

Biological Therapy and Risk of Malignancies: A Literature Review

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ABSTRACT

Data from literature show that the overall risk of cancer does not as a result from treatment with these drugs. The only cancer for which various authors have reported an increased risk, in some cases, are skin cancers, different from melanoma and melanoma. Recent results of large observational studies and meta-analyzes indicate the absence of an increased risk of lymphoma related to therapy with anti-TNF- α . It has been reported, by some authors, that there is a possible increased risk of lung cancer, especially in patients with chronic obstructive pulmonary disease. There is limited information in literature about the effects of biologics in patients with a history of cancer. Most of the guidelines indicate that treatment with biologics can be considered with caution and only in patients free of cancer since at least 5 years. Some studies report a lower oncological risk with etanercept compared to monoclonal antibodies, especially in the case of lymphoma. However, this data has not been confirmed in other studies, and has been associated with a limited period of time after starting therapy. Information about the latest biological therapies is still poor. Therefore, there is not sufficient evidence for a preferential use of certain drugs rather than others.

Keywords: Anti-TNF- α ; Skin Cancer; Lymphoma; Rheumatoid Arthritis

1. Introduction

In chronic inflammatory diseases that require long-term treatment with immunosuppressive therapies, there has always been concern that such treatments could increase the risk of developing cancer.

Biological agents acting through complex mechanisms of immunomodulation and some cytokines inhibited by these treatments (such as TNF- α) exert important biological effects, although not fully defined, which can counteract the processes of carcinogenesis and tumor progression.

Even if overall data so far issued on cancer risk in patients with biological agents are encouraging, it should be noted that the assessment of such risk is complicated by a number of factors including the following: 1) Rheumatoid Arthritis (RA) gives rise to a differential risk for various types of tumors (increased or decreased, in some cases) compared to the general population; 2) development period of a neoplasm is often long and it can exceed the period of observation of many studies; 3) tumors are relatively rare adverse events and the analysis of their impact requires data of very large populations, in order to achieve a sufficient statistical power; 4) in clinical trials

enrollment of patients with a history of cancer or high risk cancer is usually excluded; 5) in clinical practice there may be a bias in the selection of patients for therapy with biological agents. These issues must be considered in interpreting data provided by clinical and observational trials. So even if there are no specific contraindications for the use of biological drugs in relation to the risk of cancer, guidelines and consensus statements agree to maintain a high level of vigilance for the possible risk of developing cancer in patients receiving biologic therapies.

2. RA and Malignancies

Several epidemiological studies show that patients with RA, if compared with the general population, have an increased risk to develop certain type of malignancies, especially lymphoma and cancers of the hematopoietic system, lung and skin cancer other than melanoma, while the risk for colorectal, breast and endometrial cancers (lower risk by use of non-steroidal anti inflammatory drugs or cyclo-oxygenase-2) is reduced [1-7]. The relationship between RA and lymphoma has been investigated with particular attention. A meta-analysis of stud-

ies investigating the risk of overall and four specific malignancies in patients with rheumatoid arthritis compared with the general population showed a doubled risk of lymphoma with a standardized incidence ratio (SIR) of 2.08 (IC 95% 1.80 - 2.39) [8]. The risk was highest for Hodgkin's lymphoma (SIR 3.29 [95% CI 2.56 - 4.22]) compared to a non-Hodgkin's lymphoma (SIR 1.95 [95% CI 1.70 - 2.24]). The risk of developing lung cancer was also increased, SIR 1.63 (95% CI 1.43 - 1.87) and the risk of developing colorectal or breast cancer was slightly reduced in patients with RA, respectively SIR 0.77 (95% CI 0.65 - 0.90) and SIR 0.84 (95% CI 0.79 - 0.90) [8].

3. Anti-TNF- α and Risk of Malignancies

The relationship between anti-TNF- α and cancers is not fully understood and it is likely that this cytokine plays different roles in different stages of tumors and neoplastic processes. Therefore the inhibition of TNF- α may result in various effects on the oncological risk depending on the type of tumor and conditions of the patient. As far as the overall risk of developing cancer (regardless of the type of cancer) is concerned, almost all studies indicate that the risk is not increased in patients with RA treated with anti-TNF- α compared to the general population or control groups that are not exposed to such therapy. An overall increase in the incidence of cancers related to biologics in large observational studies has not been detected, including those carried out on the national Registers (NDB for Rheumatic Diseases for the US, Swedish Biologics Register for Sweden, BSRBR for the United Kingdom, BIOBADASER for Spain, LOHREN for Italy and RABBIT for Germany) and the meta-analyses of clinical trials [4,9-17]. Just in another meta-analysis concerning a clinical trial of infliximab and adalimumab it was found that there was a significant increase in the overall risk of developing cancer in patients treated with biological agents compared to those who were not (OR 3.3 [95% CI 1.2 to 9.1]) [18]. The increased risk was most evident in patients treated with higher doses. It is not clear what the main reason for this discrepancy of data in relation to other evidence of the literature is due to; some authors attribute it to methodological problems (such as the possible lack of identification of cases for the highest percentage of drop-outs in groups of comparison) [19]. A meta-analysis of etanercept, made by the same group of researchers using methods similar to the previous, showed a smaller increase in the risk of cancer with etanercept, but this was not significant (HR 1.84 [95% CI 0.79 to 4.28]) [20]. A recent meta-analysis of data presented in studies of registry and prospective observational studies confirm that the anti-TNF- α does not appear to increase the overall risk of developing cancer, with an estimated cumulative risk calculated at 0.95 (95% CI 0.85 - 1.05) [21]. An observational study of Askling

and coll. conducted on a Swedish database has analyzed the risk of cancer development in time after initiation of anti-TNF- α therapy and the duration of such therapy without encountering an increase of the oncological risk linked to these two variables [9]. Another study has assessed whether biological agents could influence the prognosis of tumors which have arisen in the course or at the end of therapy by examining any changes in clinical presentation and the outcome of these malignancies [22]. No significant differences were found in the clinical presentation of cancers or in the survival among patients exposed to anti-TNF- α compared with those not treated with the same therapies.

3.1. Lymphatic and Hematopoietic Tumors

We cannot define whether anti-TNF- α may increase the risk of lymphoma, also due to the difficulty in correctly estimating the risk in patients with RA who already have an increased risk of lymphoma compared to the general population. However, the main observational studies have not shown an increased incidence of malignant lymphoma or cancers of the hematopoietic system in patients treated with anti-TNF- α compared with cohorts of patients with RA or other patients treated with traditional drugs (DMARDs) [2,4,15,23,24]. Studies conducted on the records of the US NDB for Rheumatic Diseases and on the Swedish Biologics Register do not show an increased risk. In the study conducted by the US on 19,591 patients with RA (55% were treated with anti-TNF- α) between 1998 and 2005, the odds ratio (OR) for lymphoma in patients treated vs those not treated with biological agents corresponds to 1.0 (95% CI 0.6 to 1.8) [23]. Askling and coll. have reported 500 cases of tumors of the hematopoietic system in three Swedish cohorts of patients with RA which were analyzed: a cohort study of prevalence, a cohort of incidence and a cohort treated with anti-TNF- α (n = 4160, 1999-2003) [2]. Patients affected by RA, compared to the general population, showed an increased risk in the development of lymphoma and leukemia. The relative risk (RR) of lymphoma in patients receiving biological therapy compared with the cohort prevalence was 1.1 (95% CI 0.6 - 2.1). In a subsequent study by the same group which extended the follow-up to 2006 by analyzing data on 67,743 patients with RA, 26 cases of malignant lymphoma among 6604 patients treated with anti-TNF- α were observed vs 336 cases compared to the population not treated with these drugs, resulting in an RR of 1.35 (95% CI 0.82 - 2.11) [24]. The observational study of Geborek and coll. detected an increased risk of lymphoma related to anti-TNF- α therapy (RR 4.9 [IC 95% 0.9 - 26.2]), but such study was conducted on a limited number of cases and there is the possibility of methodological issues that may have influenced these results [14]. In the prospective

study on the RATIO register it is not possible to quantify the potential risk of lymphoma associated with the use of anti-TNF- α (this registry reports all cases of lymphoma occurred in French population in patients receiving these therapies, regardless of their disease, between 2004 and 2006, without a control cohort consisting of patients not treated with anti-TNF- α) [25]. Among 38 cases of lymphoma reported, 27 were patients with RA, with a SIR of treated patients compared with the general population of 2.3 (95% CI 1.6 - 3.3), which reflects an increased risk of lymphoma in RA related disease activity. Therefore, data of major studies give evidence of the absence of an increased risk of lymphoma or cancer of the hematopoietic system related to anti-TNF- α therapy.

3.2. Solid Tumors

Treatment with anti-TNF- α does not imply an increase in the overall risk of developing solid tumors [3,4,15]. However, several observational studies and meta-analyses show an increased incidence of skin cancers other than melanoma (NMSC) and some cases of melanoma in patients treated with biological drugs compared to control groups [3,4,16,21,26]. In particular, the study of Wolfe and coll. on the US NDB for Rheumatic Diseases has found an OR of 1.5 (95% CI 1.2 - 1.8) for NMSC and an OR of 2.3 (95% CI 0.9 - 5.4) for melanoma in patients treated with anti-TNF- α therapy vs those not exposed to such therapy [4]. The study conducted on the Swedish registers for NMSC shows a SIR of 3.6 (95% CI 1.50 - 6.5) in cohorts treated with biologics compared to 1.66 (95% CI 1.50 - 1.84) in the prevalence cohort [3]. A recent meta-analysis of clinical trials of infliximab, adalimumab and etanercept shows an increased risk of developing NMSC related to therapy with anti-TNF- α [26,16]. However not all studies have found an increased risk for skin cancer in patients exposed to anti-TNF- α , especially if they have chronic bronchitis [11,27].

4. Are There Different Effects on the Risk Cancer among Anti-TNF- α ?

Some data indicate different effects on the risk of cancer among infliximab, adalimumab and etanercept, as only a few studies have individually analyzed these three drugs. In the study of the French RATIO register which evaluated the risk of lymphoma in patients treated with anti-TNF- α vs the general population, the risk of lymphoma with etanercept was lower with a SIR of 0.9 (CI 95% 0.4 - 1.8), compared with the risk of lymphoma with adalimumab and infliximab [25]. Likely TNF- α inhibitors (similarly to methotrexate) exert a double effect on the risk of lymphoma: a beneficial effect which reduces the disease's activity and a detrimental one which depresses the immunosurveillance by the lymphocytes T; in the case

of etanercept the prevailing effect would appear favorable. One hypothesis to explain the lower incidence of lymphoma observed with etanercept (a soluble fusion protein) compared to monoclonal antibodies, is probably due to the higher affinity and stability of binding to the TNF- α membrane with respect to infliximab and adalimumab, which would lead to stronger effects on the function of immune surveillance by T suppressor lymphocyte compared to etanercept [35]. Also in the meta-analysis by Bongartz and coll., the overall cancer risk found in studies of adalimumab and infliximab was superior to that observed in studies of etanercept [18,20]. In a study of Swedish registers, differences were observed between the three anti-TNF- α on the overall risk of developing cancer but only during the first year after the start of biological therapy [9]. It is not clear why differences between drugs are found only at the beginning of treatment; this could be determined by actual differences in the biological activity but also by other external factors that are difficult to control in an observational study. There are no significant differences identified between anti-TNF- α therapies on the risk of malignancy in the various locations in the studies on the US NDB for Rheumatic Diseases [4,23]. Therefore the question whether etanercept, infliximab, adalimumab are more or less associated with clinically significant differences in the risk of developing cancer remains controversial.

5. Effects of Treatment with Anti-TNF- α Therapy in Patients with a History of Cancer

There is limited information concerning the risk of cancer related to therapy with biologic drugs in RA patients previously affected by cancer as these patients are generally excluded from clinical trials. Moreover, guidelines often advise particular caution in the use of these therapies in patients with a history of malignancy. An observational study evaluated the incidence of tumors in 239 patients enrolled in the British register BSRBR in which a malignancy had been reported (except carcinoma in situ and NMSC) [10]; 177 patients had received therapy with anti-TNF- α and 117 were treated with DMARDs. During a follow-up of 3 years the mean incidence of cancer was 25.3 events/1000 patient-years in the cohort treated with biologics vs 38.3/1000 patient-years in the comparison group, with an incidence rate ratio (IRR) of 0.58 (95% CI 0.23 - 1.43) for patients treated with anti-TNF- α vs DMARDs. A sensitivity analysis made with the exclusion of time from the first tumor did not significantly alter this data; such data also indicate that patients with a previous diagnosis of melanoma may have a higher risk of developing a new cancer. According to the results of this study the risk of malignancy in

patients with a tumor does not seem to be increased by previous therapy with biological drugs. However, it is important to consider a possible selection bias in the choice of treatment to be applied to patients, which could have influenced results of this investigation. Even in the study of the German register RABBIT, the risk of recurrence of earlier tumors in 122 patients, of whom 58 received anti-TNF- α , 9 anakinra and 55 DMARDs was analyzed [13]; fifteen occurrences of cancer were reported in 14 patients and the IRR between anti-TNF- α and DMARDs was 1.4 ($p = ns$). Also in this study the limited series does not allow definitive conclusions about the risk of cancer linked to biological therapies in patients with a previous malignancy.

6. Cancer Risk with Other Biologics Drugs

Data concerning biological drugs with a different mechanism of action than that of anti-TNF- α (as well as new generation anti-TNF- α) for an assessment of the risk of cancer are still limited. The information derives mainly from clinical trials and there are still no data about safety from large observational studies. There was no reported increased risk of solid tumors or lymphoma with rituximab [28]. As far as the risk of developing lymphoma in patients with rheumatoid arthritis is concerned, the studies of Slimani [29] and van Vollenhoven's [30] would suggest a protective role of rituximab. In the clinical development program of abatacept (which includes 4134 patients treated with this drug in clinical trials and 41,529 in observational studies), 51 tumors were reported and the overall incidence of cancer (excluding NMSC) and of four types of tumor evaluated (breast, colorectal, lung and lymphoma) in patients treated with abatacept was generally similar to that found in populations affected by RA [31]. Similarly, there were no problems linked to the possibility of an increased risk of tumors in studies on tocilizumab. An interim post marketing surveillance analysis of 3881 patients treated with tocilizumab showed an incidence rate of malignancy of 18 events year/100 patients [32].

7. Discussion

It is difficult to define whether anti-TNF- α may increase the risk of lymphoma in RA because patients with RA already have an increased risk of lymphoma compared to the general population. However, the main observational studies have not shown an increased incidence of malignant lymphoma probably because the main risk factor for lymphoma seems to lie in the severity of the disease, as demonstrated in a case-control study conducted on the Swedish Inpatient Register during 1964-1995 that showed a direct correlation between disease activity and the risk of lymphoma, with an increase of the latter in the sub-

group of patients with the highest activity of disease [33]. Therefore chronic inflammation plays a key role in the risk of lymphoma. In order to explain this effect it was assumed that in RA persistent immune stimulation can lead to a clonal selection in B lymphocytes inducing malignant transformation in CD5+ cells and reduce the number and functional activity of T suppressor lymphocytes (like those directed against the oncogenic virus, Epstein-Barr) [8]. Another study of the Swedish group investigated the possibility of a common genetic susceptibility for the development of lymphoma and RA, evaluating whether the increased risk of lymphoma was detectable even before diagnosis of RA [34]. It was observed that the risk increased only in the ten years following the diagnosis of RA, confirming the importance of the disease as a determining factor for the increased risk of lymphoma. It was not always possible to assess the actual role of therapy as the risk of cancer related to RA was calculated on populations treated with different therapies. Unlike some immunosuppressive agents, such as azathioprine for which an association with lymphoma has been highlighted, therapy with DMARDs seems not to be associated with an increased risk of lymphoma, even though cases of EBV-positive lymphoma were reported in patients treated with methotrexate, which regressed after discontinuation of the drug [33-35]. The potential effect of induction of EBV-related lymphomas by methotrexate is probably offset by the beneficial effect of this drug on the reduction of disease activity with a favorable result, as potential effect of induction of anti-TNF- α related lymphomas is offset by efficacy of these drugs on severity of the disease and chronic inflammation [35].

8. Conclusion

Patients starting anti-TNF- α therapy should be informed that there is no conclusive evidence for an increase in risk of developing solid tumors or lymphomas above that which would be expected for RA population, but ongoing vigilance is required. Patients should be investigated for potential malignancy if clinically suspected, and anti-TNF- α treatment should be stopped if malignancy is confirmed. Caution should be exercised in the use of these therapies in patients with previous malignancy. Patients should be advised that the treatment with anti-TNF- α may increase the risk of non-melanoma skin cancer and it is necessary preventative skin care and continuous skin surveillance. There are no significant differences identified between anti-TNF- α therapies on the risk of malignancy.

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