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Background

Rheumatoid arthritis (RA) is a chronic inflammatory autoimmune disease of multifactorial origin usually characterized by the destruction of joints, functional disability, deterioration of the quality of life and even shortened life expectancy. Because of its frequency, its socioeconomic repercussions and the increasing cost of its management, RA represents a real public health problem (1).The total direct cost per year is enormous. It has been estimated to range between $8,209 and $85,469 per patient in the US (2), and to be more than $1 billion for the whole rheumatoid population in Italy (3). The indirect costs are much higher and when the direct and indirect costs and the loss of earning power are added together, the total burden has been calculated to be around $5 billion in Italy (3).Tumor necrosis factor-α (TNF-α) plays a key role in the pathogenesis of RA (4). As a result, this cytokine has become an important therapeutic target for the development of new antirheumatic drugs. The TNF-α antagonists now in clinical use are etanercept (Wyeth Europe Ltd, Maidenhead, UK), infliximab (Remicade, Centocor, Malvern, Pa, USA) and adalimumab (Humira, Abbott, Abbott Park, Illinois, USA). These three compounds possess different biochemical characteristics and biological properties; they are different in terms of route and schedule of administration, half life, ability to fix complement and cytotoxicity. Etanercept is a fusion protein mimicking the TNF receptor p75, linked to the human IgG1 Fc. Infliximab and adalimumab are monoclonal antibodies (chimeric the former and fully human the latter) able to bind TNF-α on the cell membrane as well as in the fluid phase (5).

The efficacy and safety of etanercept, infliximab and adalimumab in the treatment of RA has been demonstrated in a large number of studies summarized in Tables I, II and III. Randomized controlled trials as well as open label studies have proved the efficacy of etanercept in treating RA as monotherapy or in association with MTX. Similarly, the efficacy of infliximab in combination with MTX and of adalimumab as monotherapy or in combination has been shown (6).

However the combination of a TNF blocking agent and MTX yields superior results for RA when compared with monotherapy, particularly with respect to excellent clinical responses (ACR 70, EULAR remission) and radiological outcomes (7-10) Moreover, TNF-α blocking agents have been used with a combination of background DMARDs (11). Patients have been switched from one TNF blocking agent to another but no well-controlled switch trials have been published (12, 13). These studies suggest that failure to respond to one TNF blocking agent does not preclude response to another (14).

Recommendation for the clinical use of anti-TNF-α agents in rheumatoid arthritis

The Italian Society for Rheumatology (SIR, Società Italiana di Reumatologia) has already published (in 2002) a Consensus Statement on the use of biological agents in the treatment of RA (15). The present report has been written on behalf of the SIR executive committee and is devoted to drawing up and disseminating specific recommendations for the use of anti-TNF- therapies in patients with RA.

Inclusion criteria

Patients with active RA (Disease Activity Score, DAS > 3.7 or DAS28 > 5.1) are eligible for the treatment with TNF blockers after a failure of an adequate trial of another effective DMARD, including MTX (at least 15 mg per week, for at least 12 weeks (16-21). Adalimumab and etanercept are both approved as monotherapy for RA, while infliximab is approved for use with MTX in RA; they can be added to pre-existing therapy, or, when appropriate, may replace previous DMARDs. The combination of a TNF blocking agent and MTX yields superior results for RA when compared with monotherapy, with respect to clinical responses and radiological outcomes (7, 22). The data on long-term safety and effectiveness are still scant and, along with other factors such as health economic considerations, do not allow the use of TNF

blocking agents as the first DMARD for the treatment of RA. (23, 24).

Assessment of response to, and criteria for withdrawal of anti-TNF-α therapy

A careful evaluation of the efficacy is mandatory in order to avoid unjustified potential long-term side effects and for pharmaco-economic reasons as well (17). Treatment with TNF inhibitors improves symptoms, clinical signs, laboratory parameters and radiographic progression in patients with severe, active RA either refractory to conventional DMARDs (22, 25-33) or DMARD naive (7, 34, 35). So far, there is no evidence that the same efficacy could be obtained in less active/severe RA (36).The activity criteria for patient inclusion in most of the clinical trials are ≥ 6 swollen joints, and elevation of the inflammatory indices (e.g. PCR > 20 mg/l) that means a DAS > 3.2 (17).

For clinical purposes, several European Rheumatology Societies recommend DAS to evaluate disease activity before starting therapy with anti-TNF-α drugs (37, 38). DAS is a highly reliable index (39) and offers the advantage of using the same index for measurement of disease activity as inclusion criterion and measurement of response to treatment as well (40).

Although ACR response criteria (41) have usually been employed in most of the controlled clinical trials, other composite indices like DAS, or individual indicators like HAQ, are usually recommended in clinical practice (42). Several laboratory parameters show significant changes along with clinical response. In addition to acute-phase reactants, rheumatoid factor titre and, in some studies, anti-citrullinated peptide antibody levels may show a significant decrease following TNF-α blockers (43-45). The biologic relevance and clinical usefulness of these changes still needs to be established.

Blockade of radiographic progression can be observed, especially when anti-TNF-α are given in combination with MTX (7, 22, 25, 34, 35). This effect may occur even in patients with poor clinical response (7, 22, 46). The biological, clinical and prognostic significance of this last finding is not completely understood (47, 48) so there is no definite evidence supporting that anti-TNF-α treatment should be maintained in clinically non-responsive patients. Additional imaging techniques, e.g. Power-Doppler ultrasonography or magnetic resonance, might be useful to evaluate disease activity and response to treatment (49, 50, 51). Nowadays, further efforts of standardization are needed in order to obtain reliable and reproducible evaluations in different settings (51). Waiting for more evidence-based indications over a possible temporary or intermittent use of these drugs (50, 52), the data available so far suggest that anti-TNF-α therapy should be continued indefinitely to maintain adequate clinical and radiological responses (7, 53, 54). For this reason, it is important to establish the right time to evaluate clinical response and to stop treatment in case of lack of response. On the basis of the most relevant controlled clinical trials (7-35), this time is usually 12 weeks (17, 42), and maintainment of clinical response should be further evaluated every three months.

If a satisfactory clinical response (by DAS, Table IV) is not reached at 12 weeks, the anti-TNF-α treatment should be stopped or switched to another anti-TNF-α agent (42, 55). Efficacy of switching to a different TNF-α blocker has been also reported after loss of clinical response or after infusion reactions

Table I. Major clinical studies of *ETANERCEPT* in RA patients.

Study	Design	Patient Number	Age (yrs)	Disease Duration	Drug Comparator	Treatment Duration	Outcomes
ETANERCEPT MONOTHERAPY							
Moreland 1999 & 2003	RCT/OL	234 (DMARDs refractory)	51-53 (mean)	11-13 yrs (mean)	placebo	6 mo RCT 5 yrs OL	ACR response; HAQ
COMBINATION THERAPY WITH MTX							
Weinblatt 1999 & Kremer 2002	RTC/OL	89 (MTX refractory)	48-53 (mean)	13 yrs (mean)	placebo	6 mo RCT 56 wk OL	ACR response
TEMPO 2004 Klareskog	RCT	682 (active disease)	53 (mean)	6yrs (mean)	ETA monotherapy vs ETA + MTX (20 mg)	52 wk	ACR response; radiographic progression
ETANERCEPT IN EARLY RA							
ERA 2002 Genovese & Genovese 2005	RCT/OL	632 (MTX naive)	49-51 (mean)	< 3 yrs (mean)	MTX (mean dosage: 19 mg)	2 yrs RCT 5 yrs OL	ACR response; DAS; safety; radiographic progression
ETANERCEPT IN EARLY RA vs LONG-STANDING DISEASE							
Baumgartner 2004	OL	671	51-53 (mean)	1/12 yrs (mean)	ETA	3 yrs	HAQ

Table II. Major clinical studies of *ADALIMUMAB* in RA patients.

Study	Design	Patient Number	Age (yrs)	Disease Duration	Drug Comparator	Treatment Duration	Outcomes
ADALIMUMAB MONOTHERAPY							
Barrera 2002	RCT/OL	198 (active disease)	55-57 (mean)	50-108 mo (median)	placebo/ MTX (75 ▷25 mg)	48 wk	% drop-out; EULAR response
DEO11 2002 van de Putte & van de Putte 2004	RCT/OL	544 (active disease, DMARDs refractory)	51-54 (mean)	9-11 yrs (mean)	placebo	4 yrs	ACR response
COMBINATION THERAPY WITH MTX							
ARMADA 2003 Weinblatt & DE020 2004	RCT/OL	271 (active disease, DMARDs refractory)	53-57 (mean)	11-13 yrs (mean)	placebo	24 wk RCT 3 yrs OL	ACR response
STAR 2003 Furst	RCT	636 (active disease)	55 (mean)	9-11 yrs (mean)	placebo	24 wk	ACR response; safety
DEO19 2004 Keystone	RCT	619 (active disease)	56-57 (mean)	11 (mean)	placebo	52 wk	ACR response; radiographic progression
ReAct 2005 Burmester/ Mariette/Bombardieri	OL	4241 (active disease)	549 (mean)	11 yrs	-	12 wk (ongoing)	ACR & EULAR response
ADALIMUBAB IN EARLY RA							
PREMIER 2005 van der Heijde/ Pavelka/Emery	DB	585 (active disease)	adults	< 3 yrs	ADA/MTX (max 20 mg)	2 yrs	ACR response; DAS28; radiographic progression

(56) [14] in patients who had initially demonstrated clinical response.

Warnings and withdrawal for toxicity

Infections

Generally the appearance or incidence of infections in immuno-compromised patients may be a consequence of too intensive immunosuppression, although the specific mechanism of action of the drug will help determine the specific infections that are seen. TNF play a crucial role in the body's defense against both bacterial and viral invasion, particularly in the recruitment of neutrophils, and macrophages to the sites of infection. (57). Therefore, if the effects of TNF are blocked, patients may be in a condition of an increased risk of infections. Despite this theoretical concept, practically the rates of infection seen during clinical trials of etanercept, infliximab, and adalimumab in RA patients were not significantly increased compared with those in the placebo control groups (32, 58-60).

Less important infections, such as upper respiratory tract infections, were seen frequently, but not at a rate greater than in the placebo group. However, clinical trials may not be efficient to detect an increased rate of serious infections. This is particularly true as strict inclusion and exclusion criteria may limit the study to patients at low risk of infection. Despite this, a recent phase IV study of adalimumab, which did not restrict the use of concomitant DMARDs or corticosteroids among the enrolled patients, did not detect an increase in serious infections among treated RA patients compared with placebo (30). In any case, patients with RA are already at an increased risk of serious infections in comparison with the general population (61).

An increased susceptibility to tuberculosis (TB) or re-activation of latent TB should be considered a class characteristic of TNF-blocking agents and causes the greatest concern in RA treated patients. The number of reports of TB during the clinical trials was relatively low, with one case reported during a clinical trial of 340 patients treated with infliximab, 22 and 13 cases among 2,468 patients during the clinical development phases of adalimumab (62, 63).

By contrast, there have been no cases reported during clinical trials of etanercept. There are now numerous case reports of TB developing in patients who have received infliximab. In 2001, 70 cases of TB associated with exposure to infliximab, from an unknown denominator of those treated, were reported, of which 47 had received the drug for RA (64). More than 50% of the cases were characterized by extrapulmonary infections. The majority (64%) of the cases occurred in Europe. Since that report, cases have continued to be observed in patients who have received infliximab, etanercept, and adalimumab (65-69). Most of these infections have occurred in patients with a known history of TB, suggesting a reactivated infection, but some have occurred in patients with no known previous history of the disease. Interestingly, although etanercept blocks the same cytokine, there have been very

Table III. Major clinical studies of *INFLIXIMAB* in RA patients.

Study	Design	Patient Number	Age (yrs)	Disease Duration	Drug Comparator	Treatment Duration	Outcomes
COMBINATION THERAPY WITH MTX							
Maini 1999 & Lipsky 2000 ATTRACT	RCT	428	53 (mean)	6.8 yrs	placebo	54 wk	ACR response; HAQ; SF-36; radiographic progression
Maini 2004 ATTRACT extension	RCT	259	53 (mean)	6.8 yrs	placebo	48 wk	ACR response; HAQ; SF-36; radiographic progression
Smolen 2005 ATTRACT subanalysis	RCT	237	53.3 (mean)	11 yrs	placebo	54 wk	ACR response; DAS28; radiographic progression
Fleischmann 2005 iRAMT trial	OL	210	53.2 (mean)	10.4 yrs	_	54 wk	ACR response; HAQ; DAS
INFLIXIMAB IN EARLY RA							
St. Clair 2004 ASPIRE	RCT	1049	50.5 (mean)	7 mo	Infliximab + MTX vs placebo + MTX	54 wk	ACR response; HAQ; SF-36; radiographic progression
Quinn 2005	RCT-DB	20	52 (mean)	6 mo	Infliximab + MTX vs placebo + MTX	12 mo	MRI
Goekoop-Ruiterman 2005 The BeSt Study	RCT	508	54.2 (mean)	23 wk	comparison of four different treatment strategies	54 wk	DAS44; HAQ; radiographic progression

few reports of TB after its use. During the pharmacovigilance observational period, only nine cases of TB among patients receiving etanercept had been reported to the Federal Drug Administration (FDA) compared with the 70 cases with infliximab. Possible suggestions for this discrepancy include the different mechanisms by which the two agents block TNF (70). Serious bacterial infections have been observed in patients receiving TNF blocking agents (71), but it is not clear for the most part that their incidence is higher than in patients with RA using other forms of DMARD therapy and/or corticosteroids. TNF blocking agents should not be started or should be discontinued when serious infections and/or opportunistic infections occur, including septic arthritis, infected prostheses, acute abscess, osteomyelitis, sepsis, systemic fungal infections. Treatment in such patients should only be resumed if the infections have been treated adequately.

Hepatitis

Despite several data on TNF inhibition and increased susceptibility to bacterial, fungal, and mycobacterial infections, relatively little has been described regarding the safety of these agents in the setting of chronic viral infections. Recent findings have demonstrated that TNF mediated pathways play a critical role in regulating the molecular interactions between cellular and viral factors within infected cells and that many viral pathogens have learned to exploit the TNF pathway, using it to escape control and favour their expansion (72). Viral diseases in general are characterized by three general patterns of infectivity (73). Acute infections such as influenza appear to be self-limited disease whereby the host defenses ultimately prevail and eliminate the pathogen. Herpes viral infections such as herpes simplex type 1 and 2, Epstein-Barr virus, and varicella zoster among others display a period of acute primary infection followed by a prolonged or lifelong period of latency whereby the host defense system keeps the pathogen in check. Failure of such immunological control involves reactivation, often with a different expression of disease (that is, dermatomal zoster). Finally, a few viral pathogens have the capacity to cause a primary infection and then remain in a persistent replicative state for the remainder of the life of their host. A relatively small number of viral agents are capable of such a pattern of disease, but these include hepatitis B and C viruses (HBV and HCV) and the human immunodeficiency virus (HIV) types 1 and 2. These agents are prevalent worldwide, infecting an estimated half a billion patients, and therefore it is natural to question what effect inhibition of TNF has on their natural history and clinical expression. The long term safety or efficacy of TNF blockers in chronic hepatitis B and C patients is not known. TNF blockers should not be used in patients with hepatitis B infection, although anecdotal data indicate that reactivation of HB infection after TNF blockers withdrawal can be prevented by using prophylactic antiviral therapy (74). HCV is a bloodborne pathogen that appears endemic in most areas of the world and is estimated to infect nearly 200 million people world-

Table IV. Evaluation of clinical activity and clinical response according to the EULAR disease activity score (DAS) (40).

Present DAS	DAS improvement >1.2	0.6-1.2	0.6
≤ 2.4 inactive	Good response	Moderate response	No response
> 2.4 ≤ 3.7 moderate	Moderate response	Moderate response	No response
> 3.7 very active	Moderate response	No response	No response

Table V. Recommendations for the use of biologic (TNF-α blocking) agents in the treatment of rheumatoid arthritis in Italy.

Specific point approved by the SIR executive committee*

1. Patients with active RA (DAS > 3.7 o DAS28 > 5.1) are eligible to the treatment with TNF blockers after a failure of an adequate trial of another effective DMARD, including MTX (at least 15 mg per week, for at least 12 weeks).
2. On the basis of the most relevant controlled clinical trials, the right time to evaluate clinical response and to stop treatment in case of lack of response is usually 12 weeks; maintenance of clinical response should be further evaluated every three months.
3. Failure to respond to one TNF blocking agent does not preclude response to another.
4. An increased susceptibility to tuberculosis (TB) or re-activation of latent TB should be considered a class characteristic of TNF-blocking agents; interestingly, although etanercept blocks the same cytokine, there have been very few reports of TB after its use.
5. Anti-TNF therapy appears to be safe in patients with chronic HCV infection who are candidates for treatment with these biologically active agents for other coexisting medical conditions such as RA.
6. RA patients treated with TNFa inhibitors show a NHL incidence higher than expected in the general population. However, since severe and active RA represents a predisposing factor for NHL, it is mandatory to avoid a channelling bias due to the fact that just those patients with active and severe disease are selected for anti-TNF therapy.
7. High dose infliximab (10mg/kg) appears to be associated with an increased relative risk of worsening congestive heart failure (CHF) and mortality, particularly in RA patients with NYHA Class III-IV CHF.
8. There is an increased incidence of ANA and anti-dsDNA after TNF blocking treatment, however there is no evidence that patients who develop such autoantibodies are at increased risk for development of drug-induced lupus.

The members of the executive committee are:
Bombardieri S, Cutolo M, Olivieri I, Canesi B, Carrabba M, Di Matteo L, Mathieu A, Montecucco C, Muratore M, Pucino A, Punzi L, Salvarani C, Triolo G, Valesini G, Zeni S, Modena V, Di Munno O.

wide. On the basis of the NHANES III data (21,000 people were tested for HCV), an estimated 3.9 million (1.8%) Americans were infected with HCV, and of this group, 2.7 million (74%) were estimated to have chronic infection associated with HCV viraemia (detectable serum HCV RNA) (75).

Very limited data are available on the use of existing TNF blockers in patients with chronic HCV infection. Recently, a study of 24 patients with chronic HCV infection and RA who received anti-TNF therapy (etanercept or infliximab) has been reported (76). No significant adverse events were reported in these patients, nor significant variations were noted in the liver aminotransferases or in HCV RNA viral loads, yet 16/22 patients with pretreatment and post-treatment HCV RNA evaluations showed decline in viral load. The above-reported study, even if limited, provides the first assessment of anti-TNF safety in RA patients and will likely be followed up by a prospective assessment of this important clinical question in the management of RA patients infected with HCV. Furthermore it was investigated the safety and efficacy of etanercept in HCV patients as an adjuvant to standard IFN (alfa-2b) and ribavirin through a phase II pilot study (77).

The study was a double blind, placebo controlled, randomised clinical trial in the treatment of naive adult patients with chronic HCV infection. A total of 50 subjects were randomised to one of two treatment groups (IFN/ribavirin plus etanercept or IFN/ribavirin plus placebo). HCV genotype 1 infection was found in 90% of patients. Etanercept (or matched placebo) was given subcutaneously in a dose of 25 mg two times per week for 24 weeks only. The primary endpoints of efficacy were normal for alanine aminotransferase (ALT) and showed an absence of serum HCV RNA at 24 weeks. Safety and tolerability were assessed by direct questioning of RA patients about side effects, physical examination, laboratory values, and evaluation of premature withdrawal for safety reasons.

More subjects on the etanercept branch met the primary endpoints of normal ALT and absence of serum HCV RNA. However, the placebo group showed significantly fewer patients with negative HCV RNA at 24 weeks than the etanercept group (32% in the placebo group compared with 63% in the etanercept group, $p = 0.04$). Both endpoints of normal ALT and negative HCV RNA were achieved by 28% on placebo compared with 58% in the etanercept group and the difference was statistically significant ($p = 0.04$). By considering the small number of patients in both branches of the study, strong trends were noted with the etanercept group having fewer side effects in almost every category (gastrointestinal, cardiovascular, cutaneous, neurological, and endocrine). No serious adverse effects were reported in this study and no withdrawal due to side effects.

Following these limited and preliminary data, anti-TNF therapy appears to be safe in patients with chronic HCV infection who are candidates for treatment with these biologically active agents for other coexisting medical conditions such as RA. However, monitoring of serum aminotransferases and perhaps HCV RNA during therapy should be considered because of the lack of information and absence of

prospectively obtained data. Concerning the use of anti-TNF therapy as an adjuvant to IFN/ribavirin, this triple treatment may need to be validated in large clinical trials before it can be recommended for routine use in patients with HCV. In a recent retrospective study, anti-TNF therapy for RA in the setting of HCV appeared to be safe and well-tolerated without apparent influence on the underlying HCV infection (78).

Malignancies, lymphoma

The frequency of neoplasias in RA patients receiving treatment with TNF-α inhibitors does not seem increased significantly, if we exclude a higher risk of lymphomas (79). So far, it is not clear whether such an excess of lymphomas is therapy-related or disease-related (80). Intriguingly, some preclinical findings suggest that TNF may promote cancer development and progression, which has led to propose anti-TNF therapy as a novel approach to malignancies. (81).

There is thus far no evidence that TNF-blocking agents are associated with an increased incidence of other malignancies or recurrence in patients who have had solid malignancies previously; however *v*igilance with respect to the occurrence of lymphomas and other malignancies including recurrence of solid tumors remains warranted in RA patients using these medications.

RA shows a higher incidence of non-Hodgkin's lymphomas (NHL), with a Standardized Incidence Ratio (SIR) equal or above 2. This finding has been confirmed in almost all of the studies carried out on large series of patients (82-90) and has almost remained the same in the last 30 years, despite the fact that the global incidence of lymphomas has nearly doubled (91).There is also evidence of a significant association between disease activity and risk of developing NHL in RA. In a case-control study performed by Baecklund *et al.* (92) on 41 RA patients with lymphoma compared to a group of 113 RA controls, the patients with a moderate disease activity had a relative risk 5 times higher than those with a low activity, and the risk rose to 20 times for those with high activity. In a study performed on 1,767 RA outpatients during 25 years, the risk of lymphoma was 9 times higher for the patients with ESR above 40 mm/h (93).

Disease severity was associated with a significantly increased risk as well (92). Despite a number of NHL reported during treatment with MTX (94), none of the epidemiological studies carried out so far showed an increased risk with this drug (94) as well as with cyclosporine A (95). A moderately increased risk was reported in RA with azathioprine (96).

The first data regarding TNF-α inhibitors in RA have been published by Brown *et al.* (97, 98). This paper deals with 18 lymphomas (15 in patients treated with etanercept and 3 with infliximab) reported to the U.S. Food and Drug Administration (FDA). In this report, two patients with a previous diagnosis of lymphoma died suddenly from a relapse and, as for the newly diagnosed cases, a prompt onset was reported after beginning treatment (median 8 weeks). However, two further studies (79, 85) did not confirm the latter observation.

In 2003, the FDA requested a review of all the cases studied in clinical trials with the three different TNFalpha inhibitors (99). Twenty cases of lymphomas were identified, 10 in the adalimumab group (SIR = 5.42, with a confidence interval between 2.6 and 10), 6 in the etanercept group (SIR = 2.31; 0.85-5.03), and 4 in the infliximab group (SIR = 6.35; 1.7-16.3). Three additional patients developed lymphoma after suspension of etanercept. The incidence of lymphomas shown by these data is not higher than expected in patients with severe, active RA as those included in these studies. If we focus on the infliximab treated group, the increased risk seems restricted to those patients with advanced and refractory disease.

Three population based studies have been published in the last two years. The first one (85), performed in the U.S.A., deals with a prospective evaluation of 18,572 RA patients, followed for two years, with 29 developing lymphoma (SIR = 1.9; 1.3-2.7). The SIR was 2.9 for anti-TNF-α treated patients (2.6 infliximab, 3.8 etanercept); 1.7 (0.9-3.2) for MTX alone and 1 (0.4-2.5) for other therapies. The authors conclude that the difference observed in the first group, including patients with a more severe and active disease, does not support a causative role of treatment. The second study (79) was performed in Sweden. Among 757 patients treated either with infliximab or etanercept for 1,603 persons per year, 5 cases of lymphomas were recorded (SIR = 11.5; 3.7-26.9). For comparison, among 800 RA patients from the same area treated with conventional drugs (3,948 persons per year), only two cases of lymphomas have been reported (SIR = 1.3; 0.2-4.5). Nevertheless, for the limited number of events and the short period of observation, the difference between the two groups did not reach statistical significance. The Italian national register of anti-TNF-α therapies for RA (ANTARES) has recorded 2 cases of NHL among 1,644 persons per year. NHL were diagnosed 14 and 41 months after starting treatment. The estimated incidence (1.2/1000) is high in absolute terms but lower than that reported in the Swedish study. An additional population based cohort study was performed on patients with RA (one prevalent cohort of 53,067 cases and one incident cohort of 3,703, and one TNF antagonist treated cohort 1999 through 2003 of 4,160 cases) who were linked with the Swedish Cancer Register (100). A study of 500 observed haematopoietic malignancies showed that prevalent and incident patients with RA were at increased risk of lymphoma (SIR = 1.9 and 2.0, respectively) and leukaemia (SIR = 2.1 and 2.2, respectively) but not of myeloma. Patients with RA treated with TNF antagonists had SIR = 2.9. However, after adjustment for sex, age, and disease duration, the lymphoma risk after exposure to TNF antagonists was no higher than in the other RA cohorts. As for histology, the lymphomas developed during anti-TNF-α treatment do not differ from those reported in other RA patients (104,105). A possible role of EBV, has not been investigated adequately so far (79, 85).

In conclusion, RA patients treated with TNF-α inhibitors show a NHL incidence higher than expected in the general population. However, since severe and active RA represents a predisposing factor for NHL, it is mandatory to avoid a channelling bias due to the fact that just those patients with active and severe disease are selected for anti-TNF therapy. Waiting for more detailed data, it is now advisable to perform a careful, close clinical surveillance, quickly reporting all the suspected cases according to the guidelines for post-marketing drug surveillance. Any treatment with TNF-α inhibitors should be avoided in patients with a previous history of lymphoma.

A review paper by Bongartz *et al*. (101) reports the results of a meta-analysis of nine controlled clinical trials published between 1998 and 2004 on the two TNF-α inhibitors infliximab and adalimumab and demonstrate that patients receiving these drugs have double the risk of developing serious infections and triple the incidence of malignancies. A great deal of criticism has arisen against this paper because of method deficiencies; furthermore, it contains no new data, and represents merely a collection of existing data already presented. An increased risk of TNF inhibitor-related solid tumors can not be established by this study, nevertheless clinicians should be aware of the risk of cancer in patients treated with immunosuppressants, including TNF blockers. A careful search for signs or symptoms of malignancy during therapy is recommended mainly in those patients with an increased risk of cancers, e.g. prior history of malignancy, cigarette smoking, etc.

Cardiovascular Risk

A further area of concern is in relation to cardiac disease, particularly the possibility that anti-TNF therapy may lead to worsening of congestive heart failure (CHF) (102). This concern was initially counterintuitive as serum levels of TNF are increased in patients with CHF and indeed correlate with the severity of CHF (103). Early reports suggested that treatment with a single dose of intravenous etanercept in patients with severe CHF might improve symptoms without significant side effects (104). Therefore, two large randomised, placebo controlled trials of anti-TNF agents in patients with CHF were organized. The first study, compared etanercept with placebo in RA patients with advanced heart failure (105). This study failed to detect any improvement in either CHF symptoms or mortality after etanercept treatment. The second study, compared infliximab with placebo in patients with advanced heart failure (106). This study observed an increased rate of death and admission to hospital in the infliximab group. It is not clear why treatment with infliximab should exacerbate CHF, but the increased mortality was only seen in the group receiving 10 mg/kg infliximab. For most patients, this exceeds the dose recommended for RA. However, no increased mortality was observed at the lower dose of 5 mg/kg.

A recent analysis reported the development of CHF in 47 patients who had received anti-TNF therapy, the majority for RA (107) However, case reports have also been published of other cardiac conditions in patients with RA receiving anti-TNF drugs. For example, a case of sudden death, without organic cause on necropsy, in a 64 year old man with no known underlying cardiac disease who was receiving infliximab, or a case report of new onset atrial fibrillation in a 57 year old man receiving etanercept have been described (107, 108). There is also evidence that the occurrence of anti-phospholipid antibodies after infliximab, in the presence of persistently active inflammation, can induce the occurrence of microvascular myocardial ischemia with heart failure (109). Since cardiovascular disease is the leading cause of death, with increased standardized mortality ratios, compared with the general population (110), care should be taken when interpreting the onset of CHF in RA patients treated with TNF blockers. Therefore, these increased ratios suggest that RA patients are already dying from cardiovascular disease in excess of the level expected for people in the age and sex-matched general population.

Induction of autoimmunity

Occurrence of autoantibodies, including antinuclear antibody (ANA) and anti-double stranded DNA antibodies (anti-dsDNA), following the use of TNF blockers has been documented during the clinical trials of these agents. About 60% of patients enrolled in the ATTRACT study developed a new ANA and 10% developed new anti-dsDNA during treatment with infliximab (111). The pathological value of these observations is not clear, however, only a single patient showed a lupus-like syndrome during the above reported study. The development of new ANA and anti-dsDNA has also been reported in about 10% of patients receiving either adalimumab or etanercept during phase III clinical trials, but with no cases of SLE (59). On the contrary, post-marketing surveillance of TNF blockers has disclosed numerous case reports of autoimmune diseases, particularly leucocytoclastic vasculitis and SLE (110, 112-114). In some cases, RA patients were known to have a positive ANA before the beginning of the anti-TNF therapy. However, the majority of these complications developed after starting TNF blockers, improved when it was discontinued, and were not life threatening. In addition, it is noted that patients with one autoimmune disease, such as RA, do have an increased frequency of a second autoimmune disease, particularly SLE, as well as autoimmune thyroiditis or Sjögren syndrome and autoantibodies (115). Therefore, the reports of these reactions may simply represent coincidental disease, however, the appearence of new autoantibodies with the use of TNF blockers suggests these drugs may, in some patients, have a causative role (116).

Recommendations

On the basis of the above reported evaluation, the executive committee of the Società Italiana di Reumatologia, in April 2006, approved the final recommendations summarized in Table V.

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