Review

Anti-TNF therapy and cancer

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A R T I C L E   I N F O

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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 dissapeared 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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What is the role of TNF in cancer?

Tumor necrosis factor (TNF), cloned and characterized more than 20 years ago, 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. 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. About the same time, it was found that TNF was identical to a mediator responsible for cachexia associated with cancer and sepsis, 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...
different cellular responses depending on the level of activity and might be involved in tumor genesis. 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. 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. 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. 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. 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.

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. 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. There is also a factor in the meta-analysis of the MayoClinic 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. 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. 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. Although initially there was doubts on the Swedish register, the best prepared to perform this analysis given the excellence of their national registries of cancer, particularly of wether lymphoma could be increased given wide confidence interval of risk (relative risk 4.9; 95% confidence interval, 0.9 to 26.2), 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. 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 2004 and later in 2007, reaching the same conclusion, one cannot say that the risk of lymphoma in RA is different from that expected in RA. Wolfe results are confirmed in other U.S. databases.

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, 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. In Crohn’s disease, the baseline risk of colon cancer is increased, and also, marginally, lymphoma, probably related to local maintained inflammation. 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, but cases of lymphoma have been published during the first months of treatment with anti-TNF. In psoriasis, there are published cases of cancer.
with anti-TNF therapy, 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 sarcoidosis or Wegener’s disease. Unfortunately, the number of cases is still insufficient to say anything about the risk related to anti-TNF therapy, although the analysis of a trial of etanercept in sarcoidosis is still insufficient to say anything about the risk related to anti-TNF therapy. 


