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Long-term risk of malignancy among patients treated with immunosuppressive agents for ocular inflammation: A critical assessment of the evidence

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Abstract

Purpose—To critically assess potentially carcinogenic effects of immunosuppressive therapy in the ocular inflammation setting

Design—Focused evidence assessment.

Methods—Relevant publications were identified by MEDLINE and EMBASE queries and reference list searches.

Results—Extrapolation from transplant, rheumatology, skin disease and inflammatory bowel disease cohorts to the ocular inflammation setting suggest that: 1) alkylating agents increase hematologic malignancy risk and cyclophosphamide increases bladder cancer risk, but less so with ≤ 18 months' duration of therapy and hydration respectively; 2) calcineurin inhibitors and azathioprine probably do not increase total cancer risk to a detectable degree, except perhaps some other risk factors (uncommon in ocular inflammation patients) might interact with the former to raise risk; 3) Tumor Necrosis Factor (TNF) inhibitors may accelerate diagnosis of cancer in the first 6–12 months, but probably do not increase long-term cancer risk; and 4) changes in risk with methotrexate, mycophenolate mofetil, and daclizumab appear negligible although non-transplant data are limited for the latter agents. Immunosuppression in general may increase skin cancer risk in a sun-exposure dependent manner.

Conclusion—Use of alkylating agents for a limited duration seems justifiable for severe, vision-threatening disease, but otherwise cancer risk may be a relevant constraint on use of this approach. Antimetabolites, daclizumab, TNF-inhibitors, and calcineurin inhibitors probably do not increase cancer risk to a degree that outweighs the expected benefits of therapy. Monitoring for skin cancer may be useful for highly sun-exposed patients. Data from ocular inflammation patients are needed to confirm the conclusions made in this analysis by extrapolation.

Keywords

cancer; malignancy; methotrexate; azathioprine; cyclosporine; tacrolimus; cyclophosphamide; chlorambucil; etanercept; infliximab; adalimumab; uveitis; scleritis; ocular inflammation

Management of ocular inflammatory diseases was revolutionized in the 1950's when the benefits of corticosteroid therapy were first reported.¹ Unfortunately, in many of the most severe cases—where long-term use of moderate to high doses of systemic corticosteroids would be required to prevent vision loss—use of corticosteroids is constrained by substantial toxicity. The need for less toxic, effective anti-inflammatory treatment inspired the use of immunosuppressive drugs for ocular inflammatory diseases, beginning in the late 1970s. This approach uses similar principles and agents to those which have been applied in the rheumatology and organ transplantation settings for many years, fields from which we derive much of our knowledge about the potential side effects of these agents.

Use of immunosuppressive therapy for inflammatory eye diseases has been advocated by an expert panel² in three settings: as corticosteroid-sparing therapy when disease can be controlled with oral corticosteroids, but expected toxicity is high at the dose required; for inflammation recalcitrant to oral corticosteroids; and for management of specific diseases expected to fare poorly with lower levels of therapy. The immunosuppressive agents most commonly used for

treatment of ocular inflammation include the antimetabolites azathioprine, methotrexate, and mycophenolate mofetil; the T-cell inhibitors cyclosporine and tacrolimus; and the alkylating agents chlorambucil and cyclophosphamide. “Biologics”—including monoclonal antibodies directed at components of the immunologic system, soluble receptors, and cytokines such as alpha interferon—also have been used to treat ocular inflammation in recent years. Thus far, the tumor necrosis factor (TNF) inhibitors etanercept, infliximab, and adalimumab, and the interleukin 2 (IL-2) inhibitor daclizumab are most commonly used. Use of alkylating agents has been associated with a high rate of medication-free disease remission, whereas medication-free remission is not a typical feature when ocular inflammatory disease is treated with antimetabolites, T-cell inhibitors, TNF-inhibitors or daclizumab.

Each of these immunosuppressive agents has potential toxicities in the short run, which in most instances can be overcome if recognized early using a program of surveillance for known potential side effects.² For most patients, an effective regimen that is tolerable over the intermediate- to long-term can be identified and implemented.

Although general consensus exists in the ophthalmology community regarding the effectiveness of immunosuppression for severe ocular inflammatory diseases, an important unresolved concern is whether some of these agents may increase the risk of cancer—and therefore mortality. The extent of risk of cancer or of death from cancer with such treatment has a large influence on the risk-benefit analysis considered prior to using these medications. Uncertainty regarding possible risks has led to substantial variability in clinical practices. The primary goal of this Perspective is to synthesize the available information on the putative long-term risks of malignancy with immunosuppressive therapy—primarily available from non-ocular disease cohorts—and to apply it to the eye diseases setting.

Potential Mechanisms of Carcinogenesis Related to Immunosuppression

Potential mechanisms by which immunosuppressants could promote cancer include: 1) interruption of immune surveillance for and destruction of malignant cells; 2) increased susceptibility to infection with oncogenic agents; 3) pharmacologic effects on DNA (alkylating agents) or DNA metabolism (antimetabolites); and 4) specific effects on the immune system, which could increase (or decrease) the chances of a transformed cell surviving and proliferating.

Because carcinogenesis often requires several years, longer than the duration of follow-up in most clinical trials, evaluation of data on complications of immunosuppression requires making inferences primarily from observational data. Established methods of inference for this setting are summarized in Table 1.

Malignancies Related to Immunosuppression in General

Skin and Mucosal Cancers

The post-transplantation literature is replete with reports describing the occurrence of non-melanoma skin cancers in immunosuppressed patients, particularly solid organ transplant recipients. In contrast to the general population, squamous cell carcinoma of the skin occurs more commonly than basal cell carcinoma among transplant patients, with both occurring at substantially elevated rates. The increase in skin cancer risk is reported to be 100-fold or greater for squamous cell carcinoma,^{3,4} approximately 10-fold for basal cell carcinoma,⁴ and several-fold for mucosal cancers.³ Solar-induced mutations,⁵ presumably amplified by immunosuppression-induced reduction in tumor surveillance, play an important role. Primarily sun-exposed skin and mucosa are affected, and the risk of squamous carcinoma is several-fold higher closer to the equator. Increased susceptibility or altered response to viral infection also

appears to be an important contributor. Human papillomavirus (HPV) genomes, predominantly viral subtypes associated with a high risk of cervical cancer, are present in the majority of squamous cell carcinomas of the skin in immunosuppressed transplant patients.⁶ Significantly increased risk of squamous cell cancers of the skin with increasing duration of immunosuppression has been observed,⁷ providing a dose-response relationship between immunosuppression and the risk of skin cancer.

In the rheumatology literature, reports of increased squamous cell carcinoma risk also exist, but the extent of increased risk does not appear to be as dramatic as that reported in transplant patients, and several studies have found no increased risk. The difference in the extent of risk is likely related to the uniquely high risk of cancer among transplant patients, discussed below.

Few reports of regression of skin cancer following cessation of immunosuppression exist. The clinical behavior of these skin cancers is more aggressive than among non-immunosuppressed patients, although successful treatment is usually possible with early detection.

Post-transplant Lymphoproliferative Disorder

Excess risk of lymphoid proliferations and malignancies (Post-Transplant Lymphoproliferative Disorder (PTLD)) following months to several years of chronic immunosuppression was first recognized in the late 1960s. PTLD is linked to Epstein-Barr virus (EBV) infection in 80–90% of cases; the role of EBV in pathogenesis is reviewed elsewhere.⁸ Non-Hodgkin's lymphomas, which can be either mono- or polyclonal, are included in the spectrum of disease. PTLD typically is the second most common neoplastic condition occurring in transplant cohorts, after skin cancers. While both primary infection or reactivation of latent infection have been reported to underlie this condition, primary infection is associated with a more than 10-fold higher risk.⁹ Even though several considerations suggest the development of PTLD is related to deficiency of T cell function, cases of lymphomas that reverse with cessation of immunosuppressive therapy have been reported with nearly all of the agents under consideration in this Perspective.

Over time, it has been recognized that cessation or reduction of immunosuppressive therapy absent any other intervention is followed by regression of the tumors in a substantial number of transplant patients with PTLD,¹⁰ but perhaps not the majority.^{9,11} While lesions that have become monoclonal have a poorer prognosis,¹² even some of these can regress with reduced use of immunosuppression.^{9,10} Inspection of the reports suggests that the proportion developing PTLD during several years' follow-up is probably in the 1–2% range. Because approximately 30% of cases in transplant recipients have PTLD involvement in the transplanted organ itself⁹ and theories of pathogenesis give substantial importance to chronic antigenic stimulation by the transplanted graft,¹³ patients with local ocular inflammation treated with immunosuppression probably have substantially lower risk of PTLD-like conditions.

Therapy for PTLD has been discussed elsewhere.⁹ Treatments that have been used or suggested—when simple reduction of immunosuppression fails—include surgical resection and/or radiation; antiviral therapy with ganciclovir or acyclovir; infusion of anti-B cell monoclonal antibodies such as rituximab; interferon-alpha; and standard chemotherapy (reserved for a third line approach).

Solid Tumors

Solid tumors probably do not occur with higher frequency with immunosuppression than in the general population.¹⁴ However, higher than expected rates of recurrence of prior tumors following transplantation/immunosuppression have been reported, leading to a

recommendation for a two year waiting period between cancer treatment and transplantation with its required use of immunosuppression.¹⁵ Not all agree with this recommendation, and the clinician must take into account the potential risks of postponing immunosuppressive therapy in making such a decision. However, a higher threshold for using immunosuppression probably is warranted in patients recently diagnosed with cancer.

Risk of Malignancy Associated With Particular Immunosuppressive Agents

Alkylating agents

Among the immunosuppressive agents used in ocular inflammation, the most clear-cut evidence for increased risk of malignancy is with alkylating agent therapy (Table 2).

Cyclophosphamide treatment of patients with cancer and rheumatoid arthritis has been associated with substantially increased rates of bladder cancer (as much as 30-fold),^{16–19} leukemia,^{20,21} lymphoma,¹⁹ and skin malignancies,^{17,22} with some (but not all) studies finding an increase in total malignancies.^{22,23} Bladder cancer risk was observed to be dose- and/or duration dependent in several studies.^{17,22–24} For example, a study of 6,171 two-year survivors of non-Hodgkin's lymphoma found a statistically non-significant 2.4-fold increase in the risk of bladder cancer observed with cumulative doses of less than 20 grams, and significantly increased 6.0- and 14.5-fold increases in risk associated with cumulative dosages of 20–49 grams and 50 or more grams respectively.²⁴ An ocular inflammation patient receiving 150 mg/day for one year would receive a cumulative dose of cyclophosphamide exceeding 50 grams. A rodent model also has been developed in which cyclophosphamide causes bladder cancer.²⁵

An increased risk of malignancy with cyclophosphamide therapy may not be evident until four or more years following treatment.^{17,19,26} One study projected that the risk of bladder cancer was 5% at 10 years and 16% at 15 years.²⁷ Several studies remark on an increased risk of bladder cancer among smokers, suggesting risk may be especially high in this group of patients. Patients receiving oral cyclophosphamide should be well-hydrated, to flush the metabolite acrolein out of the bladder, a primary cause of the cystitis that occurs with this drug. Cystitis in turn is associated with a substantially increased risk of bladder cancer.²⁷ Medical oncologists frequently provide intravenous hydration along with pulses of cyclophosphamide for this reason, an approach which is recommended in the eye diseases setting. Some have used mesna for prophylaxis, but a randomized clinical trial suggests hydration is as effective as mesna.²⁸ Limited data from autoimmune diseases and even transplant cohorts are available for chlorambucil, which is used primarily for medical oncology applications. One small study of rheumatoid arthritis patients found that 8 of 39 patients developed cutaneous malignancy ($p=0.03$), often multiple and recurrent.²⁹ Chlorambucil treatment for patients with neoplastic diseases has been associated with a substantially higher rate of secondary hematologic malignancies.^{30–32} Leukemia may be more frequent with chlorambucil than with cyclophosphamide. It is noteworthy that most non-bladder cancers observed with these agents typically are of the kinds seen with immunosuppression in general, rather than a broad spectrum of cancers such as might be expected if induction of mutation is the prevailing oncogenic mechanism.

T-cell inhibitors

The literature on T-cell inhibitors—particularly the calcineurin inhibitors cyclosporine and tacrolimus—suggests carcinogenic effects among transplant patients, but does not support the same conclusion in other cohorts. Several studies have proposed specific immune mechanisms whereby cyclosporine specifically might promote carcinogenesis.^{33–35} While two studies

have suggested that cyclosporine may have genotoxic effects,^{36,37} most have thought that cyclosporine does not affect DNA to an important degree.³⁸

Numerous reports of increased risk of neoplasia (especially skin cancers and PTLD) exist for transplant patients treated with cyclosporine, but given the near universal use of cyclosporine in the transplant setting, it is difficult to separate the effect of cyclosporine and of the transplant. However, a dose-dependent pattern in which the risk of malignancy was significantly lower risk with lower than with higher doses of cyclosporine has been reported in two studies.^{39, 40} Also, in a renal transplant cohort, the risk of neoplasia (mostly skin cancers, PTLD, and gastrointestinal cancers) was more than 50% lower when azathioprine had been used instead of cyclosporine; furthermore, patients who changed from azathioprine to cyclosporine-based regimes subsequently had higher cancer risk.⁴⁰

Limited information is available from inflammatory disease cohorts about cyclosporine and cancer risk, but the available evidence seems to differ from the observations in transplant cohorts. In a cohort study of several hundred rheumatoid arthritis patients—some taking part in randomized trials and some not—cyclosporine (<5 mg/kg/day for relatively short periods in most patients) was not associated with increased malignancy or mortality risk.⁴¹ Patients with psoriasis treated with cyclosporine have been observed to have an increased risk of squamous cell carcinoma of the skin that increased with duration of cyclosporine therapy, and also an increased risk of leukemia (only occurring in the short duration of therapy group, a non-consistent observation) but not lymphoma. However, 95% of all non-melanoma skin cancers in this group occurred following treatment with psoralen and ultraviolet A (PUVA),⁴² suggesting that the effect of cyclosporine may have been indirect—increasing the risk of PUVA therapy—rather than direct.

Data regarding tacrolimus are less extensive, and mostly involve comparisons to cyclosporine in transplant cohorts. Four reports have suggested an increased risk of PTLD with tacrolimus compared with cyclosporine.^{43–46} One study comparing the risk of skin cancer in transplant cohorts found lower rates with tacrolimus- than with cyclosporine-based immunosuppression,⁴⁷ and another found lower overall cancer (mostly skin cancer) incidence with tacrolimus,⁴⁸ whereas a third found no difference in total cancer risk.⁴⁹

Although not commonly used in ocular inflammation thus far, it is worth noting that sirolimus has been reported to exert biological effects expected to inhibit immunosuppression-induced neoplasia,^{50–52} Transplant cohort data suggest 50% or lower risk of neoplasms when sirolimus is used along with cyclosporine⁵⁰ or when it is used to allow withdrawal of cyclosporine.⁵³

Antimetabolites

Although many papers have been written about potential carcinogenesis with antimetabolite immunosuppressive therapy, the evidence in favor thereof is not strong, particularly outside the transplant literature.

Azathioprine—Most studies of patients with rheumatoid arthritis or inflammatory bowel disease receiving either conventional^{54–57} or high⁵⁸ doses of azathioprine have observed no significant difference in the risk of malignancy. A case-control study evaluating azathioprine exposure in multiple sclerosis patients with and without cancer also found no association.⁵⁹ A review of the risk of PTLD-like conditions in patients with inflammatory bowel disease treated with azathioprine or 6-mercaptopurine found that several hospital-based reports reported an increased risk, but that a large population-based report—which should be methodologically superior—did not.⁶⁰

In contrast to inflammatory disease cohorts, azathioprine-treated transplant patients probably do have an increased risk of malignancies compared to the general population. The incidence of squamous cell carcinoma of the skin subsequent to azathioprine-corticosteroid treatment for renal transplant has been reported as 37-fold higher (95% CI: 4.4–132) than in the general population,⁶¹ and several transplant cohorts among whom azathioprine was frequently used have reported substantially increased risk of lymphoid malignancies. This discrepancy from non-transplant patients presumably reflects the unique transplant-immunosuppression interaction described below. As mentioned previously, azathioprine-based transplant immunosuppression regimens may be associated with a lower risk of cancer compared to cyclosporine-based regimens.⁴³

Methotrexate—Among the older immunosuppressants, methotrexate has the least evidence in favor of an increased malignancy risk. Lack of increased cancer risk has been demonstrated in several cohorts with a variety of diseases.^{62–66} The main cluster of reports which might reflect a real (but very small) increase in malignancy risk describe a PTLD-like condition. Among hundreds of thousands or millions of rheumatoid arthritis patients who had taken methotrexate by 1997, 23 cases of lymphomas—some reversible with discontinuation of methotrexate—had been reported in the literature.⁶⁷ However, an outstanding large observational study following 19,591 patients over 89,710 person-years found no significant increased risk of lymphoma with methotrexate among patients with rheumatoid arthritis (standardized incidence rate=1.1, 95% CI: 0.6, 2.0).⁶⁸

Mycophenolate mofetil—As a newer drug, the literature on cancer risk with mycophenolate mofetil (MMF) is less extensive than that for the agents previously discussed, but is favorable—even though MMF is typically used in transplantation. Observational studies of MMF have found significantly and substantially reduced risk of PTLD,^{13,43} improved survival of those who did develop PTLD,⁴³ and lower risk of malignancy in general^{69,70} with respect to alternative regimens (including cyclosporine, tacrolimus, and/or azathioprine). A meta-analysis of clinical trials comparing MMF vs azathioprine in renal transplantation found no difference in the risk of overall malignancies or skin malignancies.⁷¹ On theoretical grounds, MMF has potentially beneficial effects vis-à-vis the risk of malignancy.^{72–74}

Biologics

Tumor Necrosis Factor Inhibitors

The available evidence regarding cancer risk with tumor necrosis factor (TNF) inhibitors derives primarily from rheumatic diseases and inflammatory bowel diseases cohorts, rather than transplant cohorts, and hence is probably less biased vis-à-vis the ocular inflammation setting than the agents for which primarily transplant data are available. Clinical data have been mixed regarding possibly increased risk of malignancy.

Evidence in favor of an increased risk of cancer derives primarily from two reports based on clinical trials data, with relatively short follow-up vis-à-vis the time needed for the process of carcinogenesis, but with the superior design characteristic of randomized assignment of therapy. A meta-analysis of 5014 patients with rheumatoid arthritis randomized either to anti-TNF antibody therapy (adalimumab or infliximab) vs. placebo found an increased risk of malignancies with the TNF inhibitors (pooled OR for malignancy=2.4 (95% CI: 1.2–4.8).^{75,76} Although it was noted by a correspondent that a meta-analysis which compared cancer rates to those in the general population found no significant difference,⁷⁷ the meta-analysts' response that patients meeting screening criteria for clinical trials may have a better prognosis than the general population and that as-randomized comparisons are the optimal approach for ascertaining treatment effects in clinical trials have epidemiological merit. The second report is from a randomized, controlled trial evaluating etanercept vs. placebo in addition to

conventional therapy (including alkylating agents) for Wegener's Granulomatosis, in which an excess occurrence of solid tumors was observed (standardized incidence ratio 3.12, 95% CI: 1.15–6.80),⁷⁸ suggesting a possible adverse interaction between alkylating agent and anti-TNF therapies.

In contrast, seven large, excellent observational studies of tens of thousands of patients with rheumatoid arthritis followed for many years have found no increased overall cancer risk (including solid tumors) with anti-TNF agents, with risk ratios close to 1 in every case.^{68, 79–85} One of these studies observed a decrease in total mortality of rheumatoid arthritis patients with anti-TNF therapy (RR=0.65, 95% CI: 0.46–0.93),⁸² and another study found no increased risk of cancer fatalities.⁸⁶ An eighth study of rheumatoid arthritis patients observed a non-significant trend toward an increase in lymphoma (an excess of 26 cases per 10,000 person-years; adjusted RR=4.9, 95% CI: 0.9–26.2), but no increase in total cancer risk.⁸⁷ One of the studies finding no increase in overall cancer risk (OR=1.0, 95% CI: 0.8–1.2) did observe a higher risk of non-melanoma skin cancer (OR=1.5, 95% CI: 1.2–1.8),⁸⁵ the only statistically significant result among scores of comparisons in these papers. Data from a Crohn's disease cohort also found no increased risk of neoplasia with anti-TNF agents (OR=1.33, 95% CI: 0.46–3.84).⁸⁸

Daclizumab

Clinical data evaluating the risk of malignancies with daclizumab are sparse, but one excellent meta-analysis of trial results found no increase in the risk of malignancy with daclizumab for renal transplantation (RR=0.67, 95% CI: 0.33–1.36).⁸⁹ Mechanistically, there is some suggestion daclizumab actually may be an effective a treatment for T-cell leukemia (particularly if tagged with a radioactive moiety), on the basis that the diseased T cells in patients with several lymphoid malignancies express the IL-2 receptor alpha subunit, whereas few normal cells express it.⁹⁰

Discussion

The main limitation of this Perspective is the lack of data available from ocular inflammatory diseases cohorts. The only such study available evaluated the risk of malignancy among 543 patients followed for a median of 1.34 years.⁹¹ While it is reassuring that this study found no increase in cancer risk with the immunosuppressive agents used, only a several-fold difference in risk could have been detected with the available study power, and carcinogenic effects occurring after two years would have been missed. Further study of eye diseases cohorts with sufficient follow-up time to evaluate the risk of cancer and its impact on survival is clearly needed. Health utility studies evaluating ocular inflammation patients' perspectives on how cancer or other adverse events compare to blindness also may help inform decision-making, particularly regarding the decision of whether to use alkylating agents. Studies of the potential benefits of immunosuppression, such as possible reductions in the risk of cardiovascular disease given the inflammatory aspect of atherosclerosis⁹² also would be valuable; the potential benefits of immunosuppressive therapy are too frequently overlooked. Finally, studies evaluating mortality risk in eye diseases patients treated with immunosuppressants, which is the ultimate concern, are few, and would be of great value in interpreting the potential adverse effects of these treatments.

Because of limited data from eye diseases cohorts, our analysis relies on reports from systemic inflammatory disease and transplant cohorts. Transplant patients in particular have an extremely high risk of malignancy, which does not appear to be entirely explained by the intensity of immunosuppression used in the transplant setting, probably arising from chronic antigenic stimulation by the graft and/or other factors.¹³ Immunosuppression may interact with other cancer risk factors among transplant patients to multiply risk in a manner that probably

does not occur—or occurs rarely—in patients with inflammatory eye disease. Results from systemic autoimmune disease cohorts also may reflect a higher intrinsic risk of malignancy than may pertain to eye diseases cohorts, but to a lesser degree than transplant cohorts. For instance, rheumatoid arthritis itself also is associated with an approximate two-fold increased risk of lymphoma, apart from any anti-inflammatory treatment.^{68,93} Therefore, the risks observed in these cohorts—particularly the transplant cohorts—probably overestimate the risk of inflammatory eye diseases patients. Furthermore, lower risk may pertain in the eye diseases setting because a lower intensity of immunosuppression often is used in eye diseases than in systemic inflammatory disorders.² Finally, publication bias is likely to lead to disproportionately high reporting of malignancies in patients receiving immunosuppressive agents in the literature. Because in most cases these biases would tend to reduce further an already low estimate of malignancy risk, our evaluation of the malignancy risk associated with immunosuppressive agents used in ophthalmology provides conclusions which are mostly reassuring.

It is unclear whether the conclusions we have reached, derived nearly entirely from adult research, are generalizable to children. In general, children have a low risk of cancer, any carcinogenic effects that may exist to produce even smaller increases in absolute risk in the pediatric population than in the adult population. Nevertheless, pediatric eye diseases data would be needed to confirm this argument. Likewise, it is difficult to evaluate whether the risk of cancer among patients who have underlying systemic diseases associated with their ocular inflammation might be higher than those who appear to have isolated ocular inflammation without data providing a direct comparison.

This analysis suggests some useful applications of other fields' observations to the eye diseases setting. The general observations about an increased risk of skin cancers in patients receiving immunosuppression may warrant regular use of dermatologic examination in patients who are receiving chronic immunosuppressive therapy for eye diseases, particularly for patients who have received a high degree of solar irradiation in their lifetime, and have light-colored skin. Counseling to avoid excessive sun exposure and smoking might be helpful. Cyclophosphamide should perhaps be avoided when possible for smokers. It remains to be seen whether vaccination against high risk HPV subtypes⁹⁴ will be valuable to prevent HPV-associated squamous cell carcinoma. The potential reversibility of lymphomas in the setting of immunosuppression should be recognized when the occasional patient develops a PTLD-like lesion during immunosuppression. Based on the apparently ability of EBV to cause PTLD, and observations of increased severity of PTLD in the setting of primary infection with EBV,⁹ infectious mononucleosis may provide an indication for temporary interruption of immunosuppressive therapy in the eye diseases setting. Finally, it may be appropriate to avoid initiation of immunosuppressive therapy, if possible, in the early years following apparently successful treatment of cancer, because of concerns that immunosuppression may promote relapse. When such treatment is of high importance, use of immunosuppressive agents which seem to have less impact in populations at elevated risk for cancer—such as methotrexate, mycophenolate mofetil or daclizumab—may be prudent.

Evidence from the available literature about cancer risk in patients receiving the immunosuppressants most commonly used for ocular inflammation does not indicate a level of concern sufficient to make any of the agents contraindicated (see Table 2). The available evidence suggests a clinically important increase in the risk of cancer with alkylating agent therapy, which probably is applicable to the eye diseases setting to at least some extent. However, with appropriate precautions such as limiting the cumulative dose (perhaps by substituting an antimetabolite after 12–18 months when necessary) and using hydration (for cyclophosphamide) the risk of cancer probably is not sufficient to outweigh the benefit of such therapy if it is needed to control severe, vision-threatening disease and to induce long-term,

medication-free remission in a high proportion of such cases. A risk-benefit analysis that incorporated the severe impact of blindness would likely support the use of these agents in appropriate settings. However, they should be used with caution in vision-threatening situations where alternative immunosuppressive agents are unlikely to succeed or have failed.

Evidence for increased cancer risk is much more limited for calcineurin inhibitors, azathioprine, and TNF-inhibitors. It is likely that there is no or little increase in the absolute risk of cancer with these agents in an inflammatory eye diseases setting. For cyclosporine, there exists persuasive evidence of an increased risk of cancer in transplant patients, less convincing evidence of increased risk among psoriasis patients mostly treated with PUVA, and no evidence of increased risk among rheumatoid arthritis patients. Data are limited to evaluate whether tacrolimus and cyclosporine qualitatively differ, although they do not appear to in the transplant setting. Calcineurin inhibitors may have permissive effects for cancer in a subset of patients with strong risk factors (such as the present of a transplant or PUVA therapy); however, such patients are likely to be even more rare in an eye diseases setting than the rheumatoid arthritis setting, suggesting little if any increase in cancer risk for such patients. However, more data on risk from non-transplant cohorts would be particularly helpful for calcineurin inhibitors, because our conclusions rest on a small number of non-transplant studies. The available data regarding sirolimus suggest it would have appeal as an immunosuppressive agent for eye diseases if evidence emerges suggesting it is effective.

For azathioprine, cancer risk in the transplant setting also is supported, but may be less than with calcineurin inhibitors. However, the lack of increased cancer risk in several rheumatologic cohorts suggests that eye diseases patients are likewise unlikely to have increased cancer risk with azathioprine.

The observation in randomized trials of an increased risk of cancer within 6 months of initiating TNF-inhibitor treatment,⁷⁵ combined with the consistent absence of any observed effect on cancer risk in numerous large, high quality observational studies with several years of follow-up suggest that TNF-inhibitors may allow pre-existing cancers to progress faster, but probably not induce cancer. The largest observational study of these agents reported a trend toward increased cancer risk at an early stage of follow-up,⁹⁵ which after increased follow-up converged to 1.0,⁶⁸ which seems to support this theory.

In summary, the use of calcineurin inhibitors, azathioprine, and TNF-inhibitors in the eye diseases setting can be viewed as warranted in situations with a moderate or greater risk of vision loss, or where alternative treatments such as corticosteroids are likely to have adverse systemic effects. The risk of cancer with these treatments is probably unaffected or increased to a degree that is less important than the potential benefits of therapy.

Methotrexate, mycophenolate mofetil, and daclizumab have the least evidence to suggest carcinogenicity among the agents used for inflammatory eye disease. The evidence supporting non-carcinogenicity for methotrexate—other than exceptionally rare cases of PTLD-like conditions—is particularly extensive. Given that the drug has been suggested to reduce cardiovascular mortality among rheumatoid arthritis patients,⁹⁶ there does not seem to be a good reason to hesitate in using this agent for ocular inflammation based on the available evidence. The evidence supporting an absence of carcinogenic effects for mycophenolate mofetil and daclizumab is less ideal in its extent and/or generalizability, but there are theoretical reasons to expect that these agents would be less likely to induce cancer than other immunosuppressants, and a rationale exists that they might even prevent cancer. Furthermore, available data suggest less carcinogenic effects with MMF than with calcineurin inhibitors in the transplant setting—which may or may not be relevant in the eye diseases setting. Based on the presently available information, cancer risk does not appear to have any important role in

decision-making regarding the use of methotrexate, mycophenolate mofetil, and daclizumab for inflammatory eye diseases.

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Factors Relevant to Causal Inference Regarding the Risk of Mortality and Malignancy in the Setting of Immunosuppressive Therapy Given for Eye Diseases*

Table 1

Factor Suggesting Causality	Explanation	Supportive Observations(s)	Alternative Explanations of the Supportive Observation(s)
Strength of Association	A stronger association of the putative risk factor ("exposure") with disease is more likely to reflect a causal relationship than a weaker association	Large (or small) risk ratios	Strong confounding or bias
Consistency	A real effect, particularly one that is of wide generalizability, often will be observed consistently across many different circumstances	The association is observed in different populations under different circumstances	Repetition of a bias in study design or patterns of confounding across several studies
Temporality	A cause must precede an effect	Exposure precedes the purported effect	Not applicable
Biologic Gradient	The effect of exposure increases with increased exposure	Dose-reponse effects	Strong relationship of dose with a strong confounder
Biologic Plausibility	A reasonable biological explanation of the association can be made	A conclusion of causality is consistent with plausible theories of pathogenesis	Existing theories of pathogenesis are erroneous or are incorrectly questioned
Experimental Evidence	An experiment appropriately designed to test the relationship between exposure and disease is likely to affirm or refute the hypothesis of causation	Clinical trial/experiment randomizing to exposure or no exposure finds increased risk of mortality or malignancy	Random error

* Adapted from Hill AB. The environment and disease: association or causation? *Proc R Soc Med* 1965; 16:1667–1670.

Table 2
 Summary of Evidence Regarding the Risk of Cancer Associated with Specific Immunosuppressants Used for Treatment of Ocular Inflammation*

Agent Class	Specific Agent	Likely Impact on Cancer in Ocular Inflammation Patients				Quality of Clinical Data Regarding Possible Carcinogenic Effects				
		Evidence Suggests a Direct Effect Increasing Cancer Risk to a Clinically Important Degree	Evidence Suggests Drug May Interact to Increase Cancer Risk in (Rare) High Risk Patients	Possible Anti-Neoplastic Biological Effects	Biologically Plausible Mechanism for Carcinogenesis	Adequate Amount of Person-Time Observed	Generalizability (Extent of Available Data from Non-Transplant, Non-Cancer Cohorts)	Consistency of Reported Observations	Strength of Association	Dose-response Relationship
Alkylating Agents	Cyclophosphamide	Yes	Yes	-	+++	+++	+++	+++	+++	+++
	Chlorambucil	Yes	Yes	-	+++	++	+	+++	+++	-
T-cell Inhibitors	Cyclosporine	No	Yes	-	+++	++	++	+	+	++
	Tacrolimus	No	Yes	-	+++	+	+	++	++	-
Anti-metabolites	Azathioprine	No	Inconclusive	-	++	+++	+++	+	+	+
	Methotrexate	No	No	-	++	+++	+++	N/A	N/A	N/A
	Mycophenolate Mofetil	No	No	Yes	+	+++	+	N/A	N/A	N/A
Biologics	Tumor Necrosis Factor Inhibitors	No	No	-	++	+++	+++	+	+	-
	Daclizumab	No	No	Yes	+	+	+	N/A	N/A	N/A

* A higher number of + 's refers to a higher level of the attribute specified; - indicates no or trivial evidence exists. N/A indicates not applicable or no association.