are based on unselected, routinely treated patients followed up for a long period of time, and therefore more closely reflect everyday clinical practice. However, the true risk of anti-TNF drugs in patients with a history of malignancy is still unclear and, in the case of a malignancy occurring during or after a first anti-TNF drug, it is not known whether it is safer to start treatment with a biological agent that has a different mechanism of action.

Anti-TNF therapy is associated with an increase in lipid levels, but the atherogenic index remains stable and qualitative changes in lipid particles may reduce the risk of CV disease, although more research is still required in this area.

Future perspective

The ideal for both patients and clinicians would be to optimize and personalize medical care in order to improve the risk/benefit ratio of prescribed medications and simultaneously reduce costs. It is known that approximately one-third of patients currently fail to respond satisfactorily to their first anti-TNF therapy and others encounter side effects, but the future use of demographic data, clinical characteristics and probably biomarkers will target the most appropriate agent to each patient in order to achieve a prompt response and prevent adverse events. Many pharmacogenetic studies have attempted to link gene polymorphisms to anti-TNF response, infection or cardiovascular events but, although some interesting findings have emerged, very few of have been validated by independent groups in distinct patient cohorts.

Authors' contribution

F Atzeni drafted the manuscript; V Varisco, TR, MC Ditto, L Gianturco helped to draft the manuscript and researched

Executive summary

- There are now five TNF blockers that can be used to treat patients with rheumatoid arthritis.
- All anti-TNF agents are associated with an increased risk of serious infections in comparison with nonbiological disease modifying antirheumatic drugs; etanercept is associated with a lower risk of opportunistic infections, particularly tuberculosis.
- There does not seem to be an increased risk of lymphomas or solid tumors other than nonmelanoma skin cancer.
- The available data suggest that anti-TNF treatment reduces the risk of cardiovascular diseases in patients with severe/moderate rheumatoid arthritis.

the literature. P Sarzi-Puttini and M Turiel commented on and participated in critical editing of this manuscript. All of the authors read and approved the final manuscript.

Financial & competing interests disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

No writing assistance was utilized in the production of this manuscript.

References

Papers of special note have been highlighted as:
• of interest; •• of considerable interest.

1 Caporali R, Pallavicini FB, Filippini M *et al.* Treatment of rheumatoid arthritis with anti-TNF-alpha agents: a reappraisal. *Autoimmun. Rev.* 8, 274–280 (2009).

2 Agarwal SK. Biologic agents in rheumatoid arthritis: an update for managed care professionals. *J. Manag. Care Pharm.* 17, S14–S18 (2011).

3 Atzeni F, Benucci M, Sallì S, Bongiovanni S, Boccassini L, Sarzi-Puttini P. Different effects of biological drugs in rheumatoid arthritis. *Autoimmun. Rev.* 12, 575–579 (2013).

4 Doran MF, Crowson CS, Pond GR, O'Fallon WM, Gabriel SE. Frequency of infection in patients with rheumatoid arthritis compared with controls. A population-based study. *Arthritis Rheum.* 9, 2287–2293 (2002).

• **A paper describing the characteristics of rheumatoid arthritis patients.**

5 Horiuchi T, Mitoma H, Harashima S *et al.* Transmembrane TNF-alpha: structure, function and interaction with anti-TNF agents. *Rheumatology* 49, 1215–1228 (2010).

6 Harris J, Hope JC, Keane J. Tumor necrosis factor blockers influence macrophage responses to *Mycobacterium Tuberculosis*. *J. Infect. Dis.* 198, 1842–1850 (2008).

7 Harris J, Keane J. How tumour necrosis factor blockers interfere with tuberculosis immunity. *Clin. Exp. Rheum.* 161, 1–9 (2010).

8 Winthrop KL. Risk and prevention of tuberculosis and other serious opportunistic infections associated with the inhibition of tumor necrosis factor. *Nat. Clin. Pract. Rheumatol.* 2, 602–610 (2006).

•• **An excellent paper on tuberculosis.**

9 Keane J, Bresnihan B. Tuberculosis reactivation during immunosuppressive therapy in rheumatic diseases: diagnostic and therapeutic strategies. *Curr. Opin. Rheumatol.* 20, 443–449 (2008).

10 Souto A, Maneiro JR, Salgado E, Carmona L, Gomez-Reino JJ. Risk of tuberculosis in patients with chronic immune-mediated inflammatory diseases treated with biologics and tofacitinib: a systematic review and meta-analysis of randomized controlled trials and long-term extension studies. *Rheumatology (Oxford)* 53(10), 1872–1885 (2014).

•• **A very interesting systematic review with a meta-analysis useful in clinical practice.**

11 Smith MY, Attig B, McNamee L, Eagle T. Tuberculosis screening in prescribers of anti-tumor necrosis factor therapy in the European Union. *Int. J. Tuberc. Lung Dis.* 16(9), 1168–1173 (2012).

12 Latent tuberculosis infection: a guide for primary health care providers. US Department of Health and Human Services Centers for Disease Control and Prevention National Center for HIV/AIDS, Viral Hepatitis, STD and TB Prevention (2013). www.cdc.gov/tb/publications

13 Mazurek GH, Jereb J, Vernon A, LoBue P, Goldberg S, Castro K. Updated Guidelines for Using Interferon Gamma Release Assays to Detect Mycobacterium tuberculosis Infection – USA, 2010; Morbidity and Mortality Weekly Report (2010). www.cdc.gov/mmwr

14 Atzeni F, Benucci M, Sarzi-Puttini P. Infections during treatment with biological agents and possible treatment in clinical practice. *Expert Rev. Clin. Immunol.* 9, 193–195 (2013).

15 Dixon WG, Watson K, Lunt M, Hyrich KL, Silman AJ, Symmons DP. Rates of serious infection, including site-specific and bacterial intracellular infection, in rheumatoid arthritis patients receiving anti-tumor necrosis factor therapy: results from the British Society for Rheumatology Biologics Register. *Arthritis Rheum.* 54, 2368–2376 (2006).

• **A very relevant paper on infections in patients treated with anti-TNF drugs.**

16 Tsiodras S, Samonis G, Boumpas DT, Kontoyiannis DP. Fungal infections complicating tumor necrosis factor a blockade therapy. *Mayo Clin. Proc.* 83, 181–189 (2008).

17 Galloway JB, Hyrich KL, Mercer LK *et al.* Risk of septic arthritis in patients with rheumatoid arthritis and the effect of anti-TNF therapy: results from the British Society for Rheumatology Biologics Register. *Ann. Rheum. Dis.* 70(10), 1810–1814 (2011).

18 Davies R, Dixon WG, Watson KD *et al.* Influence of anti-TNF patient warning regarding avoidance of high risk foods on rates of listeria and salmonella infections in the UK. *Ann. Rheum. Dis.* 72, 461–462 (2013).

19 Listing J, Strangfeld A, Kary S *et al.* Infections in patients with rheumatoid arthritis treated with biologic agents. *Arthritis Rheum.* 52, 3403–3412 (2005).

20 Che H, Lukas C, Morel J, Combe B. Risk of herpes/herpes zoster during anti-tumor necrosis factor therapy in patients with rheumatoid arthritis. Systematic review and meta-analysis. *Joint Bone Spine* 81, 215–221 (2014).

21 Wendling D, Auge B, Bettinger D *et al.* Reactivation of a latent precore mutant hepatitis B virus related chronic hepatitis during infliximab treatment for severe spondyloarthropathy. *Ann. Rheum. Dis.* 64, 788–789 (2005).

22 Caporali R, Bobbio-Pallavicini F, Atzeni F *et al.* Safety of tumor necrosis factor alpha blockers in hepatitis B virus

occult carriers (hepatitis B surface antigen negative/anti-hepatitis B core antigen positive) with rheumatic diseases. *Arthritis Care Res. (Hoboken).* 62(6), 749–754 (2010).

23 Cantini F, Boccia S, Goletti D *et al.* HBV reactivation in patients treated with antitumor necrosis factor-alpha (TNF-α) agents for rheumatic and dermatologic conditions: a systematic review and meta-analysis. *Int. J. Rheumatol.* 2014, 926836 (2014).

• **A very interesting systematic review with a meta-analysis useful in clinical practice.**

24 Vassilopoulos D 1, Calabrese LH. Management of rheumatic disease with comorbid HBV or HCV infection. *Nat. Rev. Rheumatol.* 8(6), 348–357 (2012).

25 Ji J, Liu X, Sundquist K, Sundquist J. Survival of cancer in patients with rheumatoid arthritis: a follow-up study in Sweden of patients hospitalized with rheumatoid arthritis 1 year before diagnosis of cancer. *Rheumatology (Oxford)* 50, 1513–1518 (2011).

26 Askling J, Fored CM, Baecklund E, Brandt L *et al.* Haematopoietic malignancies in rheumatoid arthritis: lymphoma risk and characteristics after exposure to tumour necrosis factor antagonists. *Ann. Rheum. Dis.* 64, 1414 (2005).

27 Baecklund E, Smedby KE, Sutton LA, Askling J, Rosenquist R. Lymphoma development in patients with autoimmune and inflammatory disorders – what are the driving forces? *Semin. Cancer Biol.* 24, 61–70 (2014).

• **A very useful paper.**

28 Baecklund E, Ekbom A, Sparen P, Feltelius N, Klareskog L. Disease activity and risk of lymphoma in patients with rheumatoid arthritis: nested case–control study. *Br. Med. J.* 317, 180–181 (1998).

29 Mariette X, Matucci-Cerinic M, Pavelka K *et al.* Malignancies associated with tumour necrosis factor inhibitors in registries and prospective observational studies: a systematic review and meta-analysis *Ann. Rheum. Dis.* 70, 1895–1904 (2011).

30 Carmona L, Abasolo L, Descalzo MA *et al.* BIOBADASER Study Group, EMECAR Study Group. Cancer in patients with rheumatic diseases exposed to TNF antagonists. *Semin. Arthritis Rheum.* 41, 71–80 (2011).

•• **Very interesting paper on malignancies.**

31 Wolfe F, Michaud K. The effect of methotrexate and anti-tumor necrosis factor therapy on the risk of lymphoma inrheumatoid arthritis in 19,562 patients during 89,710 person-years of observation. *Arthritis Rheum.* 56, 1433–1439 (2007).

32 Lopez-Olivo MA, Tayar JH, MD, Martinez-Lopez JA *et al.* Risk of malignancies in patients with rheumatoid arthritis treated with biologic therapy. a meta-analysis. *JAMA* 308, 898–908 (2012).

33 Zintzaras E 1, Voulgarelis M, Moutsopoulos HM. The risk of lymphoma development in autoimmune diseases: a meta-analysis. *Arch. Intern. Med.* 165, 2337–2344 (2005).

34 Moulis G, Sommet A, Benè J *et al.* Cancer risk of anti-TNF-α at recommended doses in adult rheumatoid arthritis: a meta-analysis with intention to treat and per protocol analyses. *PLoS ONE* 7, e48991 (2012).

• **A very interesting paper.**

35 Atzeni F, Sarzi-Puttini P. Autoantibody production in patients treated with anti-TNF-alpha. *Expert Rev. Clin. Immunol.* 4, 275–280 (2008).

36 Atzeni F, Talotta R, Salaffi F *et al.* Immunogenicity and autoimmunity during anti-TNF therapy. *Autoimmun. Rev.* 12, 703–708 (2013).

37 van Schouwenburg PA, van de Stadt LA, de Jong RN. Adalimumab elicits a restricted anti-idiotypic antibody response in autoimmune patients resulting in functional neutralisation. *Ann. Rheum. Dis.* 72(1), 104–109 (2013).

• **An excellent paper on autoimmunity and anti-TNF therapy.**

38 Vultaggio A, Matucci A, Nencini F *et al.* Anti-infliximab IgE and non-IgE antibodies and induction of infusion-related severe anaphylactic reactions. *Allergy* 65, 657–661 (2010).

39 Benucci M, Saviola G, Meacci F *et al.* No correlations between the development of specific iga and igm antibodies against anti-TNF blocking agents, disease activity and adverse side reactions in patients with rheumatoid arthritis. *Open Rheumatol. J.* 7, 75–80 (2013).

40 Ramos-Casals M, Brito-Zeron P, Munoz S *et al.* Autoimmune diseases induced by TNF-targeted therapies: analysis of 233 cases. *Medicine* 86, 242–251 (2007).

41 Moulis G, Sommet A, Lapeyre-Mestre M *et al.* Is the risk of tumour necrosis factor inhibitor-induced lupus or lupus-like syndrome the same with monoclonal antibodies and soluble receptor? A case/non case study in a nationwide pharmacovigilance database. *Rheumatology (Oxford)* 53, 1864–1871 (2014).

42 Carmona L, Cross M, Williams B, Lassere M, March L. Rheumatoid arthritis. *Best Pract. Res. Clin. Rheumatol.* 24, 733–745 (2010).

43 Jacobsson LT 1, Turesson C, Gülfe A *et al.* Treatment with tumor necrosis factor blockers is associated with a lower incidence of first cardiovascular events in patients with rheumatoid arthritis. *J. Rheumatol.* 32, 1213–1218 (2005).

44 Barnabe C, Martin BJ, Ghali WA. Systematic review and meta-analysis: anti-tumor necrosis factor α therapy and cardiovascular events in rheumatoid arthritis. *Arthritis Care Res. (Hoboken)* 63, 522–529 (2011).

45 Dixon WG, Watson KD, Lunt M *et al.* Reduction in the incidence of myocardial infarction in patients with rheumatoid arthritis who respond to anti-tumor necrosis factor alpha therapy: results from the British Society for Rheumatology Biologics Register. *Arthritis Rheum.* 56(9), 2905–2912 (2007).

46 Dadoun S, Zeboulon-Ktorza N, Combescure C *et al.* Mortality in rheumatoid arthritis over the last fifty years: systematic review and meta-analysis. *Joint Bone Spine* 80, 29–33 (2013).

• **A very relevant paper on cardiovascular disease.**

47 Bili A, Tang X, Pranesh S, Bozaite R *et al.* Tumor necrosis factor α inhibitor use and decreased risk for incident coronary events in rheumatoid arthritis. *Arthritis Care Res. (Hoboken)* 66, 355–363 (2014).

48 Turiel M, Tomasoni L, Sitia S *et al.* Effects of long-term disease-modifying antirheumatic drugs on endothelial

function in patients with early rheumatoid arthritis. *Cardiovasc Ther.* 28, e53–e64 (2010).

49 Dulai R, Perry M, Twycross-Lewis R, Morrissey D, Atzeni F, Greenwald S. The effect of tumor necrosis factor-α antagonists on arterial stiffness in rheumatoid arthritis: a literature review. *Semin. Arthritis Rheum.* 42, 1–8 (2012).

50 Sarzi-Puttini P, Atzeni F, Shoenfeld Y, Ferraccioli G. TNF-alpha, rheumatoid arthritis, and heart failure: a rheumatological dilemma. *Autoimmun. Rev.* 4, 153–161 (2005).

51 Daïen CI 1, Duny Y, Barnetche T, Daurès JP, Combe B, Morel J. Effect of TNF inhibitors on lipid profile in rheumatoid arthritis: a systematic review with meta-analysis. *Ann. Rheum. Dis.* 71, 862–868 (2012).

52 Ramiro S 1, Gaujoux-Viala C, Nam JL *et al.* Safety of synthetic and biological DMARDs: a systematic literature review informing the 2013 update of the EULAR recommendations for management of rheumatoid arthritis. *Ann. Rheum. Dis.* 73(3), 529–535 (2014).

•• **A useful paper in clinical practice.**

53 Thalayasingam N 1, Isaacs JD. Anti-TNF therapy. *Best Pract. Res. Clin. Rheumatol.* 25(4), 549–567 (2011).