



Review

Anti-TNF therapy and cancer

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ARTICLE INFO

Article history:

Received November 13, 2008

Accepted January 15, 2009

Keywords:

Infliximab
Etanercept
Adalimumab
Cancer
Adverse event

Palabras clave:

Infliximab
Etanercept
Adalimumab
Cáncer
Efecto adverso

ABSTRACT

Tumor necrosis factor (TNF) is implicated in the control of tumoral growth in addition to the systemic inflammatory response. TNF blockage produces a comprehensible reservation in patients with risk factors for cancer. No clear evidence for this came out from pre-clinical or clinical trials. Biosafety registries established in the post-marketing phase have concluded that, in general, cancer cases have not increased over what is expected in a population with RA exposed to the prolonged use of anti-TNF drugs. A meta-analysis of clinical trials which used infliximab and adalimumab for RA treatment showed an increase of up to three times the risk of developing cancer, but this disappeared after correcting for time. Biobadaser shows evidence that support long-term safety. In the long-term, and if the inflammatory disease activity is truly under control, the risk of developing cancer is the same as with any other patient.

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Terapias anti-TNF y neoplasias

RESUMEN

El factor de necrosis tumoral (TNF) está implicado en el control del crecimiento de tumores además de en la respuesta inflamatoria sistémica. El bloqueo del TNF produce un recelo comprensible en pacientes con riesgo de cáncer. Ni en el desarrollo preclínico ni durante los ensayos clínicos de los anti-TNF se detectaron alarmas claras. Los registros de seguridad de biológicos establecidos en el período poscomercialización han concluido que el cáncer en general no está aumentado con respecto de lo esperado en una población de AR con el uso prolongado de anti-TNF. Un meta-análisis de ensayos clínicos de infliximab y adalimumab mostró un aumento de hasta tres veces el riesgo de cáncer, pero al corregir la exposición por el tiempo en los mismos no se encontró. En BIOBADASER tenemos evidencias que apoyan la seguridad a largo plazo. A largo plazo, y si realmente la actividad inflamatoria de la enfermedad subyacente está controlada, el riesgo de desarrollar un cáncer es igual que el de cualquier paciente.

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What is the role of TNF in cancer?

Tumor necrosis factor (TNF), cloned and characterized more than 20 years ago,¹ was originally described as a macrophage-derived endogenous mediator that could induce hemorrhagic necrosis of solid tumors and destroy some tumor cell lines *in vitro*.² Unfortunately, its promising use as an anticancer agent was limited by its toxicity as seen with the first clinical trials with TNF in the treatment of cancer.³ About the same time, it was found that TNF was identical to a mediator responsible for cachexia associated with cancer and sepsis,^{4,5} named cachectin. This research led to the conclusion that

TNF is, in fact, the main lethal mediator of sepsis, as well as the publication of a large number of articles showing that TNF inhibits the toxic effects of bacterial endotoxins, something which is now described as the systemic inflammatory response. Although clinical trials with anti-TNF in sepsis were not very successful, these studies ultimately led to the identification of TNF as a key inflammatory mediator and the development of anti-TNF molecules (soluble receptors and antibodies) for the treatment of Rheumatoid Arthritis (RA) and Crohn's disease.

TNF inhibitors as anticancer drugs

While it may seem contradictory, given the involvement of TNF precisely in cancer control, several studies show that TNF produced

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different cellular responses depending on the level of activity and might be involved in tumor genesis.⁶ Based on this hypothesis, brought to light in parallel with the marketing of anti-TNF for the treatment of inflammatory diseases during the last decade, studies have been conducted to evaluate the effectiveness of anti-TNF drugs on specific cancers without being able to determine either a clear acceleration of tumor stabilization or even a clear effect on cachexia.^{7–11}

What is the evidence of cancer risk with anti-TNF clinical trials?

With TNF blockade there is always a concern about its possible side effects, due in general to the versatility of TNF and in particular, for its initially recognized ability to maintain tumors at bay. However, we detected a clear warning to that effect either during preclinical development or in clinical trials of anti-TNF agents in inflammatory diseases. While biological safety databases that were established in the post-marketing period have still not detected a clear signal, in 2006 a group from the Mayo Clinic published a controversial meta-analysis of clinical trials of infliximab and adalimumab in which the risk of cancer after being exposed to these drugs was increased three times compared to placebo groups.¹² Besides not including etanercept for no clear reason, one of the biggest problems in its interpretation, otherwise impeccable, was that this meta-analysis included the open phases of studies, in which patients passed onto active therapy, and the time of study was then higher in those exposed than in those unexposed, with a greater probability to develop cancer. In fact, a subsequent meta-analysis corrected the exposure time in the same clinical trials, plus in another with etanercept and moreover did not find the great association seen by Bongartz.¹³ There is also a factor in the meta-analysis of the Mayo Clinic that should be underlined and it is the clear association with higher doses of anti-TNF.

What is the evidence after marketing?

Although the meta-analysis by Bongartz was based on clinical trials, it was published in the postmarketing period, and had other sources of information seemingly contradicting the risk of cancer of anti-TNF therapy. On the one hand, the FDA reports (MedWatch) showed up to 26 cases of lymphoma that appeared soon after initiation of anti-TNF, with two cases in which the lymphoma remitted spontaneously after cessation of anti-TNF therapy.¹⁴ However, as noted in these reports, the risk of lymphoma in RA is high and only one conclusion could be reached after poring over information from cohorts of patients exposed versus those unexposed. This information is being provided by biological drug use databases. In particular, the Swedish register concludes that cancer risk is not generally increased over what is to be expected in a population of RA with longer use of anti-TNF drugs.¹⁵ Although initially there were doubts on the Swedish register, the best prepared to perform this analysis given the excellence of their national registries of cancer, particularly of whether lymphoma could be increased given wide confidence interval of risk (relative risk 4.9; 95% confidence interval, 0.9 to 26.2),¹⁵ a subsequent analysis adjusted for gender, age and duration of illness does not show a significant increase, except that the type of lymphoma is different from that expected in RA.¹⁶ Wolfe, in the U.S., analyzed the rates of lymphoma in the *National Data Bank* and in the database of epidemiological data of SEER in 2004¹⁷ and later in 2007,¹⁸ reaching the same conclusion, one cannot say that the risk of lymphoma in RA is different in patients receiving anti-TNF, receiving methotrexate or even not treated and if you look at the slightly increased risk, this may be due to anti-TNF used in patients with sustained high levels of inflammation throughout time and therefore most likely to develop lymphoma.¹⁹ Wolfe results are confirmed in other U.S. databases.²⁰

In BIOBADASER we have even more evidence for it. First, the overall cancer risk does not increase in exposed vs non exposed to anti-TNF RA patients in the long run.²¹ Second, the rate of cancer in patients with anti-TNF varies with exposure time, being higher in the first 2–4 months for lung cancer and breast cancer and up to six months for lymphoma and clearly decreases over time, probably as result of control of inflammation.²² Thirdly, there seems to be a trend, but must yet be demonstrated, that the risk for skin cancer, melanoma or otherwise, may be specifically increased, without a seasonal pattern as seen in the others.²² Finally, cancer mortality is not increased with respect to what is expected, probably reflecting the low rate, not only of cancer, but of the close monitoring of patients with these treatments.²³

As an argument explaining the discrepancy between the lack of long-term association with cancer vs short-term increase, in reference to the meta-analysis of clinical trials, we must remember that cancer can present, as associated symptoms, joint manifestations that can be confused with a rheumatic disease²⁴ as well as an increase in acute phase reactants that may be interpreted as an increase in the activity of an underlying inflammatory disease.²⁵ This can cause the clinician to misinterpret the signs of underlying cancer as a serious inflammatory disease that should be treated with anti-TNF drugs.

What cancers are the most frequently reported?

The type of cancer that is observed in association with anti-TNF therapy may also give us clues to their relationship or lack thereof with the drug. So far we have seen that the records indicate no significant differences in RA patients not exposed to anti-TNF drugs, but we have not spoken of patterns of presentation. Apart from what has been said for lymphoma, records have identified a possible increase in skin cancers and associated with tobacco use and a decrease in breast and colorectal cancer.²⁶ Among the reported cases there is a lot of lymphoma and those associated (hepatosplenic T cells,^{27–29} B cells,^{30,31} monoclonal gammopathy of uncertain origin³²), lung cancer and skin cancer.^{33,34} Lymphoma can be explained by the relationship of this cancer with sustained inflammation, which could be a form of cancer actually not increased by blocking anti-TNF, but the patients who are given anti-TNF are more likely to develop it since before treatment is begun. The tobacco-related cancers may also have increased not by blocking TNF, but by the use of tobacco itself, and this may occur because tobacco is associated with increased severity of illness³⁵ and, therefore more likely to be treated with anti-TNF drugs. As to why there has been an increase in the risk for skin cancers, this is one of the unknowns that remain to be solved in the relationship between anti-TNF therapy and cancer.

Do anti-TNF drugs increase the risk of cancer in other diseases other than RA?

Another way to determine whether there is an increased cancer incidence related to treatment and unrelated to the underlying disease is to know and compare what happens with other diseases in which anti-TNF therapy is used. While there have been reports of lymphoma in ankylosing spondylitis,³⁶ there is still no evidence that the risk is increased in this disease. What seems likely is that the baseline risk is equal to that of the general population without spondylitis.³⁷ In Crohn's disease, the baseline risk of colon cancer is increased, and also, marginally, lymphoma, probably related to local maintained inflammation.^{38,39} As might be happening with RA, the effective control of inflammation in principle and with or without anti-TNF therapies, somewhat reduces the cancer rate,⁴⁰ but cases of lymphoma have been published during the first months of treatment with anti-TNF.⁴¹ In psoriasis, there are published cases of cancer

with anti-TNF therapy,⁴² but the risk has not studied compared to unexposed patients. In other chronic inflammatory diseases there also appears to be an increased risk of cancer at baseline, as well as in sarcoidosis⁴³ or Wegener's disease.⁴⁴ Unfortunately, the number of cases is still insufficient to say anything about the risk related anti-TNF therapy, although the analysis of a trial of etanercept in Wegeners' suggests an increased risk after adding etanercept to cyclophosphamide.⁴⁵

Is it possible to safely administer these drugs in patients who have a history of cancer?

This question is perhaps the most worrisome to the clinician and, unfortunately, the answer is not easy. Among other things, because anti-TNF therapies are rarely prescribed to patients with a previous history of malignancy, and in clinical trials this was a exclusion criteria and national guidelines also exclude these cases,^{46,47} all based on theoretical safety reasons, but there really is no currently published evidence regarding the safety of anti-TNF drugs in patients with prior malignancy. The experience of the UK biological drug database (BRBSR) is the only one available and limited to what has been reported at conferences.⁴⁸ This database Identified patients both exposed and unexposed to anti-TNF with a history of neoplasia, which were identified by crosschecking records with the National Bureau of Statistics. In total, 177 (1.6%) patients with anti-TNF and 118 (3.6%) with DMARDs had a prior history of cancer, of whom 11 (6%) and 10 (8%) patients developed local recurrences or metastasis during 2 years of follow-up, with no difference in risk after adjustment for age and gender (incidence rate ratio 0.53, 95% CI 0.22 to 1.26).

Concluding remarks

Similarly, evidence of a single clinical trial is not sufficient to support the efficacy of a drug. To establish the safety of a drug it is necessary to have information from many sources. Physiological tests are contradictory: sometimes they show TNF decreases and in others it increases tumor size. Clinical trials of anti-TNF for cancer treatment are no better. Trials of anti-TNF in patients with inflammatory diseases are more homogeneous than one might think, showing there is a clear risk of increased long-term cancer, but in the short term there may be specific to some cancers negatively affected by TNF blocking. What is this initial risk? Well, either occult cancers are being unmasked, because of enhanced vigilance over patients, or because it really was latent cancer and TNF blockade accelerates its growth, or signs of cancer are being confused (high sedimentation rate, leukocytosis, asthenia) with increased inflammatory disease activity. In any case, we are talking about a problem with a low incidence, one cancer case per 1,000 exposed per year in the worst cases, a rate not very different from the risk any normal person has, so the search for markers of cancer or full-body scans should not be recommended.

The only two concerns about cancer in patients treated with anti-TNF are skin cancer, because the information is less clear and it is possible that some of the events that are detected frequently in the skin in patients exposed to anti-TNF could be precursors to skin cancer, and patients with previous cancers, where it is necessary to study the risk for cancer and the time since referral. Both areas clearly need further investigation.

Disclosures

The author has no disclosures to make.

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