Editorial

Rheumatoid Arthritis, Methotrexate, and Lymphoma: Risk Substitution, or Cat and Mouse with Epstein-Barr Virus?

Several studies document that patients with rheumatoid arthritis (RA) have an increased risk of developing non-Hodgkin's lymphoma[1-4]. There are likely multiple factors that contribute to this increased risk, including disease activity and the use of immunosuppressive drugs. Recently, reports have linked development of lymphoma in patients with RA taking methotrexate (MTX) with the ubiquitous transforming herpes virus, Epstein-Barr virus (EBV). Although not all lymphomas developing in patients with RA involve EBV or MTX, a relationship between EBV, MTX, and development of lymphoma in some patients appears highly probable.

Evidence linking MTX, EBV, and development of lymphomas in patients with RA takes 3 forms: multiple case reports of the presence of EBV RNA within lymphoma cells, regression of the lymphoma after stopping MTX, and the biological plausibility of the association, reflecting the well recognized relationship between EBV induced lymphoproliferative disorders in other states of chronic immunosuppression. To date, more than 50 cases of lymphoma occurring in patients with RA taking MTX have been reported[5]. EBV RNA can be found in pathologic tissue using *in situ* hybridization in these tumors. In some cases, support for the role of EBV in the emergence of the malignancy has been observation of monoclonal EBV genomic material in the lymphoma tissue[6]. Importantly, MTX withdrawal has resulted in regression of the EBV positive lymphomas in multiple patients[7].

Immunosuppressed patients have an increased risk of developing a B cell lymphoproliferative disorder that involves EBV[8,9]. Patients undergoing various forms of solid organ transplants are at particular risk for this complication, especially if the immunosuppression is highly T cell selective. In addition to posttransplant patients, patients with immunodeficiency that is congenital, acquired, or iatrogenically induced also have a significantly higher risk of acquiring similar EBV induced lymphoproliferative disorders. Nearly 90% of posttransplant lymphoproliferative disorders are associated with EBV[8]. The common theme in these disorders is impaired T cell immunity that results in loss of control against proliferation of EBV infected B cells[10]. The progression from polyclonal lymphoproliferation induced by EBV to monoclonal malignancy is complex[11]. In some of these patients, regression of EBV associated lymphomas occurs when immunosuppression is stopped, suggesting that at some stages these tumors are under immunomodulatory control. The presence of BCL-6 gene mutations predicts shorter survival and refractoriness to reduced immunosuppression, and may be a useful clinical marker to determine whether reduction in immunosuppression should be attempted or more aggressive therapy should be instituted[12].

Patients with RA are known to have a defect in EBV directed suppressor T cell function[13]. Whether weekly low dose MTX in RA augments this defect in suppressor T cell function has not been established, although opportunistic infections are clearly associated with MTX use[14].

Thus, there is compelling evidence for an association between MTX, EBV, and development of lymphoma in some patients with RA. Combining two recent series of 44 non-Hodgkin's lymphomas occurring in MTX treated patients with RA, 13 (30%) had EBV RNA[15,16]. However, it is also clear that the development of such lymphomas is uncommon. What is the incidence of MTX associated lymphoma in RA? First, no studies describe an increased risk of developing lymphoma in RA associated with MTX use. Moder, *et al* found 39 hematologic malignancies in a cohort of 16,263 patients with RA[17]. No increase in lymphoma was observed in patients taking MTX. Beauparlant, *et al* reviewed studies showing an association between cancer and RA, but found none that showed MTX increases the risk[18]. Second, there is general acceptance that MTX is not oncogenic[19]. The lack of reports of increased lymphoma risk in psoriasis treated with MTX supports this view[20].

As noted, however, several studies show an increased background risk of lymphoma in RA, which confounds the analysis of the MTX associated risk. Of particular note are two recent studies that indicate the risk of lymphoma in RA is related to disease activity or extraarticular manifestations. Baecklund, *et al* did a case control study of all RA patients admitted to the hospital between 1965 and 1983 in Upsala, Sweden[21]. Few of these patients received immunosuppressives. Forty-two cases of lymphoma in the 11,683 patients were identified. Each patient was matched to controls and the data were analyzed in relation to inflammatory activity of RA. Strikingly, the risk of lymphoma increased as the inflammatory activity increased. Patients judged to have high levels of inflammatory activity had an odds ratio of over 25 of developing lymphoma. In a study of US veteran men with Felty's syndrome, considered to be an extraarticular complication reflecting active RA, Gridley, *et al* found that patients with

Felty's syndrome had a nearly 12-fold increased risk of developing lymphoma compared to RA patients without Felty's[22]. These findings are consistent with the notion that several chronic infectious and inflammatory diseases increase the risk of B cell lymphomas[23,24].

Thus, active RA itself may contribute to an increased risk of developing lymphoma. However, EBV appears not to play a role in such lymphomas. Kamel, *et al* found that in a population based case control study of non-Hodgkin's lymphoma in patients with RA, only one of 42 lymphomas was EBV positive[25]. Since few of these patients were receiving immunosuppressive therapy, it seems likely that EBV induced lymphoproliferation represents a minority of lymphomas in the general RA population. It is possible that MTX or other immunosuppressive drugs, by reducing disease activity of RA, actually decreases the risk of lymphoma, but that in some cases, development of an EBV associated lymphoproliferative disorder is an unfortunate result. This hypothesis could be supported by studies of lymphomas developing in RA patients that determine the presence of EBV in lymphoma tissue and the relationship to MTX treatment and disease activity.

What are the implications for patients with RA? First, there appears to be a risk of "doing nothing." Patients with active RA appear to have an increased risk of developing lymphoma. It is likely that treatment with MTX could reduce this risk by effectively treating RA. Although the risk of developing lymphoma while taking MTX appears to be low, we need to inform our patients that a number of lymphomas have been reported and that it is uncertain whether there is an increase in the incidence of lymphoma after MTX treatment. Indeed, the package insert for MTX has this warning. Second, in those patients who develop lymphoma, it seems reasonable to determine the EBV status of the lymphoma and to halt MTX therapy and observe for a period of several weeks before beginning cytotoxic chemotherapy or radiation therapy in EBV positive patients, since these lymphomas may regress after discontinuation of MTX[7]. Finally, in patients whose lymphoma progresses in spite of stopping MTX, consideration should be given to treating those positive for EBV with the anti-CD-20 monoclonal antibody, rituximab[26-28].

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