Cyclophosphamide for Ocular Inflammatory Diseases

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Purpose: To evaluate the outcomes of cyclophosphamide therapy for noninfectious ocular inflammation.

Design: Retrospective cohort study.

Participants: Two hundred fifteen patients with noninfectious ocular inflammation observed from initiation of cyclophosphamide.

Methods: Patients initiating cyclophosphamide, without other immunosuppressive drugs (other than corticosteroids), were identified at 4 centers. Dose of cyclophosphamide, response to therapy, corticosteroid-sparing effects, frequency of discontinuation, and reasons for discontinuation were obtained by medical record review of every visit.

Main Outcome Measures: Control of inflammation, corticosteroid-sparing effects, and discontinuation of therapy.

Results: The 215 patients (381 involved eyes) meeting eligibility criteria carried diagnoses of uveitis (20.4%), scleritis (22.3%), ocular mucous membrane pemphigoid (45.6%), or other forms of ocular inflammation (11.6%). Overall, approximately 49.2% (95% confidence interval [CI], 41.7%–57.2%) gained sustained control of inflammation (for at least 28 days) within 6 months, and 76% (95% CI, 68.3%–83.7%) gained sustained control of inflammation within 12 months. Corticosteroid-sparing success (sustained control of inflammation while tapering prednisone to 10 mg or less among those not meeting success criteria initially) was gained by 30.0% and 61.2% by 6 and 12 months, respectively. Disease remission leading to discontinuation of cyclophosphamide occurred at the rate of 0.32/person-year (95% CI, 0.24–0.41), and the estimated proportion with remission at or before 2 years was 63.1% (95% CI, 51.5%–74.8%). Cyclophosphamide was discontinued by 33.5% of patients within 1 year because of side effects, usually of a reversible nature.

Conclusions: The data suggest that cyclophosphamide is effective for most patients for controlling inflammation and allowing tapering of systemic corticosteroids to 10 mg prednisone or less, although 1 year of therapy may be needed to achieve these goals. Unlike with most other immunosuppressive drugs, disease remission was induced by treatment in most patients who were able to tolerate therapy. To titrate therapy properly and to minimize the risk of serious potential side effects, a systematic program of laboratory monitoring is required. Judicious use of cyclophosphamide seems to be beneficial for severe ocular inflammation cases where the potentially vision-saving benefits outweigh the substantial potential side effects of therapy, or when indicated for associated systemic inflammatory diseases.

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Corticosteroids, first introduced for ophthalmic use in 1951,[1] remain a mainstay of treatment for ocular inflammation.[2] However, dose-dependent side-effects resulting from chronic use (particularly with systemic corticosteroids) and sometimes inadequate response are limitations of such therapy.[3] Immunosuppressive agents are indicated for the management of ocular inflammatory diseases in these settings, for diseases that have shown better response to early initiation of immunosuppression, or both.[3]

Cyclophosphamide, an alkylating agent developed for cancer chemotherapy, first was introduced in 1952 for treatment of uveitis of unknown cause[4] and has been used subsequently for various forms of ocular inflammation.[3] It acts by exerting a cytotoxic effect on rapidly proliferating cells by alkylating nucleophilic groups on DNA bases—particularly the 7-nitrogen position of guanine. This leads to cross-linking of DNA bases, abnormal base pairing, or DNA strand breakage, damaging cells when they undergo mitosis. This action profoundly suppresses the function of both T cells and B cells, broadly inhibiting the immune system.[5,6] Cyclophosphamide can be administered both orally (1–2 mg/kg daily) and intravenously (750-1000 mg/m^2 body surface area every 3 to 4 weeks).[5]

Cyclophosphamide has been reported to be effective for the treatment of ocular manifestations of systemic autoimmune diseases including Wegener's granulomatosis,[7–14]

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rheumatoid vasculitis,[15,16] polyarteritis nodosa,[17,18] systemic lupus erythematosus,[19,20] and mucous membrane pemphigoid (MMP),[21–26] as well as for primary ocular inflammatory conditions including Mooren's ulcer,[27] Behçet's disease,[28–30] and Vogt-Koyanagi-Harada syndrome.[31,32] Most of these reports, however, have been based on series with small numbers of patients, resulting in imprecise estimates of success and of side effects. To provide more information regarding the use of cyclophosphamide for ocular inflammatory diseases, the outcomes of 215 patients followed up from the point of initiation of cyclophosphamide at 4 ocular inflammation referral centers in the United States are reported herein.

Patients and Methods

Study Population

The Systemic Immunosuppressive Therapy for Eye Diseases Cohort Study is a multicenter cohort study for identifying long-term treatment adverse events, the methods of which have been described previously.[33] For this report, all patients at 3 academic subspecialty centers with noninfectious ocular inflammation since the inception of the center and an approximate 40% random sample of such patients from a fourth center potentially were eligible. Sampling was carried out because of logistical constraints; to avoid selection bias, computer-generated random numbers were used with a probability of selection based on the site of inflammation (such that conditions with greater likelihood of using immunosuppression—the primary focus of the study—were oversampled). Patients from a fifth center participating in the study were not included in this analysis because the center's comanagement approach to treatment produced a bias in ascertaining time-to-treatment success, because most visits were conducted at partner centers—both delaying the time-to-ascertainment of treatment success and reducing the likelihood that successfully managed patients would return.

Patients observed to start cyclophosphamide during follow-up were eligible for inclusion in the present analysis. Patients who were taking another immunosuppressant in addition to cyclophosphamide were excluded to isolate better the effects of cyclophosphamide therapy, but patients were not excluded if they used corticosteroids; systemic corticosteroid-sparing effects were a primary outcome of the study.

Because patients had to have had at least 1 visit in which they were not taking cyclophosphamide, 1 when they started cyclophosphamide, and at least 1 or 2 additional visits to ascertain outcomes (depending on the outcome), effectively patients had to have at least 3 visits to be included in analyses of outcomes (see below). Patients were followed up until discontinuation of cyclophosphamide, until addition of a second immunosuppressive drug, until cessation of patient visits at the study clinic, or until the end of data collection, whichever occurred first.

Data Collection

A database developed in Access (Microsoft Corporation, Redmond, WA) for the Systemic Immunosuppressive Therapy for Eye Diseases Cohort Study with an extensive suite of real-time quality control checks was used to collect information on every eye of every patient at every visit by trained expert reviewers.[33] Information on demographic characteristics, ophthalmologic examination findings, presence or absence of systemic illnesses, all medications in use at every clinic visit (including all use of corticosteroids and immunosuppressive drugs), and reasons for stopping cyclophosphamide were used for this analysis.

Main Outcome Measures

The main outcomes studied were measures of effectiveness (control of inflammation and corticosteroid-sparing effects) and of toxicity leading to discontinuation of cyclophosphamide therapy. Inflammatory status was categorized as active, slightly active, or inactive for every eye at every visit according to the clinician's judgment at the time of each visit, where slightly active inflammation reflected activity that was minimally present, described also by terms such as *mild*, *few*, or *trace cells*, and inactive indicated there was no active inflammation, also expressed by words such as *quiet*, *quiescent*, or *controlled*. Control of inflammation was evaluated as the transition from either active or slightly active to inactive. A sensitivity analysis evaluating transition from active either to slightly active or inactive also was performed. The time to success in reducing the prednisone dose to 10 mg, 5 mg, or 0 mg without recurrence of ocular inflammation activity was evaluated in patients who did not meet these success criteria at the beginning. When corticosteroids other than prednisone were used, their equivalent doses were calculated for evaluation of corticosteroid-sparing success.[34] For study of time to discontinuation of cyclophosphamide, the dates and the reasons for discontinuation of cyclophosphamide were noted.

Statistical Methods

Statistical analyses used SAS software version 9.1 (SAS, Cary, NC). The distribution of demographic and clinical characteristics at the outset of therapy was tabulated. Control of inflammation and corticosteroid-sparing effects were evaluated according to the time to success using survival analysis. To avoid counting a transient improvement as a success, these outcomes were not accepted unless they were observed over 2 visits or more spanning 28 days. Sensitivity analyses evaluating time to success observed at a single visit also were performed to allow comparisons with other reports using various immunosuppressive drugs that have used such an approach. Discontinuation of therapy was assessed using a simple time-to-discontinuation approach. Kaplan-Meier methods were used to summarize the occurrence of success and failure by person, by eye, or both. Factors potentially associated with success or failure, such as demographic characteristics, anatomic location of inflammation, dosage, and prior use of immunosuppressive therapies were evaluated by multiple regression analysis using Cox proportional hazards models.[35]

Results

Two hundred fifteen patients (77.2% with bilateral ocular inflammation; 381 eyes) were identified who started cyclophosphamide as a single immunosuppressive agent during follow-up, with or without local or systemic corticosteroids and nonsteroidal anti-inflammatory drugs. The demographic and clinical characteristics of this cohort are summarized in Table 1. The overall median age was 61.3 years (range, 11.5–91.4 years). Most patients were white (83.3%) and female (58.1%). The patients with uveitis were younger than the patients with other forms of ocular inflammation. Mucous membrane pemphigoid was the most common diagnosis in affected eyes (45.6%), followed by scleritis (22.3%) and uveitis (20.4%). A total of 86 patients (40.0%) had received some form of immunosuppressive therapy before starting cyclophosphamide; 161 eyes (42.3%) had a visual acuity of 20/50 or worse at presentation.