**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 regimens 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 Stockholm. 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.

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.

Infections
Tuberculosis
With both biologics 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 infliximab 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

<table>
<thead>
<tr>
<th>Table I. Opportunistic infections associated with TNF inhibition.</th>
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<tr>
<td><strong>Patients exposed</strong></td>
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<tr>
<td><strong>Tuberculosis</strong></td>
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<tr>
<td><strong>Atypical mycobacterium</strong></td>
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<tr>
<td><strong>Histoplasmosis</strong></td>
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<td><strong>Listeriosis</strong></td>
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<td><strong>Candidiasis</strong></td>
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<td><strong>Aspergillosis</strong></td>
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<td><strong>Pneumocystis carinii</strong></td>
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**Table II. Adverse events of TNF inhibition (FDA August 17, 2001).**

**AE reports** | **Infliximab Deaths** | **Total % of total** | **Etnancercept Deaths** | **Total % of total**
<table>
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<tbody>
<tr>
<td>All reports</td>
<td>201</td>
<td>2,300</td>
<td>100</td>
<td>290</td>
</tr>
<tr>
<td>Demyelination</td>
<td>1</td>
<td>1</td>
<td>0.04</td>
<td>0</td>
</tr>
<tr>
<td>Aplastic anemia</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>5</td>
</tr>
<tr>
<td>Intestinal perforation</td>
<td>3</td>
<td>4</td>
<td>0.2</td>
<td>0</td>
</tr>
<tr>
<td>Systemic lupus</td>
<td>1</td>
<td>1</td>
<td>0.04</td>
<td>1</td>
</tr>
<tr>
<td>Infections</td>
<td>228</td>
<td>901</td>
<td>39</td>
<td>291</td>
</tr>
<tr>
<td>Lymphoma</td>
<td>2</td>
<td>10</td>
<td>0.4</td>
<td>4</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>10</td>
<td>19</td>
<td>0.8</td>
<td>11</td>
</tr>
</tbody>
</table>

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

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 psosas abscess secondary to Mycobacterium avium intracellularare, 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).
a suspicion or a high risk of exposure
to TNF agents. Preemptive treatment with
INF 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-positi-
ve or who have x-ray evidence of ex-
position to mycobacteria or a recent his-
tory 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
long term 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 carcino-
ma 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 lymp-
phomas and we can only report from
published results. Looking at all studies
with infliximab, 17 (1.2%) of the pa-
tients who had received at least one
dose of infliximab reported a malig-
nancy (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 in-
creased 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 Swed-
en 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 pancytope-
nia on infliximab have been reported
(FDA data base).

Neurologic disorders
In the FDA database, there are 16
reports on demyelinating disease in pa-
tients receiving TNF antagonists, in 15
cases associated with etanercept. This
has been recently reported (29). In ear-
lier days, 2 patients with multiple scler-
rosis developed such lesions while being
with infliximab (30). The reason for the exacerbation or introduc-
tion of the demyelinating disorders
is unclear (31). Furthermore, 6 cases of
optic neuritis, 8 cases of central demye-
lisation 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 pa-
tients should be examined and ques-
tioned about earlier symptoms of de-
myelinating 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 infliximab 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 be-
cause of lack of benefit. The data regard-
ings 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 re-
ports 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 vasculi-
tis 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 de-
defined term) occurred very rarely in
0.4% of all patients studied. Develop-
ment 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 pa-
tients 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 re-
ported in a patient on etanercept (35).
Patients have been tested for the devel-
opment of antibodies to infliximab
(anti-chimeric antibodies = HACA). In
the ATTRACT trial, the overall inci-
dence 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 in-
dication to add methotrexate to inflix-
imab to prevent infusion reactions.

Infusion/injection site reactions
The most frequent adverse event with
etanercept are local injection site reac-
tions 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, in-
fusion 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 reac-
tions were rare (0.9%). Discontinuation
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 hypersensitivi-
ty reactions were infrequent. These pa-
tients received an older liquid formula-
tion of infliximab which has been re-
placed by a hydrophylised product.
It is not clear whether immunosuppres-
sants such as methotrexate or azathio-
prin should or can be successfully added to infliximab to prevent antibody formation and allergic side effects. Data from trials with infliximab in patients suffering from AS, SpA or psoriasis 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 (EMA/ 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 should or can be successfully added to infliximab and prevent antibody formation or etanercept increase the risk. 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 should or can be successfully added to infliximab.

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 development of ANAs, lupus like syndromes, 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**

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