Immunosuppressive Therapy and Cancer Risk in Ocular Inflammation Patients: Fresh Evidence and More Questions

Naira Khachatryan, MD, DrPH - Philadelphia, Pennsylvania
John H. Kempen, MD, PhD - Philadelphia, Pennsylvania

Although there is strong scientific evidence indicating the effectiveness of immunosuppression for severe ocular inflammatory disease,1 patients and health care providers often ask whether the benefits of systemic immunosuppressive therapy warrant potentially associated risks. The risk of developing a significant illness, such as cancer, is of particular interest. Accurate information about the long-term risks associated with immunosuppressive therapy is needed to inform clinical decision making and develop standards of care for these patients.

Because clinical trials typically do not have sufficient sample sizes and durations of follow-up to detect such adverse events, much of the evidence available must come from the studies that are, by design, observational. Observational studies potentially are subject to indications-for-treatment bias: the conditions that serve as indications for immunosuppression therapy often themselves are associated with an increased risk of cancer, and the patients with more severe disease are more likely to receive the treatment. Regarding the question of the relationship between cancer and immunosuppression, this concern is particularly applicable in the setting of immunosuppression to prevent transplant rejection, whence comes much of the evidence on the subject, and which seems to have a uniquely high risk of cancer.2

However, there generally is consensus based on data from non-eye disease cohorts that immunosuppression is associated with a higher risk of nonmelanoma skin cancers and of lymphomas associated with Epstein-Barr virus, which sometimes (but not always) remit with reduction of immunosuppression.3 There has been limited information available regarding the long-term risk of cancer in patients with ocular inflammation, who may not have a fundamentally different cancer risk than the general population.2,3 However, a well-powered multicenter retrospective cohort study of inflammatory eye disease (IED) patients (the Systemic Immunosuppressive Therapy for Eye Diseases [SITE] Cohort Study) found no excess risk of death resulting from malignancy with use of antimetabolites or T-cell inhibitors over 5 to 7 years of follow-up: azathioprine (adjusted hazard ratio [HR] for cancer mortality, 1.13; 95% confidence interval [CI], 0.60–2.14), methotrexate (adjusted HR, 0.89; 95% CI, 0.48–1.63), mycophenolate mofetil (adjusted HR, 0.83; 95% CI, 0.20–3.52), and cyclosporine (adjusted HR, 0.82; 95% CI, 0.40–1.67).4

In this issue, Yates et al1 begin to address this deficit of evidence regarding immunosuppression and cancer in an eye diseases cohort, reporting an observational study of 190 adults with IED who were treated with either corticosteroids or with systemic immunosuppression plus corticosteroids for more than 6 months. This is a well-defined retrospective cohort of patients with IED diagnosed and treated between 1985 and 2007 in a single center in Sydney, Australia. The investigators conducted medical record review to obtain information regarding IED diagnosis, type, and duration of treatments. In addition, a questionnaire on personal and family history of malignancy, smoking history, and skin complexion was administered to all patients. Those few patients who could not be contacted to complete the questionnaire were classified as being lost to follow-up. Self-reported malignancy diagnoses were confirmed by chart review. Patients were classified into 2 exposure groups: (1) corticosteroids only treatment group (n = 58; 31%) and (2) corticosteroids and immunosuppression treatment group (n = 132; 69%). Immunosuppression treatment included antimetabolites, T-cell inhibitors, alkylating agents, or a combination thereof.

The study analysis has several strengths. These patients were followed up prospectively for a median of approximately 7 years, on the same order as the SITE Cohort Study’s follow-up for mortality.3,5 Cancer incidence was studied directly. The median duration of exposure to immunosuppressant medications was 4.0 years. The number of patients lost to follow-up was small (n = 9), and a sensitivity analysis including these patients was performed in which results did not differ qualitatively. Appropriate statistics were used, adjusting for confounders. However, the report also has its weaknesses, the most important one being the lumping together of all the immunosuppressive drugs. Some of these previously have been thought to have minimal impact on cancer risk (or even be protective against cancer in the transplant setting in the case of mycophenolate mofetil), whereas for others, an increased risk of cancer is convincingly established (e.g., alkylating agents).2,6 This problem makes application of the results difficult.

The study reported 25 primary incident malignancies, including 2 in the corticosteroid only group and 23 in the
immunosuppressed group, a significantly higher risk of all malignancies (taken in aggregate) in the immunosuppression group. Most were nonmelanoma skin cancers (n = 12) or lymphomas (n = 4), consistent with the experience of immunosuppression in other settings, as pointed out by the authors. It is surprising that none of the lymphomas remitted with reduction of immunosuppression, because some would have been predicted to do so if they were the Epstein-Barr virus-associated lymphomas reported in the immunosuppressive context in non-ocular disease cohorts. However, this may have been a random occurrence given the small number of cases. Other cancers were miscellaneous, with no more than 2 of each observed, such that elevated risk of these types of cancers is not established reliably absent replication of the findings in additional studies. After excluding skin cancers, the risk of all other cancers in aggregate still was statistically significantly elevated in the immunosuppression group compared with the general population. However, the risk of first malignancy was not statistically significantly elevated compared with the comparison group cohort, for which more precise covariate information was available (the risk did tend to be higher in the immunosuppression group).

Most importantly, the **absolute** risk of these malignancies was low, with the estimated excess risk attributable to immunosuppression being 0.0089 per person-year, and there were no cancer-related deaths observed during the reasonably long period of observation.

Based on the data provided, a 97.5% 1-sided upper confidence interval of 0.0034 can be calculated, suggesting that the risk of death resulting from cancer in the immunosuppressed subset of this cohort is estimated at least less than 0.34% per person-year, with the most probable effect estimate being no effect (within the study period). Balancing potential cancer risks, it is important to interpret these results remembering that any potential benefits of immunosuppression regarding general health, such as prevention of clinically manifest rheumatologic disease, were not considered (single articles cannot report everything).

In our view, the article provides reasonably strong evidence that we as practitioners ought to be alert to the possibility of skin cancer developing over time in our patients, particularly in regions of high sun exposure such as Australia, where risk is expected to be higher. Taken along with previous evidence, the results also are not inconsistent with the thesis that immunosuppression-related lymphomas occur at a low level with immunosuppression, consistent with prior reports from other fields, as we summarized previously. The report also suggests a slightly higher risk of overall cancer, but given the lumping together of agents that probably have heterogeneous effects on cancer malignancy, it is unclear whether this concern applies to all of the drugs. Clearly we need data on the subject that separate out any effects of the various agents. Pending such an analysis, our view is that the risk-to-benefit ratio of immunosuppression for eye disease is not changed greatly based on these observations, and that immunosuppression remains preferable to long-term, high-dose corticosteroid therapy. In particular, the immunosuppressive agents most popular with uveitis specialists—mycophenolate mofetil and methotrexate—have substantial information available from other disease cohorts indicating very little association with incident malignancy and no association with cancer mortality in the IED setting. Cyclosporine and azathioprine also had encouraging results with respect to cancer mortality in the SITE Cohort Study, although data primarily from the transplant setting convincingly suggest these agents are carcinogenic (at least in that context). Therefore, these agents may be somewhat less preferred to mycophenolate mofetil and methotrexate absent a clear reason to prefer their use, such as intolerance or anticipated intolerance of the alternative drugs. Use of alkylating agents already taken into account a likely increased cancer risk, which is one reason these agents are used infrequently, predominantly when long-term, disease-free remission (a well-established property of this drug class) is essential to prevent blindness. A medium-sized, single-center report questioned whether the short-term, high-dose chlorambucil treatment approach has a higher risk of cancer. Tumor necrosis factor inhibitors were represented minimally in this study, such that any generalization from these results to tumor necrosis factor inhibitor therapy is difficult.

Regarding the call for targeted malignancy prevention strategies, the available evidence supports counseling patients to watch for changes in their skin and referring those with an extensive sun exposure history for periodic dermatologic screening. Prior cancers, especially within the last 5 years, may be a relative contraindication to immunosuppression. Given the rarity of other malignancies, it is difficult to imagine other cost-effective prevention strategies other than those achieved via recommended general vigilance for complications of immunosuppression given the low absolute risk if malignancies and the considerable uncertainty regarding whether risk indeed is increased to a clinically important degree with the most commonly used agents. The authors rightly call for more precise data regarding these issues, which we hope will be forthcoming.

**References**


Footnotes and Financial Disclosures

Financial Disclosure(s): The author(s) have made the following disclosure(s):

J.H.K.: Consultant — AbbVie (Worcester, MA), Alcon (Sinking Spring, PA), Allergan (Irvine, CA), Can-Fite (Waltham, MA), Clearside (San Francisco, CA), Lux Biosciences (Jersey City, NJ), Xoma (Berkley, CA), Sanofi-Pasteur (Cambridge, MA), Roche (San Francisco, CA), Santen (Emerville, CA); Grants — EyeGate, Food and Drug Administration, Lions Club International Foundation, National Eye Institute (grant no. 5R01EY014943-11); Employment — University of Pennsylvania.