Side effects of anti-TNF therapy: Current knowledge

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ABSTRACT

The development of the anti-TNF therapies is a milestone in the therapy of rheumatic diseases. As in all new treatment opportunities it is of concern whether all potential undesired side effects have been evaluated within the clinical trials which have lead to approval of the drugs. Postmarketing experience and pharmacovigilance programs are necessary to determine the overall safety profile of the new agents. From the clinical trials and the practical experience of the first years we know that side effects have occurred in patients treated with anti-TNF agents. Sufficient knowledge about these partly specific side effects is critical for rheumatologists who treat their patients with these very effective biologic drugs.

Introduction

There are different sources from which safety information about a new drug can derive: 1. The clinical studies performed before and after approval of the drug, 2. FDA or EMIA public information about safety information the agencies achieve from clinical trials and spontaneous reports, 3. The data released by the drug companies, 4. National cohorts which have been installed after the marketing of the new biologicals. 5. Case or group reports of clinical investigators 6. Personal experience.

Every source has its advantages, but also its shortcomings. Clinical studies normally use controlled and randomised trial designs; therefore they obtain the best data with respect to comparing the risk of the new drug against placebo or a comparative drug. The disadvantage is the selection of the 'ideal' patient. Behind clinical trials we need information about the treatment of non-selected patients and off label use (new indications, combination treatment and different dosing regiments used from physicians in daily practice). Reports to the FDA are relevant and form part of the pharmacovigilance of each new product. The reports reflect how the product is used in clinical practice but they are uncontrolled and they lead to both underestimation and overestimation of the real risk due to the Weber effect and reporting bias. Data from the drug companies should be the most complete but the reports are also difficult to control and the reports are potentially influenced by the true financial interests of the companies. Case reports and single experiences may not be at all relevant overall, but they may nevertheless induce strong feelings because of personal experience.

Thus, we have to select an optimal mixture from these different sources to arrive at valid statements and this is not easy. At the present moment, final statements are still difficult because of the paucity of data available. This paper reports data derived from publications about clinical trials and safety issues about anti-TNF treatment, the FDA home-page and – to be as updated as possible – data from companies which was available to the authors and was presented at the EULAR meeting 2002 in Stockhom. We did not use data from the national registries in Europe because they are still short in duration and the initial data have not been published yet. Nevertheless these cohorts will be in the end the best tool to investigate long-term safety. They monitor in large controlled cohorts and over a sufficient time period, the outcome of actual treatment. For example, the German cohort includes 1000 new patients on each TNF-inhibitor and 2000 control patients with a change in their DMARD therapy in a prospective five-year follow-up study.

After the first years of anti-TNF therapy the following 7 types of adverse events seem to be of special concern for patients treated with anti-TNF therapy: 1. infections including sepsis and tuberculosis, 2. malignancies such as lymphoma, 3. other hematologic disorders such as anemia and pancytopenia,

4. demyelinating disorders/neuropathy, 5. worsening of congestive heart failure, 6. occurrence of autoantibodies and autoimmunity and 7. infusion/ injection and hypersensitivity reactions.

Mortality

Within the clinical trials and their follow-up no increased mortality has been observed for etanercept and infliximab. For etanercept a death rate of 0.9 per 100 patients year has been reported (11 in 628 treated patients) which was comparable to placebo and which did not increase during follow-up (1). In a 3-year follow-up of nearly 2000 infliximab patients from clinical trials and 192 placebo-treated patients, 4 deaths (2%) in the placebo group and 20 deaths (1%) in the infliximab group have been reported (2). The FDA collected trial and post-marketing data until August 2001 and we are aware of about 18,400 adverse events for etanercept and 2,300 for infliximab, including 290 deaths among patients treated with etanercept and 201 with infliximab (reported at an FDA Advisory Committee Meeting August 17, 2001 and accessed through the FDA homepage July 2002, http://www.fda.gov/ohrms/dockets/ac/ 01/briefing/3779b2_01_cber_safety_revision2.htm). However, this does not indicate that the mortality is increased and there is also no reason to think that there is a difference in mortality between the two compounds. The estimated overall frequency of treatments having occurred until August 2001 is about 200,000 for infliximab and 150,000 for etanercept worldwide. The main reason for the different numbers of adverse events reported is that there was a telephone system installed for etanercept which facilitates reporting, also by the patients themselves, extensively.

Table I. Opportunistic infections associated with TNF inhibition.

	Infliximab	Etanercept
Patients exposed	170,000	104,000
Tuberculosis	92	11
Atypical mycobacterium	3	8
Histoplasmosis	9	1
Listerosis	11	1
Candidasis	7	3
Aspergillosis	6	2
Pneumocystis carinii	12	5

ACR Hotline. FDA Advisory Committee reviews safety of TNF inhibitors.

Table II. Adverse events of TNF inhibition (FDA August 17, 2001).

AE reports	Infliximab			Etanercept		
	Deaths	Total	% of total	Deaths	Total	% of total
All reports	201	2,300	100	290	18,400	100
Demyelenation	1	1	0.04	0	15	0.08
Aplastic anemia	0	0	0	5	7	0.04
Intestinal perforation	3	4	0.2	0	3	0.02
Systemic lupus	1	1	0.04	1	25	0.14
Infections	228	901	39	291	5,143	28
Lymphoma	2	10	0.4	4	26	0.1
Congestive heart failure	10	19	0.8	11	66	0.4

Safety update on TNF-a antagonists: Infliximab and etanercept. FDA CBER. Arthritis Advisory Committee (17 August 2001).

Infections

Tuberculosis

With both biologicals the outstanding and most frequent problem are infections, accounting for 28% of all reports on etanercept and 39% for infliximab. There were 5,143 infections with 291 deaths reported with etanercept and 901 infections with 228 deaths reported with infliximab (double reporting possible, see above).

As recently reported, there seems to be an association of infection with mycobacteria and anti-TNF therapy, as it now stands, mainly for infliximab (3). At the end of November 2001 a total of 117 cases had been reported to the agency (4). The actual 5th safety update (Feb/02) of the safety data base from Centocor contains 181 reports of Tbc with inflixmab from which 64 occurred in the USA by 271152 patients treated worldwide and 75,853 in the EU (data on file Centocor). In total the number of new cases per month are declining compared to the increase of new patients treated with infliximab (Fig. 1). The risk of developing TB in the first year of infliximab therapy has been estimated at 0.03% in the U.S. and 0.2% in non U.S. citizens. However, there are also 18 cases of tuberculosis including 5 deaths (up to June 30, 2001) associated with etanercept therapy, one case of osteoarticular tuberculosis in a child has been published (5). At the moment it is unclear whether the demographics of the patients treated with etanercept are comparable to those who received infliximab. This may possibly explain differences – especially if it becomes clear that etanercept treated patients lived in a safer environment. Infliximab is mainly (80%) marketed in the USA whereas 80% of all Tbc cases with infliximab occurred outside of the USA mainly in countries with a high incidence of Tbc like Spain (data on file Centocor). One reason for the difference in the incidence of Tbc between infliximab and etanercept might be that etanercept has not been fully marketed yet in the countries with a high Tbc incidence. Another explanation may be that the antibody infliximab is able to introduce complement mediated cell lysis of TNF expressing cells which has not been shown for etanercept yet and has a different binding to the TNF trimer than etanercept (6, 7). In relatively small

randomized European trials in Berlin for AS (8) and in Belgian for SpA (9) with infliximab disseminated tuberculosis occurred in one case at each site.

What is the reason for this increased frequency of Tbc? Since most of the infections of patients treated with infliximab occurred during months 2-5 after the initiation of therapy, reactivation of latent TB seems to be the most likely explanation. However, both activation of latent tuberculosis and also new infections in the case of challenge with virulent microbes may occur (4). Reactivation of TB has also been described in vaccinated patients (10).

Studying infections in TNF-deficient mice, these had similar survival rates in a conventional environment but were clearly more susceptible to a challenge with mycobacteria than normal controls (11). Indeed, TNF seems to influence several aspects of the immune response to mycobacteria including IFNg-independent but TNF-dependent non-specific mycobactericidal effects of macrophages (4). However, the immunologic mechanisms that explain the link between TNF blockade and the failure of granuloma to contain bacilli are poorly understood. The T-cells in TNF deficient mice, infected with Tbc seem to function normally (12). But the mechanism against Tbc is dependent on the type of T-cell (13). Beside the knowledge that TNF is neccessary to keep the formation of the granuloma, other work showed that TNF can be used by the mycobacteria as an evasion mechanism and that the addition of anti-TNF antibodies can reduce the replication rate of the bacteria (14).

Taken together, TNF is clinically important and influences relevant immune functions which need to be effective for clearance of intracellular microbes including mycobacteria. Whether an upcoming infection is more due to a heavy bacterial load or a genetically determined functional variant or alteration of the immune system needs to be determined. For example, there are at least partially genetically determined differences in the capacity to secrete cytokines such as TNF between individuals and between patients and controls (15).

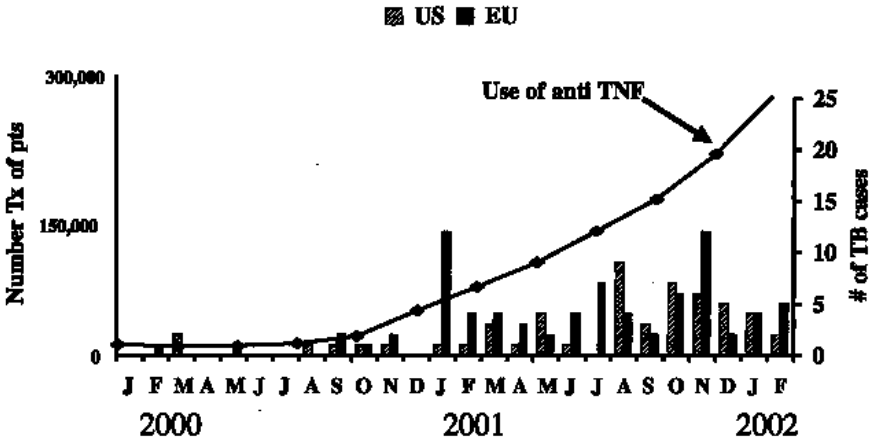

Fig. 1. Number of tuberculosis cases in the United States and the European Union.

Other infections

Other types of infection have occurred in patients treated with both anti-TNF agents this includes fatal cases with severe pneumonia (16, 17), meningitis (18), sepsis (19), histoplasmosis (4, 20) and aspergillosis (21) were reported. Furthermore, infections with listeria, pneumocystis carinii, coccidiomycosis, candidiasis having occurred are listed in the FDA database.

Looking at the Centocor database with data from all studies performed (n = 1372) there were 22% serious adverse events (SAE) on infliximab compared with 16% on placebo. In all studies with infliximab, there were 63% of the patients who had at least one infection vs. 51% of the control patients (n = 192). Treated infections were identified in 36% vs. 26%. Serious infections, however, occurred in 6.3% of infliximab treated patients vs. 6.8% on placebo. The most frequent localisation was the respiratory tract. A serious pneumonia was reported in 1% of the infliximab treated patients as compared to 0.5% among the control group.

In recent open label multicenter trials with infliximab in 553 RA patients the US (22) 8.5% serious adverse events have been reported and out of 263 RA patients in Germany (23) 25 withdrew because of side effects (9.5%), and 6 patients had a serious infection.

In a recent retrospective medical record review of 180 patients (24), most with RA (n = 144) started on etanercept 81% of the patients remained on therapy for > 6 months and 43% for > 12 months. Corticosteroid dose reduction was possible in 56% and 51% of the patients tapered their methotrexate dosages. Forty-three patients (26%) discontinued etanercept, partly because of serious adverse events (2.9%), mostly infections including psoas abscess secondary to Mycobacterium avium intracellulare, septic wrist, bacteremia, and septic total hip replacement. Two deaths associated with infection were seen.

In the FDA database, there were also reports on infections without an identified organism with 28 deaths while on or after etanercept and 11 with infliximab.

Taken together, fatal infections may occur with both agents. Compared to recent published infection rates of 0.03 - 0.9 serious infections in RA per patient/year neither etanercept or infliximab showed an increase in infection over all (25, 26). Tuberculosis has been more frequently reported with infliximab. Before treatment, patients should be informed about their immunocompromised status, especially in the first months of therapy, and educated to take signs of infection seriously and present to the responsible physician as soon as possible. Thus, all patients who are treated with anti-TNF therapy should be carefully screened for infections and treated with antibiotics if there is a suspicion of bacterial infection. Before starting anti-TNF therapy, caution is needed since latent cases such as subclinical pulmonary but also abdominal tuberculosis in patients with Crohn's disease may be overlooked (27). If there is

a suspicion or a high risk of exposure patients should not be treated with anti-TNF agents. Preemptive treatment with INH for the first 9 months of therapy should be performed in patients which need and have agreed to start infliximab treatment and who are PPD-positive or who have x-ray evidence of exposition to mycobacteria or a recent history of confirmed tuberculosis contact.

Malignancy/ hematologic disorders

At the FDA hearing in August 2001, 26 cases of lymphoma were reported with etanercept and 10 with infliximab. In a longterm follow up of patients treated with etanercept no increased incidence of malignancies was observed (1). The same is true for infliximab (2). Rapid development of squamous cell carcinoma has been reported in a few patients treated with etanercept (28). The 5th safety data base update of infliximab showed 64 lymphoma reports in 270,000 treated patients (data on file Centocor) which is still in the expected range. In contrast the authors did not receive from the company the actual total numbers for etanercept and lymphomas and we can only report from published results. Looking at all studies with infliximab, 17 (1.2%) of the patients who had received at least one dose of infliximab reported a malignancy (including lymphomas), while in the control group only 1 case was noted (0.5%). Since both, patients with RA and with Crohn's disease have an increased risk of malignancy, particularly lymphoma, no final conclusions can be drawn but, also due to the limited time frame of follow up so far, the issue has not been completely clarified yet. The prospective national cohorts from Sweden and Germany will most likely be able to answer this question in some years.

There are 7 cases of aplastic anemia with 5 deaths reported of patients on etanercept. Only 2 cases of pancytopenia on infliximab have been reported (FDA data base).

Neurologic disorders

In the FDA database, there are 16 reports on demyelinating disease in patients receiving TNF antagonists, in 15 cases associated with etanercept. This has been recently reported (29). In earlier days, 2 patients with multiple sclerosis developed such lesions while being treated with infliximab (30). The reason for the exacerbation or introduction of the demyelinating disorders is unclear (31). Furthermore, 6 cases of optic neuritis, 8 cases of central demyelisation and 4 cases of Guillain-Barré syndrome have been reported in the 5th update of the Centocor data base. This numbers are within in the normal range of incidence of the diseases and further observations are needed. Patients have to be informed about the risks and patients should be examined and questioned about earlier symptoms of demyelinating diseases before initiation of anti-TNF treatment.

Heart failure

Patients with congestive heart failure may not be treated with either agent. After early encouraging results, clinical studies with both agents showed that more patients died on anti-TNF therapy than on placebo. In the phase II trial of infliximab from 150 patients 9 died in the inflixmab group and 1 in the control group. In all clinical trials in RA and Crohn's disease no increase in heart insufficiency has been reported (data on file Centocor). The clinical trials with etanercept had been stopped because of lack of benefit. The data regarding deaths in the treatment vs. the control group have not been presented yet. On the FDA data base (data through June 30, 2001) ten death reports from etanercept and congestive heart failure are shown.

Miscellaneous disorders

Development of diabetes mellitus has been reported in a young patient on etanercept (32). Some cases of vasculitis have been described in patients treated with either agent (33, 34).

Autoantibodies

Anti-TNF therapy is associated with the formation of certain autoantibodies. Looking at all patients treated with infliximab in which samples before and after therapy were available (n =1058), 55% became ANA-positive at any time point, while 19% became positive on placebo. Of the ANA-positive patients at baseline 36% became ANA-negative during the study. Autoimmune diseases such as drug-induced lupus or lupus-like syndrome (a not very sharply defined term) occurred very rarely in 0.4% of all patients studied. Development of ANA or DNA antibodies was not predictive for the development of such symptoms. In an overview of all studies until 6/2001 data of 1897 patients and 192 controls 4.3% vs. 2%, 2.3% discontinued; 16% develop anti-dsDNA, 0.2% developed clinical signs of lupus-like syndrome (n = 4). Four cases of drug-induced lupus were reported in a patient on etanercept (35).

Patients have been tested for the development of antibodies to infliximab (anti-chimeric antibodies = HACA). In the ATTRACT trial, the overall incidence of HACA was 8.5%. Although there is a small trend towards a higher incidence of infusion reactions in HACA-positive patients, there is no indication to add methotrexate to infliximab to prevent infusion reactions.

Infusion/injection site reactions

The most frequent adverse event with etanercept are local injection site reactions which are generally not a serious problem.

Infusion reactions due to infliximab were defined as any reaction during or one hour after the end of the infusion. During the studies with infliximab, infusion reactions occurred in 20% of all patients treated and in approximately 5% of all infusions given. The most common symptoms in this regard were headache (3.8%) dizziness (2.8%) and nausea (3.1%). Serious infusion reactions were rare (0.9%). Discontinuation of treatment due to infusion reactions occurred in 2.6% of the patients.

Delayed adverse reactions 3 – 12 days after the infusion were reported in one study with Crohn's disease patients. Overall delayed type of hypersensitivity reactions were infrequent. These patients received an older liquid formulation of inflixmab which has been replaced by a hydrophylised product.

It is not clear whether immunosuppressants such as methotrexate or azathio-

prin should or can be succesfully added to infliximab to prevent antibody formation and allergic side effects. Data from trials with infliximab in patients suffering from AS, SpA or psorisias showed no increase side effect rate compared to the RA trials in which the co-treatment with MTX was mandatory.

Discussion

Overall the risk benefit analysis of both products is in favour of using the drugs in the approved indications. Both the European and the US agencies (EMIA/FDA) have supported this statement. However, the reactivation of tuberculosis by anti-TNF treatment is certainly a great concern. If the differing incidences are real drug effects and not a class effect, or if they are rather due to different marketing strategies remains unclear. There is no doubt that at least the treatment with infliximab increases risk of reactivation of Tbc. Patients treated with etanercept have also developed tuberculosis. The near future will tell if the intense information about this risk and the preventive strategies such as initial chest x-rays, PPD testing and prophylactic treatment with isoniazide, are able to reduce the incidence of tuberculosis in the patients on anti-TNF therapy.

As published in large recent trials on patients with RA or Crohn's disease, other severe infections were not to significantly increased compared to placebo. However, the investigator reports about severe infections after initiation of TNF-blockade keeps us aware of a certain risk.

The lymphoma rate is also still in the expected range but only the long-term cohort registries will be able to answer the question if the treatments with infliximab or etanercept increase the risk. The developement of ANAs, lupus like syndroms, infusion reactions, allergic reactions, neurologic disorders has been described but they seem either to be rare and can be easily treated.

The data from cohorts from Wolfe and Rau showed that treatment with MTX not only reduces disease activity but also positively influences the mortality of RA patients (36, 37). The biologicals have to prove in the next years that they can reach not only long-lasting symptomatic improvement and prevention of radiographic progression but finally also a reduction of mortality of the treated patients.

References

1. MORELAND LW, COHEN SB, BAUMGARTNER SW *et al.*: Long-term safety and efficacy of etanercept in patients with rheumatoid arthritis. *J Rheumatol* 2001; 28:1238-44.
2. KAVANAUGH A,KEENAN GF, DEWOODY K *et al.*: Long-term follow-up of patients treated with remicade (Infliximab) in clinical trials. *Arthritis Rheum* 2001; 46: S81.
3. KEANE J, GERSHON S, WISE RP *et al.*: Tuberculosis associated with infliximab, a tumor necrosis factor alpha- neutralizing agent. *N Engl J Med* 2001; 345: 1098-104.
4. KEANE J, GERSHON S, BRAUN MM: Tuberculosis associated with infliximab, a tumor necrosis factor alpha- neutralizing agent (letter). *N Engl J Med* 2002; 346: 625-6.
5. MYERS A, CLARK J, FOSTER H: Tuberculosis and treatment with infliximab. *N Engl J Med* 2002; 346: 623-6.
6. SCALLON B, CAI A,SOLOWSKI N *et al.*: Binding and functional comparisons of two types of tumor necrosis factor antagonists. *J Pharmacol Exp Ther* 2002; 301: 418-26.
7. BARONE D, KRANTZ C, LAMBERT D, MAGGIORA K, MOHLER K: Comparative analysis of the ability of etanercept and infliximab to lyse TNF-expressing cells in a complement dependent fashion. *Arthritis Rheum* 1999; 42: S90.
8. BRAUN J, BRANDT J, LISTING J *et al.*: Treatment of active ankylosing spondylitis with infliximab: A randomised controlled multicentre trial. *Lancet* 2002; 359: 1187-93.
9. VAN DEN BOSCH F, KRUITHOF E, BAETEN D *et al.*: Randomized double-blind comparison of chimeric monoclonal antibody to tumor necrosis factor alpha (infliximab) versus placebo in active spondylarthropathy. *Arthritis Rheum* 2002; 46: 755-65.
10. LIM WS, POWELL RJ, JOHNSTON ID: Tuberculosis and treatment with infliximab. *N Engl J Med* 2002; 346: 623-6.
11. RIMINTON S, PEARCE N, ANTONY B: Tuberculosis and treatment with infliximab. *N Engl J Med* 2002; 346: 623-6.
12. BEAN AG, ROACH DR, BRISCOE H *et al.*: Structural deficiencies in granuloma formation in TNF gene-targeted mice underlie the heightened susceptibility to aerosol *Mycobacterium tuberculosis* infection, which is not compensated for by lymphotoxin. *J Immunol* 1999; 162: 3504-11.
13. STENGER S, MAZZACCARO RJ, UYEMURA K *et al.*: Differential effects of cytolytic T cell subsets on intracellular infection. *Science* 1997; 276: 1684-7.
14. ENGELE M, STOSSEL E, CASTIGLIONE K *et al.*: Induction of TNF in human alveolar macrophages as a potential evasion mechanism of virulent *Mycobacterium tuberculosis*. *J Immunol* 2002; 168: 1328-37.
15. WESTENDORP RG, LANGERMANS JA, HUIZINGATW *et al.*: Genetic influence on cytokine production and fatal meningococcal disease. *Lancet* 1997; 349: 170-3.
16. RITZ MA, JOST R: Severe pneumococcal pneumonia following treatment with infliximab for Crohn's disease. *Inflamm Bowel Dis* 2001; 7: 327.
17. SMITH D, LETENDRE S: Viral pneumonia as a serious complication of etanercept therapy. *Ann Intern Med* 2002; 136:174.
18. MAROTTE H,CHARRIN JE,MIOSSEC P: Infliximab-induced aseptic meningitis. *Lancet* 2001; 358: 1784.
19. BAGHAI M, OSMON DR, WOLK DM, WOLD LE, HAIDUKEWYCH GJ, MATTESON EL: Fatal sepsis in a patient with rheumatoid arthritis treated with etanercept. *Mayo Clin Proc* 2001; 76: 653-6.
20. ZHANG Z, CORREA H, BEGUE RE: Tuberculosis and treatment with infliximab. *N Engl J Med* 2002; 346: 623-6.
21. WARRIS A, BJORNEKLETT A, GAUSTAD P: Invasive pulmonary aspergillosis associated with infliximab therapy. *N Engl J Med* 2001; 344: 1099-100.
22. SHERGY WJ, ISERN RA, COOLEY DA *et al.*: Open label study to assess infliximab safety and timing of onset of clinical benefit among patients with rheumatoid arthritis. *J Rheumatol* 2002; 29: 667-77.
23. ANTONI C,DECHANT C,HAENTZSCHEL H *et al.*: Safety and efficacy of infliximab in 263 patients with active rheumatoid arthritis despite methotrexate therapy-a German open label trial. *Arthritis Rheum* 2001; 46: S84.
24. PHILLIPS K, HUSNI ME, KARLSON EW, COBLYN JS: Experience with etanercept in an academic medical center: Are infection rates increased? *Arthritis Rheum* 2002; 47: 17-21.
25. SINGH G, RAMEY DR, RAUSCH PL, SCHETLER JD: Serious infections in rheumatoid arthritis: Relationship to immunosuppressive use. *Arthritis Rheum* 1999; 42: S242.
26. DORAN MF, CROWSON CS, O'FALLON WM, GABRIEL SE: Infections in rheumatoid arthritis (RA). *Arthritis Rheum* 2000; 43: S167.
27. DE ROSA FG, BONORA S, DI PERRI G: Tuberculosis and treatment with infliximab. *N Engl J Med* 2002; 346: 623-6.
28. SMITH KJ, SKELTON HG: Rapid onset of cutaneous squamous cell carcinoma in patients with rheumatoid arthritis after starting tumor necrosis factor alpha receptor IgG1-Fc fusion complex therapy. *J Am Acad Dermatol* 2001; 45: 953-6.
29. MOHAN N, EDWARDS ET, CUPPS TR *et al.*: Demyelination occurring during anti-tumor necrosis factor alpha therapy for inflammatory arthritides. *Arthritis Rheum* 2001; 44: 2862-9.
30. VAN OOSTEN BW, BARKHOF F, TRUYEN L *et al.*: Increased MRI activity and immune activation in two multiple sclerosis patients treated with the monoclonal anti-tumor necrosis factor antibody cA2. *Neurology* 1996; 47: 1531-4.
31. ROBINSON WH, GENOVESE MC, MORELAND LW: Demyelinating and neurologic events reported in association with tumor necrosis factor alpha antagonism: by what mechanisms could tumor necrosis factor al-

pha antagonists improve rheumatoid arthritis but exacerbate multiple sclerosis ? *Arthritis Rheum* 2001; 44: 1977-83.

32. BLOOMBJ: Development of diabetes mellitus during etanercept therapy in a child with systemic-onset juvenile rheumatoid arthritis. *Arthritis Rheum* 2000; 43: 2606-8.
33. GALARIA NA, WERTH VP, SCHUMACHER HR: Leukocytoclastic vasculitis due to etanercept. *J Rheumatol* 2000; 27: 2041-4.
34. MCCAIN ME, QUINET RJ, DAVIS WE: Etanercept and infliximab associated with cutaneous vasculitis. *Rheumatology (Oxford)* 2002; 41: 116-7.
35. SHAKOOR N, MICHALSKA M, HARRIS CA, BLOCK JA: Drug-induced systemic lupus erythematosus associated with etanercept therapy. *Lancet* 2002; 359: 579-80.
36. CHOI HK, HERNAN MA,SEEGER JD, ROBINS JM, WOLFE F: Methotrexate and mortality in patients with rheumatoid arthritis:A prospective study. *Lancet* 2002; 359: 1173-7.
37. KRAUSE D, SCHLEUSSER B, HERBORN G, RAU R: Response to methotrexate treatment is associated with reduced mortality in patients with severe rheumatoid arthritis. *Arth - ritis Rheum* 2000; 43: 14-21.