Benefits and risks of biological agents: Lymphomas

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ABSTRACT

Lymphomas are uncommon malignancies of unknown aetiology. Rheumatoid arthritis is a known risk factor for lymphoma, and some studies show that this risk is higher in patients with more severe disease. The causes of the association between RA and lymphoma are not understood. Conventional anti-rheumatic agents may increase the risk for lymphoma, but these associations are relatively weak at most. For the currently available TNF-α antagonists, available data include the possibility of a somewhat higher risk for lymphoma than for patients not treated with such agents, but also point to several sources of bias that could explain a possible association. Current practice recommendations should probably not go further than an awareness of the possibility of lymphoma in any patient with RA exhibiting unexplained systemic symptoms.

Lymphoma

Lymphomas represent a heterogeneous group of malignancies originating from lymphocytoid cells with widely varying clinical manifestations. The annual incidence rate of lymphoma is approximately 20 per 100,000 in the US (1), and in Sweden the lifetime risk of acquiring lymphoma is about 1% (2). The risk of lymphoma increases with age and is somewhat higher for men than for women.

Intense interest has been aroused by the observation that the incidence of lymphoma has increased dramatically over the past several decades, although this increase appears to have levelled off more recently (2). This increase is believed to have resulted in part from improved abilities to diagnose, but also from the increasing use of immunosuppressive medications that may raise the risk of acquiring lymphoma (as discussed below), as well as from other causes. Lymphomas may be divided into Hodgkin's lymphomas (10%), B-cell lymphomas (90%) and T-cell lymphomas (10%), and are subdivided into more than 40 different types and subtypes.

Historically, several different classifications have been proposed and used, although at present the 2001 WHO classification appears to have achieved a fair degree of consensus (3). In clinical practice, non-Hodgkin's lymphomas are divided into low-grade, intermediate-grade, and high-grade to reflect the aggressiveness of the disease as well as indicating the likelihood of being able to treat with conventional cytotoxic agents. Such agents have been far more effective in treating high-grade than low-grade lymphomas, while the relatively new agent rituximab (monoclonal anti-CD20 antibodies) has been singularly effective in treating low-grade B-cell lymphomas (4, 5).

Incidence of lymphoma in RA

A number of studies have suggested that the risk of acquiring lymphoma is increased for individuals who suffer from rheumatoid arthritis (RA) (6-15). In fact, RA remains one of the few clearly identified risk factors for lymphoma. Thus, studies from the 1970's onwards have indicated a 2- to 4-fold increased risk for patients with RA compared to the population as a whole of acquiring lymphoma. Importantly, this increase in relative risk did not increase further during the decades for which cohort data have been studied, despite the obvious increase in the use of DMARDs, including immunosuppressive agents from the 1960's to the current era. In the very large study by Ekström *et al.* (15) an overall relative risk (RR) of 2.0 was noted but there was no clear difference in the RR for the patients diagnosed and treated during earlier times and for those studied later. Thus, the increased risk of lymphoma for patients with RA is well established across geographical and chronological boundaries.

The cause of the association of RA and lymphoma, on the other hand, remains unclear. A number of different possible

explanations have been offered (Fig. 1). First, it has been suggested that genetic factors could contribute both to the risk of acquiring RA and to that of acquiring lymphoma. However, Ekström *et al.* (15) did not find an increased lymphoma risk in first-degree relatives of patients with RA, so that any such effect for genetic factors would have to be small. Similar considerations would apply to the so-called "shared environmental factors" as defined in genetic studies. A second possibility would be that certain environmental factors engender risk for both RA and lymphoma. However, few environmental risk factors for RA have been identified, with the exception of smoking which was shown to be a risk factor for seropositive RA (16). Inconclusive data suggest that smoking may be associated with lymphoma, albeit weakly (17), and it would appear that these two weak associations could not, by themselves, explain the excess lymphoma risk for patients with RA.

A third possibility is that the generalized immunological activation in RA may in itself predispose to the oncogenic events resulting in the development of lymphoma. Both in RA and lymphoma, usage of heavy-chain genes appears to be biased towards the same genes, among them VH3-21 (18-21). It is tempting to speculate that the recurrent or chronic activation by foreign or self-antigens of certain B-cell subsets in the pathogenesis of RA might lead to a higher risk of acquiring the mutations and transformations involved in the pathogenesis of lymphoma.

Sjögren's syndrome is associated with a significantly increased risk for lymphoma (22), and it has been suggested that patients with RA who suffer from (secondary) Sjögren's syndrome likewise have an increased risk (23). However, this was not confirmed in a prospective study of patients with secondary Sjögren's syndrome (24).

Additional evidence to suggest that immunological activation associated with RA itself may lead to a higher risk for lymphoma comes indirectly from the observation that the lymphoma risk increases with disease severity. Thus, in a nested case-control study Baecklund *et al*. (25) demonstrated that patients with moderate RA had an approximately 5-fold increased risk of lymphoma compared to patients with mild RA, while those with severe disease had a more than 20-fold higher risk of lymphoma, irrespective of treatment. Similarly, US data published in abstract form suggested an association between lymphoma and disease severity but not with treatment (26).

However, notwithstanding these last comments, it remains possible that certain treatments given for RA could result in an increased risk for the acquisition of lymphoma. This possibility will be discussed in more detail below.

Influence of treatment

Several medications used in the treatment of RA have been associated with the risk of lympho-reticular malignancies. This is best established for alkylating agents such as cyclophosphamide and chlorambucil, which are sometimes used to treat severe extra-articular complications of RA (i.e., rheumatoid vasculitis). However, the overall use of these agents in RA is minimal and it does not appear that these agents by themselves could explain the excess risk of lymphoma.

Immunosuppressive agents such as azathioprine and cyclosporine A are used widely in the prevention of transplant rejection, and the transplant literature has accurately defined the risks associated with these medications (27). Much of the excess risk in this setting has been for Epstein Barr virus (EBV)-related lymphomas, and it has been demonstrated that both the intensity and the duration of immunosuppressive therapy correspond to the risk of such lymphomas. Importantly, however, the underlying disease and its complications (for instance, graft-versus-host reactions) also have significant predictive power. Thus, it is very hard to define the exact magnitude of risk associated with each agent, as seen separately from the disease under treatment.

In RA, one study suggested that mostly EBV-related lymphomas were seen (28), but in another study this was not confirmed (29). The use of cyclosporine A in RA does not appear to increase the risk of lymphoma (30), but treatment with azathioprine (31, 32) or MTX (33, 34) may be associated with slightly increased risks. It could be argued that these increases in lymphoma risk reflect the fact that the patients receiving these agents have more severe RA (channelling bias, see below).

Some case reports have pointed out the possibility of acquiring EBV-related lymphoma during treatment with methotrexate (MTX), followed by regression of the lymphoma upon discontinuation of the treatment (35).

Biological therapies

TNF-α, originally named thus for its lytic capacity for certain tumor cells, has as yet incompletely defined roles in natural defense mechanisms pertaining to cancer. Both pro- and anti-neoplastic effects for TNF-α have been described and debate continues regarding the role of this cytokine, which may well differ considerably for types of cancer, and the specifics of local molecular concentrations.

In the considerable number of randomized clinical trials reported to date with TNFα-antagonists, no excess of malignancies as a whole has been reported. In contrast, lymphoma has been regarded with particular concern, possibly due in part to the emergence of lymphoma in one of the very first patients treated with infliximab. In 2002, 3 years after the introduction of TNF-α antagonists in clinical practice, Brown *et al*. (36) reviewed the 26 reports of lymphomas that had been reported to the FDA through the year 2000. Although this report relied on spontaneous reporting and had no accurate denominator, and did not prove that the number was increased compared to numbers expected, it did provide a signal of some concern in that the median time elapsed between treatment onset and lymphoma diagnosis was brief, with a median of 6-8 weeks. This observation, when taken to its logical conclusion, would suggest that these patients may have already harboured lymphomatous cells that subsequently became clinically detectable – a situation not unlike the concerns regarding activation of tuberculosis associated with

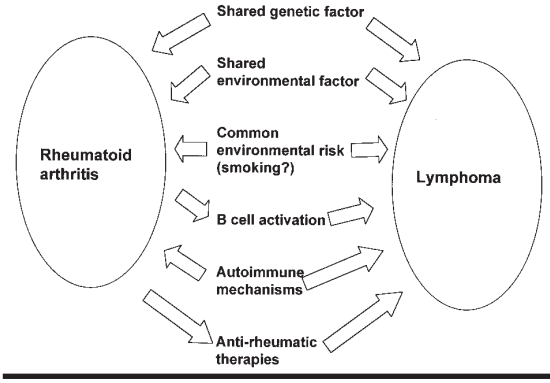

Fig. 1. Possible pathways mediating the epidemiological assocation between RA and lymphoma.

Table I. Relative risks of lymphoma with TNFα antagonists as noted in randomized clinical trials. Adapted from ref. 37. SIR: standardized incidence ratio.

TNF antagonist	No. of lymphoma cases observed	No. of lymphoma cases expected	SIR	95% confidence intervals
Adalimumab	10	1.85	5.42	2.6 – 10.0
Etanercept	6	2.59	2.31	0.85 - 5.03
Infliximab	4	0.63	6.35	1.73 - 16.26

TNF-α antagonists, where the majority of cases appear to reflect a reactivation of latent tuberculosis rather than *de novo* infection. An additional observation in this study, also supporting the idea of "latent" lymphoma becoming clinically manifest, was the inclusion of two patients with pre-existing lymphoma, regarded previously as cured, who experienced rapid and in both cases fatal relapses. More encouraging was the inclusion in the same report of two patients whose lymphomas regressed upon discontinuation of TNF-α antagonist therapy.

A more recent review of lymphoma data with currently available TNF-α antagonists by the FDA (37) focused on the observations from controlled clinical trials, in which a total of 20 lymphomas had been reported with the three agents, infliximab, etanercept and adalimumab. Based on the relevant denominators and exposure times for each agent, standardized incidence ratios were shown to be elevated from 2.3 to 6.4, indicating that the relative risk of lymphoma was increased with each of the agents compared to healthy controls (Table I). On the other hand, inasmuch as these increases were not inconsistent with the relative risks seen in patients with moderate to severe RA (as discussed above), it was felt that much, if not all, of this increase could be explained by the underlying disease. Recently, Wolfe and Michaud published lymphoma data from the National Data Bank for Rheumatic Diseases, based on self-reporting by more than 18,000 patients (38). Consistent with previous data, the overall standardized incidence ratio (SIR) for lymphoma in RA was found to be elevated at 1.9 (95% confidence interval 1.3–2.7). Interestingly, for patients receiving neither MTX nor biologicals, no increase in SIR was seen, whereas the SIR for patients treated only with MTX was similar to that for the patient population as a whole. For patients treated with biologicals, the SIR was even higher at 2.9 (95% confidence interval 1.7-4.9). The authors argue that the increases in the risk for lymphoma with MTX and, even more so with biologicals, most likely reflect channelling bias; that is, the patients with the more severe disease are more likely to receive such therapies, while at the same time they are at higher risk for lymphoma due to disease severity. In this study, the time elapsed between the initiation of TNF-α antagonist therapy and the diagnosis of lymphoma was fairly evenly distributed during the available follow-up periods.

An additional cautionary note needs to be added. We have previously encountered at least one patient in whom TNF-α antagonist therapy was initiated when a significant worsening of the underlying disease (in that case, Crohn's disease) was suspected on clinical grounds. In that patient, brief improvement with the TNF-α blocker was followed by a rapid deterioration and death. At autopsy, it became clear that an intestinal lymphoma was present without any evidence of activity of the autoimmune disease. Thus, when reviewing reports of lymphoma being diagnosed shortly after the initiation of any new therapy, it is prudent to bear in mind the possibility that it was the lymphoma that caused the clinical worsening and hence led to the initiation of that therapy. In other words, the attribution of lymphoma-related symptoms to RA may have led to the initiation of TNF-α blocking therapy, and the subsequent appearance of a lymphoma early during such treatment.

In summary, the available evidence to date shows that the crude risk of lymphoma is increased by a 2- to 7-fold margin for patients with RA who are being treated with TNF-α antagonists compared to individuals without RA, but also suggests a number of sources of bias that could well explain these associations. It is to be noted that the *absolute* risk for lymphoma in patients with RA remains small, whether treated with biologicals or not.

Practice recommendations

Based on the above discussion, it would appear that the risk of lymphoma should have a limited impact on practice decisions in rheumatic diseases. An exception would be the case of a patient who is known to have had a lymphoma, but where the lymphoma is considered to be cured or in long-standing complete remission. Here, a risk of relapse may be present that would tilt the balance against TNF-α antagonist treatment, but data concerning this point are scarce. Some other exceptional situations in which patients are at high *a priori* risk of lymphoma might also be (relative) contraindications. For all other patients, concerns about lymphoma should not unduly influence

treatment decisions. Importantly, however, unexplained systemic symptoms such as fever, night sweats, and weight loss in a patient with RA should be worked up and not simply assumed to be disease-related symptoms until adequate investigations have been performed.

Conclusion

The risk of lymphoma is increased for patients with RA, and the risk is increased even further for those with more severe disease. The cause of this association remains poorly understood, but factors inherent in the RA disease process may well play important roles. An effect of pharmacological treatments on lymphoma risk has been suggested for agents such as azathioprine and MTX, but conclusive evidence has not been presented. An association of TNF-α antagonist therapy with a lymphoma risk has been seen, though its implications have been debated and studied intensely. The risks seen with these agents remain close to the range of what is seen in the overall RA population, and the slight increases in the actual number of cases observed may be explained by channelling and other types of biases.

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