

# 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,<sup>1</sup> remain a mainstay of treatment for ocular inflammation.<sup>2</sup> However, dose-dependent side-effects resulting from chronic use (particularly with systemic corticosteroids) and sometimes inadequate response are limitations of such therapy.<sup>3</sup> 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.<sup>3</sup>

Cyclophosphamide, an alkylating agent developed for cancer chemotherapy, first was introduced in 1952 for treatment of uveitis of unknown cause<sup>4</sup> and has been used subsequently for various forms of ocular inflammation.<sup>3</sup> 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.<sup>5,6</sup> Cyclophosphamide can be administered both orally (1–2 mg/kg daily) and intravenously (750–1000 mg/m<sup>2</sup> body surface area every 3 to 4 weeks).<sup>5</sup>

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

rheumatoid vasculitis,<sup>15,16</sup> polyarteritis nodosa,<sup>17,18</sup> systemic lupus erythematosus,<sup>19,20</sup> and mucous membrane pemphigoid (MMP),<sup>21–26</sup> as well as for primary ocular inflammatory conditions including Mooren's ulcer,<sup>27</sup> Behçet's disease,<sup>28–30</sup> and Vogt-Koyanagi-Harada syndrome.<sup>31,32</sup> 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.<sup>33</sup> 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.<sup>33</sup> 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.<sup>34</sup> 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.<sup>35</sup>

## 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.

Table 1. Presenting Characteristics of Patients with Ocular Inflammation at the Time of Starting Cyclophosphamide

Characteristic	Uveitis	Scleritis	Mucous Membrane Pemphigoid	Other	Total
Person-specific characteristics					
No. of patients	44	48	98	25	215
Median age (range), yrs	43.3 (11.5–76.4)	56.3 (21.2–81.4)	68.7 (42.8–91.4)	61.3 (30.3–82.1)	61.3 (11.5–91.4)
Female gender (%)	27 (61.4%)	33 (68.8%)	50 (51.0%)	15 (60.0%)	125 (58.1%)
Race (%)					
White	33 (75.0%)	36 (75.0%)	87 (88.8%)	23 (92.0%)	179 (83.3%)
Black	7 (15.9%)	6 (12.5%)	6 (6.1%)	1 (4.0%)	20 (9.3%)
Other	4 (9.1%)	6 (12.5%)	5 (5.1%)	1 (4.0%)	16 (7.4%)
Duration of inflammation (range), yrs	3.2 (0.0–35.5)	0.7 (–0 to 21.5)	1.0 (0.0–18.1)	0.7 (0.0–9.8)	1.0 (–0 to 35.5)
Bilateral inflammation	37 (84.1%)	28 (58.3%)	91 (92.9%)	10 (40.0%)	166 (77.2%)
Prednisone dose $\leq$ 10 mg/day	14 (31.8%)	20 (41.7%)	33 (33.7%)	14 (56.0%)	81 (37.7%)
Maximum cyclophosphamide dose $\leq$ 75 mg/day	19 (43.2%)	21 (43.8%)	38 (38.8%)	12 (48.0%)	90 (41.9%)
75 mg/day < maximum cyclophosphamide dose $\leq$ 100 mg/day	4 (9.1%)	8 (16.7%)	13 (13.3%)	5 (20.0%)	30 (14.0%)
100 mg/day < maximum cyclophosphamide dose $\leq$ 150 mg/day	10 (22.7%)	7 (14.6%)	30 (30.6%)	6 (24.0%)	53 (24.7%)
150 mg/day $\geq$ maximum cyclophosphamide dose	11 (25.0%)	12 (25.0%)	17 (17.3%)	2 (8.0%)	42 (19.5%)
Oral cyclophosphamide	32 (72.7%)	40 (83.3%)	89 (90.8%)	21 (84.0%)	182 (84.7%)
Prior cyclophosphamide	3 (6.8%)	6 (12.5%)	3 (3.1%)	1 (4.0%)	13 (6.0%)
Prior antimetabolites (other than cyclophosphamide)	18 (40.9%)	18 (37.5%)	28 (28.6%)	7 (28.0%)	71 (33.0%)
Prior alkylating	4 (9.1%)	1 (2.1%)	1 (1.0%)	0 (0.0%)	6 (2.8%)
Prior T cell	14 (31.8%)	6 (12.5%)	1 (1.0%)	2 (8.0%)	23 (10.7%)
Prior biologics	4 (9.1%)	1 (2.1%)	0 (0.0%)	1 (4.0%)	6 (2.8%)
Prior immunosuppressive agent	25 (56.8%)	23 (47.9%)	30 (30.6%)	8 (32.0%)	86 (40.0%)
Eye-specific characteristics					
No. of affected eyes	81	76	189	35	381
20/50 or worse	44 (54.3%)	23 (30.3%)	76 (40.2%)	18 (51.4%)	161 (42.3%)
20/200 or worse	27 (33.3%)	8 (10.5%)	41 (21.7%)	12 (34.3%)	88 (23.1%)
Ocular complications in affected eyes (%)	31 (38.3%)	18 (23.7%)	38 (20.1%)	8 (22.9%)	95 (24.9%)
Overall activity					
Inactive	64 (79.0%)	48 (63.2%)	120 (63.5%)	25 (71.4%)	257 (67.5%)
Slightly active	7 (8.6%)	6 (7.9%)	17 (9.0%)	2 (5.7%)	32 (8.4%)
Active	10 (12.3%)	22 (28.9%)	52 (27.5%)	7 (20.0%)	91 (23.9%)
Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.9%)	1 (0.3%)

Table 2 and Figure 1 summarize the therapeutic outcomes of cyclophosphamide therapy by patient using Kaplan-Meier estimates. Within 6 months, complete control of inflammation (inactive), sustained over at least 2 visits spanning at least 28 days, was observed in 50.2% of patients with uveitis, in 53.3% of patients with scleritis, in 43.0% of patients with ocular MMP, and in 72.0% of patients with other forms of ocular inflammation. When the success criterion was eased to count either completely inactive or slightly active categories by 6 months as a success, the percentage of improvement changed to 52.5%, 61.5%, 56.4%, and 78.0%, respectively, for uveitis, scleritis, MMP, and other forms of ocular inflammation. Success continued to improve through 12 months, by which time sustained, complete inactivity was observed in 81.3% patients with uveitis, in 82.2% of patients with scleritis, in 68.7% of patients with MMP, and in 89.5% of patients with other forms of ocular inflammation. In a sensitivity analysis omitting the requirement that control of inflammation be sustained for at least 28 days, the proportion achieving success increased by approximately 10%. Outcomes were similar within subgroups of uveitis patients, although results for anterior and intermediate uveitis were imprecise because small numbers of patients were treated.

The overall corticosteroid-sparing success rate for complete, sustained control of inflammation at a prednisone dose of 10 mg/day or less within 6 months was 30.1% (95% confidence interval [CI], 23.8%–37.6%), which improved to 61.2% (95% CI,

53.0%–69.5%) by 12 months. The success in reducing corticosteroids to less than 5 mg and 0 mg by 6 months while maintaining complete, sustained control of inflammation was 22.8% and 3.3%, respectively, and 47.8% (95% CI, 39.9%–56.4%) and 12.6% (95% CI, 8.3%–18.9%), respectively, by 12 months. As with control of inflammation, the proportion with corticosteroid-sparing success continued to improve over time. In the sensitivity analysis, omitting the criterion that success be sustained resulted in the overall proportion achieving corticosteroid-sparing success within 6 months increasing to 43.9%.

Disease remission leading to discontinuation of cyclophosphamide occurred in a large proportion of patients, given enough time (see Fig 2 and Table 4). The rate of remission was 0.32/person-year (95% CI, 0.24–0.41), mostly observed after the first year of therapy (clinicians typically continued therapy for 1 year before attempting discontinuation in controlled patients). The estimated proportion of patients with remission at or before 2 and 3 years, respectively, was 63.1% (range, 51.5%–74.8%) and 74.8% (range, 61.6%–86.3%). A Cox regression of time to remission found no relationship between maximum dose and the likelihood of remission ( $P = 0.55$ ). The mean follow-up of patients after remission was 6.2 years.

Factors potentially affecting the likelihood of a favorable outcome were evaluated using multiple regression analysis (see Table 3). Compared with white persons, black persons had a similar

Table 2. Therapeutic Outcomes of Cyclophosphamide Therapy for Inflammatory Eye Disease

Outcome	Uveitis	Scleritis	Mucous Membrane Pemphigoid	Other	Total
Used as only immunosuppressive drug therapy	44	48	98	25	215
Treatment success at or before 6 mos, % (95% confidence interval)					
Controlled inflammation					
No activity at 6 mos	50.2 (33.8–69.2)	53.3 (37.4–71.0)	43.0 (33.0–54.5)	72.0 (49.1–91.0)	49.2 (41.7–57.2)
No activity or slightly active at 6 mos	52.5 (34.4–73.1)	61.5 (45.1–78.1)	56.4 (45.4–68.0)	78.0 (55.0–94.3)	58.9 (51.0–67.0)
Corticosteroid sparing					
Controlled inflammation and prednisone ≤10 mg/day	30.9 (18.3–49.1)	30.2 (17.8–48.1)	25.6 (17.6–36.3)	50.2 (29.1–75.7)	30.1 (23.8–37.6)
Controlled inflammation and prednisone ≤5 mg/day	29.4 (17.0–48.0)	17.9 (8.91–34.1)	19.7 (12.7–29.8)	33.6 (17.3–58.6)	22.8 (17.3–29.7)
Controlled inflammation and prednisone 0 mg/day	5.71 (1.46–21.0)	0.00 (0.00–0.00)	2.22 (0.56–8.60)	10.7 (2.76–36.8)	3.31 (1.50–7.23)
Treatment success at or before 12 months, % (95% confidence interval)					
Controlled inflammation					
No activity at 12 mos	81.3 (63.6–93.8)	82.2 (65.4–94.0)	68.7 (57.0–80.1)	89.5 (65.4–99.2)	76.3 (68.3–83.7)
No activity or slightly active at 12 mos	88.9 (70.8–98.0)	80.0 (62.5–92.9)	80.8 (68.5–90.5)	89.0 (64.2–99.1)	83.4 (75.3–90.0)
Corticosteroid sparing					
Controlled inflammation and prednisone ≤10 mg/day	64.8 (46.5–82.6)	60.5 (44.0–77.5)	58.5 (46.8–70.6)	68.9 (43.6–90.7)	61.2 (53.0–69.5)
Controlled inflammation and prednisone ≤5 mg/day	49.1 (32.6–68.6)	37.8 (23.7–56.7)	48.4 (37.0–61.2)	64.6 (40.7–87.2)	47.8 (39.9–56.4)
Controlled inflammation and prednisone 0 mg/day	16.2 (7.0–34.9)	15.9 (6.90–34.1)	7.65 (3.49–16.3)	23.5 (9.41–51.5)	12.6 (8.30–18.9)

chance of gaining control of inflammation with cyclophosphamide, but were less likely to achieve corticosteroid-sparing success to ≤10 mg than whites (hazard ratio [HR], 0.38; 95% CI, 0.19–0.76). A similar pattern was observed for corticosteroid-sparing success to ≤5 mg (HR, 0.47; 95% CI, 0.23–0.97) and for discontinuation of all steroids (HR, 0.29; 95% CI, 0.12–0.73).

Although patients with ages between 40 to 54 years (HR, 2.28; 95% CI, 1.07–4.86), 55 to 64 years (HR, 2.32; 95% CI, 1.05–5.17), and 65 years or more (HR, 2.35; 95% CI, 1.11–4.99) tended to have greater likelihood than young adults between 18 and 39 years of achieving corticosteroid-sparing success to ≤10 mg, the effect was not consistent for corticosteroid-sparing success to ≤5 mg or 0 mg, nor for control of inflammation. Neither the site of ocular inflammation, prior use of immunosuppression, nor the

presence of autoimmune systemic diseases (not including MMP, which was counted as synonymous with its associated cicatrizing conjunctivitis) were predictive of response to cyclophosphamide. Use of moderate to high dosages of between 100 and 150 mg daily was associated with significantly greater success in controlling inflammation (HR, 1.86; 95% CI, 1.08–3.20) than lower doses of cyclophosphamide (≤75 mg) and was associated with a nonsignificant increase in corticosteroid-sparing success (HR, 1.68; 95% CI, 0.93–3.04). Comparing oral versus intravenous routes of administration, no statistically significant differences in time to control of inflammation (HR, 1.55; 95% CI, 0.82–2.94) or in corticosteroid-sparing success ≤10 mg (HR, 0.90; 95% CI, 0.46–

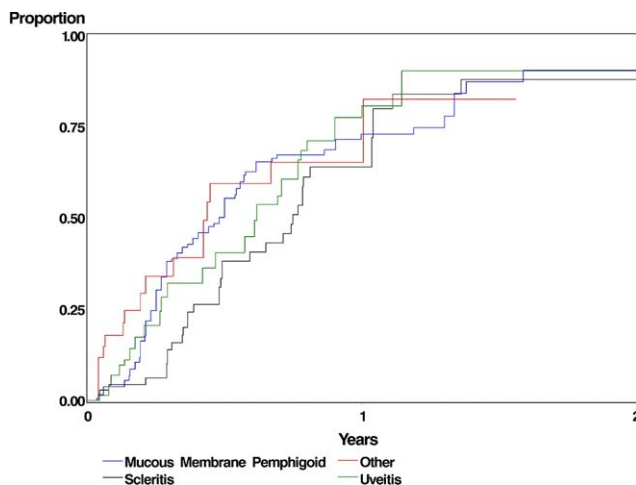


Figure 1. Graph showing the time to complete control of ocular inflammation while taking cyclophosphamide.

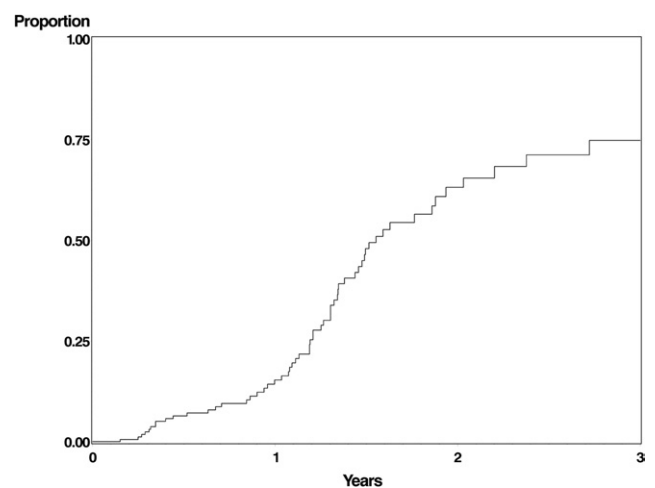


Figure 2. Graph showing the time to remission of ocular inflammation after cyclophosphamide therapy. Many clinicians do not attempt discontinuing cyclophosphamide until disease has been controlled without corticosteroids for an extended period.<sup>3</sup>

Table 3. Reasons for Discontinuation of Cyclophosphamide\*

Reason	No. of Affected Patients	Events per Person-Year (95% Confidence Interval)	Kaplan-Meier Estimate for ≤1 Year (95% Confidence Interval)
Favorable reason			
Remission	61 (28%)	0.32 (0.24–0.41)	†
Unfavorable reasons			
Ineffectiveness	19 (8.8%)	0.099 (0.060–0.15)	9.7 (5.7–16.4)
Discontinuation for side effects	75 (35%)	0.39 (0.31–0.49)	33.5 (26.8–41.4)
Low leukocyte count	38 (18%)	0.20 (0.14–0.27)	18.1 (12.7–25.3)
Low platelet count	3 (1.4%)	0.016 (0.0032–0.046)	1.7 (0.4–7.2)
Anemia	7 (3.3%)	0.036 (0.015–0.075)	3.6 (1.6–8.1)
Opportunistic infection	5 (2.3%)	0.026 (0.0084–0.061)	1.3 (0.3–5.2)
Fatal pneumocystosis	1 (0.5%)	0.0052 (0.0001–0.029)	0.5 (0.1–3.5)
Cystitis/blood in urine	14 (6.5%)	0.073 (0.040–0.12)	7.7 (4.1–14.2)
Sterility	1 (0.5%)	0.0052 (0.0001–0.029)	0.5 (0.1–3.5)
Malaise	1 (0.5%)	0.0052 (0.0001–0.029)	0.5 (0.1–3.6)
Gastrointestinal upset	1 (0.5%)	0.0052 (0.0001–0.029)	0.5 (0.1–3.6)
Liver problem	1 (0.5%)	0.0052 (0.0001–0.029)	0.5 (0.1–3.5)
Other side effects	12 (5.6%)	0.062 (0.032–0.11)	7.9 (4.5–13.6)
Reasons unknown	20 (9.3%)	0.10 (0.064–0.16)	7.7 (4.3–13.3)
Total stopping cyclophosphamide for any reason	164 (76%)	0.85 (0.72–0.99)	50.5 (43.5–57.9)

\*More than one cause could have been scored as contributing to discontinuation of the drug.

†In most cases, clinicians do not attempt discontinuation on grounds of potential disease remission until disease has been quiescent for an extended period after discontinuation of corticosteroids.<sup>3</sup> The Kaplan-Meier estimate for discontinuation on grounds of remission at 2 and 3 years, respectively, was 63.1% and 74.8%.

1.75) were observed, although for control of inflammation, success tended to be greater with oral administration. All these results were similar in a sensitivity analysis where control of inflammation to either the slightly active or inactive level was considered a success.

Cyclophosphamide was discontinued by 33.5% (95% CI, 25.9%–39.6%) of patients within 1 year because of side effects, usually of a reversible nature. Another 10.8% stopped cyclophosphamide for unknown reasons. Low white cell count and cystitis or

Table 4. Cox Regression: Factors Associated with Successful Cyclophosphamide Therapy

Characteristic Name	Variable	Control of Inflammation (Inactive)		Corticosteroid-Sparing Success (≤10 mg Prednisone)	
		Crude Hazard Ratio (95% Confidence Interval)	Adjusted Hazard Ratio (95% Confidence Interval)	Crude Hazard Ratio (95% Confidence Interval)	Adjusted Hazard Ratio (95% Confidence Interval)
Gender	Male	1.46 (1.05–2.03)	1.28 (0.88–1.86)	1.33 (0.92–1.92)	1.17 (0.77–1.78)
Race	White	1.00	1.00	1.00	1.00
	Black	0.64 (0.36–1.14)	0.65 (0.38–1.12)	0.38 (0.20–0.71)	0.38 (0.19–0.76)
	Other	0.61 (0.31–1.20)	0.70 (0.34–1.41)	0.57 (0.26–1.21)	0.64 (0.28–1.43)
Age (yrs)	<18	6.75 (3.89–11.72)	3.17 (0.27–37.95)	37.25 (17.91–77.46)	5.95 (0.71–50.19)
	18–39	1.00	1.00	1.00	1.00
	40–54	1.25 (0.72–2.15)	1.13 (0.57–2.26)	2.09 (1.11–3.94)	2.28 (1.07–4.86)
	55–64	1.08 (0.58–2.00)	0.92 (0.42–2.01)	2.08 (1.08–3.99)	2.32 (1.05–5.17)
	65 or more	0.93 (0.58–1.50)	0.85 (0.44–1.65)	2.05 (1.15–3.64)	2.35 (1.11–4.99)
Type of inflammation	Mucous membrane pemphigoid	1.00	1.00	1.00	1.00
	Uveitis	1.08 (0.71–1.64)	1.07 (0.59–1.93)	0.96 (0.60–1.54)	1.49 (0.79–2.79)
	Scleritis	0.97 (0.64–1.48)	1.09 (0.70–1.69)	0.71 (0.46–1.10)	0.88 (0.56–1.37)
	Other	1.58 (0.84–2.96)	1.39 (0.67–2.86)	1.25 (0.57–2.73)	1.46 (0.64–3.35)
Previous cyclophosphamide	Yes	0.82 (0.41–1.64)	1.17 (0.50–2.73)	1.15 (0.57–2.30)	1.31 (0.56–3.06)
Antimetabolite(s) before treatment	Yes	0.77 (0.53–1.11)	0.84 (0.53–1.34)	0.98 (0.66–1.46)	0.84 (0.51–1.37)
Biologic(s) before treatment	Yes	3.53 (0.89–13.96)	4.82 (0.41–56.46)	10.04 (2.59–38.87)	7.52 (0.90–62.73)
Alkylating agent(s) before treatment	Yes	0.82 (0.52–1.29)	1.42 (0.67–3.03)	0.56 (0.17–1.78)	1.08 (0.43–2.71)
Route (oral)	Yes	1.95 (1.18–3.20)	1.55 (0.82–2.94)	1.27 (0.76–2.14)	0.90 (0.46–1.75)
Dosage (mg)	≤75	1.00	1.00	1.00	1.00
	75 < dose ≤ 100	1.31 (0.73–2.37)	1.05 (0.57–1.95)	1.12 (0.62–2.03)	1.26 (0.67–2.36)
	100 < dose ≤ 150	2.14 (1.33–3.45)	1.86 (1.08–3.20)	1.67 (1.00–2.77)	1.68 (0.93–3.04)
	Dose > 150	1.71 (1.04–2.82)	1.63 (0.93–2.87)	0.99 (0.56–1.73)	1.18 (0.61–2.26)
Systemic (extraocular) autoimmune disease	Yes	1.12 (0.76–1.64)	1.36 (0.86–2.17)	1.01 (0.68–1.49)	1.08 (0.67–1.76)

blood in the urine were the most common toxicities, leading to discontinuation in 18.1% and 7.7%, respectively, within the first year of therapy. Opportunistic infections led to discontinuation in 3.0% (95% CI, 1.2%–7.1%) of the patients in the first year, including *Pneumocystis carinii* pneumonia leading to death in 1 patient (0.5%) who had been managed in accordance with commonly accepted guidelines,<sup>2</sup> but who had not taken preemptive *Pneumocystis* prophylaxis. Therapy was discontinued within 1 year in 9.7% (95% CI, 5.7%–16.4%) of the patients because of failure to control inflammation.

A search for factors affecting discontinuation of cyclophosphamide for toxicity using multiple regression analysis showed that black persons were less likely to discontinue cyclophosphamide because of side effects compared with white persons (adjusted HR, 0.23; 95% CI, 0.10–0.56). Patients receiving doses between 100 to 150 mg daily tended to discontinue cyclophosphamide for toxicity more often than patients receiving lesser doses (adjusted HR, 1.81; 95% CI, 0.94–3.48).

## Discussion

This report confirms the beneficial effects of cyclophosphamide therapy for ocular inflammation. Cyclophosphamide was successful in achieving complete control of inflammation in 49.2% and 76.3% by 6 months and 12 months, respectively. Similarly, corticosteroid-sparing success (sustained control of inflammation while tapering prednisone to 10 mg or less) was gained by 30.1% and 61.2% by 6 and 12 months, respectively. At or before 2 years after initiation of treatment, 63% were able to discontinue therapy because of disease remission. Other studies have suggested varying success rates of cyclophosphamide in treating different forms of ocular inflammation with small sample sizes, using different outcome definitions, which makes comparison between studies difficult.<sup>9,22,36–41</sup>

However, the success in terms of control of inflammation observed in this study seems lower than in some of these prior reports,<sup>36,38,39</sup> likely because of the more stringent definition of success, the inclusion of only patients observed from the initiation of therapy who did not have the benefit of treatment before the initiation of observation time, and perhaps publication bias (particularly for the small case series reported). Although the conservative success criterion, requiring documentation of success at visits spanning at least 28 days, might have resulted in a lower success rate, it is arguably a more satisfactory definition of success. Sensitivity analysis at which success in control of inflammation or corticosteroid sparing omitted the requirement for sustained success indeed improved success to levels more similar comparable with some of the above studies (76%). Although all centers participating in the study were tertiary centers, which tend to see more severe disease than less specialized centers, most other reports derive from tertiary centers as well. Nevertheless, all the available reports suggest that cyclophosphamide is effective for the control of most, but not all, patients with ocular inflammation.

Sixty-one patients discontinued cyclophosphamide after achieving remission at the rate of 0.32 remissions/person-year, which is lower than the 0.50/person-year (95% CI, 0.37–0.67/person-year) rate in a report of an overlapping group of ocular pemphigoid patients,<sup>38</sup> although the former

reflects the rate of remission among all patients treated and the latter is the rate of remission only among the 82.9% subset of patients whose disease initially was controlled by cyclophosphamide. Thus, although the estimate of the remission rate is lower, it is unlikely that the result is different to a statistically significant degree. Two possible reasons why this study observed a lower remission rate include the possibility that some patients scored as discontinuing cyclophosphamide for toxicity might have gone on to have disease remission but not be counted as such and the exclusion of patients who had the benefit of starting cyclophosphamide therapy before cohort entry—who may have reached remission sooner. In addition, the definition of remission was based on the reason for discontinuation of therapy, rather than using a definition based on follow-up after discontinuation,<sup>38</sup> because of constraints of the data available. In any case, the results suggest that the substantial majority of patients able to continue therapy are likely to achieve medication-free remission in 2 years or less, a much higher rate of remission than that observed in studies of methotrexate,<sup>42</sup> azathioprine,<sup>43</sup> mycophenolate mofetil (to be published separately), and cyclosporine (to be published separately).

Full doses in the range of 100 to 150 mg were more effective in controlling inflammation compared with doses of <100 mg, but were more likely to lead to dose-limiting toxicity, confirming that clinicians should use full dosing (1–2 mg/kg) whenever it can be tolerated.<sup>5</sup> Guidelines about how to implement such treatment are available.<sup>2</sup> The observation that black persons tended to be less likely to achieve corticosteroid-sparing success compared with white persons, but had no significant difference with respect to control of inflammation, may be a random effect or a true difference and requires confirmation by supplemental studies. Neither the site of ocular inflammation nor prior use of immunosuppressive therapy seemed to affect the likelihood of success with cyclophosphamide.

A consensus panel on immunosuppression for ocular disease concluded, based on previous available studies,<sup>41,44</sup> that pulsed cyclophosphamide therapy for uveitis is less effective than oral cyclophosphamide.<sup>3</sup> A randomized clinical trial<sup>45</sup> in Wegener's granulomatosis patients concluded that pulse cyclophosphamide was as effective as oral cyclophosphamide in achieving initial remission and was associated with fewer side effects and lower mortality. However, in the long term, treatment with pulse cyclophosphamide neither maintained remission nor prevented relapses as well as oral cyclophosphamide had. In the authors' experience, the likelihood of treatment success tended to be higher with oral cyclophosphamide, but not to a statistically significant degree. Bladder toxicity and bladder cancer risk, some of the major toxicities of cyclophosphamide, may be reduced when the drug is administered intermittently via the intravenous route, compared with oral daily dosing.<sup>46,47</sup> Thus, although the available information suggests that oral administration may be more effective than intravenous administration of cyclophosphamide, considerations regarding the potentially lower risks of side effects with intravenous cyclophosphamide leave open the question as to which should be the preferred approach for ocular inflammation.

Although—given enough time—cyclophosphamide usually was successful in controlling ocular inflammation, a clinically important degree of side effects occurred, requiring discontinuation of therapy in a large minority of patients and leading to 7 (3.3%) opportunistic infections with 1 death. The most common side effects leading to drug discontinuation were leukopenia (18.1%) and cystitis or hematuria (7.7%). Various other studies have reported a higher incidence of the side effects in the range of 18% to 46% for leukopenia and 8% to 33% for hemorrhagic cystitis.<sup>25,48–51</sup> These differences in results probably derive from the fact that only problems resulting in discontinuation of therapy were recorded. Gonadal dysfunction has been observed in 60% of the patients after 6 months of treatment with cyclophosphamide.<sup>52</sup> In this study, only 1 patient discontinued because of sterility, although patients likely anticipated this risk when starting the medication. Ocular side effects including dry eyes, blurred vision, and rise in intraocular pressure have been noted,<sup>53</sup> which this study did not address. Based on the authors' experience with opportunistic infections, they have adopted the routine use of trimethoprim-sulfamethoxazole prophylaxis in patients treated with cyclophosphamide. This approach is frequent, but not universal, among rheumatologists using cyclophosphamide for systemic inflammatory diseases.<sup>54</sup>

There is considerable evidence suggesting that cyclophosphamide increases the risk of certain kinds of malignancy, and perhaps the overall risk of malignancy.<sup>47,55,56</sup> A study of ocular inflammation patients also demonstrated that cyclophosphamide is not associated with a statistically significant increase in overall mortality (adjusted HR, 1.14;  $P = 0.45$ ), but found that cancer mortality tended to be higher with respect to unexposed cohort (adjusted cancer mortality HR, 1.61;  $P = 0.17$ ) and the United States general population (cancer-specific standard mortality ratio, 1.42;  $P = 0.056$ ).<sup>57</sup> Thus, the results may be consistent with a clinically important increase in overall cancer mortality, as suggested by a minority of reports based on the clinical experience in other fields.<sup>47,58,59</sup> These toxicity considerations suggest that use of cyclophosphamide should be limited to the most vision-threatening cases of ocular inflammation and to cases where associated systemic disease provides an indication for the use of cyclophosphamide.

Cyclophosphamide also is teratogenic, causing skeletal and central nervous system abnormalities.<sup>60,61</sup> Therefore, use of effective contraception during cyclophosphamide therapy is required. Cyclophosphamide also can be excreted in breast milk, suggesting that mothers of infants should not breastfeed if cyclophosphamide therapy must be used.<sup>60,62</sup>

Limitations of this retrospective, observational study include potential indications-for-treatment bias, missing data in chart notes, incomplete follow-up, and potential referral bias. Alkylating agents typically have been reserved for severe cases, and it is possible that results would have been better if the drugs were used in milder cases. However, the side effect concerns suggest that limiting use to more severe cases is appropriate. The centers involved were selected in part because of their habits of maintaining complete records to minimize missing data problems. Data were collected by trained expert ophthalmologist reviewers as per protocol in all the centers<sup>63</sup> to minimize ascertainment bias. Ascertain-

ment of treatment success and side effects likely was good because the patients typically are assessed every 4 to 6 weeks with monitoring blood work more often than that at all centers, although occasional successes and adverse effects might have been missed. The survival analysis approach assumes that patients lost to follow-up are similar to patients continuing in the study; that patients starting a second immunosuppressive drug were censored might have resulted in a slight overestimation of benefits in the analyses of successes. Referral bias is a concern in studies from tertiary care centers, but these results should be generalizable to tertiary ocular inflammation centers, where aggressive immunosuppression with cyclophosphamide typically is managed.

Strengths of the study include the large size of the cohort, assessment of the effects of cyclophosphamide as a single agent to avoid ascribing effects from second agents to cyclophosphamide, observation of patients from the time of initiation of therapy, and the ability to compare oral and intravenous therapies with respectable statistical power. Uniform data collection was promoted by quality control checks within the data system and by using data centers with extensive ophthalmologic clinical experience.<sup>33</sup> More comprehensive analyses were carried out than have been used by most prior reports; also, a more realistic measure of treatment success than some prior reports was used. In addition, sensitivity analyses were conducted by changing the treatment success criteria to assess the robustness of the results.

In summary, these data suggest that—given enough time—cyclophosphamide is effective for most patients with uveitis, scleritis, ocular MMP, and other forms of ocular inflammation. Cyclophosphamide also has the advantage of a high rate of medication-free remission after treatment, which in the authors' experience usually is not seen with alternative immunosuppressive treatments. However, the risk of side effects is substantially greater than that associated with alternative agents and requires very careful monitoring and possibly preemptive antiopportunistic infection prophylaxis.<sup>64,65</sup> This concern, along with the apparent increase in the risk of cancer after therapy, suggests that cyclophosphamide is best reserved for patients at high risk of substantial vision loss for whom other forms of treatment have failed or are unlikely to succeed. However, clinicians should not be hesitant to use cyclophosphamide in instances where underlying systemic inflammatory diseases require such therapy, where cyclophosphamide may be life saving. If tolerable, doses in the 100 to 150 mg/day range seem to be more likely to succeed than lower doses.

## References

1. Gordon DM, McLean JM, Koteen H, et al. The use of ACTH and cortisone in ophthalmology. *Am J Ophthalmol* 1951;34:1675–86.
2. Foster CS, Vitale AT. Treatment of uveitis: overview. In: Foster CS, Vitale AT, eds. *Diagnosis and Treatment of Uveitis*. Philadelphia: W.B. Saunders; 2002:142.
3. Jabs DA, Rosenbaum JT, Foster CS, et al. Guidelines for the use of immunosuppressive drugs in patients with ocular in-

- flammatory disorders: recommendations of an expert panel. *Am J Ophthalmol* 2000;130:492–513.
4. Roda Perez E. Nitrogen mustard therapy of uveitis of unknown etiology [undetermined language]. *Rev Clin Esp* 1952;44:173–80.
  5. Hemady R, Tauber J, Foster CS. Immunosuppressive drugs in immune and inflammatory ocular disease. *Surv Ophthalmol* 1991;35:369–85.
  6. Gery I, Nussenblatt RB. Immunosuppressive drugs. In: Sears ML, ed. *Pharmacology of the Eye*. Berlin: Springer-Verlag; 1984:586–609. *Handbook of Experimental Pharmacology*. vol. 69.
  7. Tervaert JW, Stegeman CA. Treatment of patients with Wegener's granulomatosis or ANCA-associated vasculitis [in Dutch]. *Ned Tijdschr Geneesk* 2003;147:2265–7.
  8. Leavitt RY, Fauci AS. Wegener's granulomatosis. *Curr Opin Rheumatol* 1991;3:8–14.
  9. Biswas J, Babu K, Gopal L, et al. Ocular manifestations of Wegener's granulomatosis: analysis of nine cases. *Indian J Ophthalmol* 2003;51:217–23.
  10. Charles SJ, Meyer PA, Watson PG. Diagnosis and management of systemic Wegener's granulomatosis presenting with anterior ocular inflammatory disease. *Br J Ophthalmol* 1991;75:201–7.
  11. Cuende E, Mena AR, Andonegui J, et al. Ocular involvement in Wegener's granulomatosis responding to intravenous cyclophosphamide [letter]. *Rheumatology (Oxford)* 2001;40:1066–8.
  12. Fauci AS, Haynes BF, Katz P, Wolff SM. Wegener's granulomatosis: prospective clinical and therapeutic experience with 85 patients for 21 years. *Ann Intern Med* 1983;98:76–85.
  13. Reinhold-Keller E, Kekow J, Schnabel A, et al. Influence of disease manifestation and antineutrophil cytoplasmic antibody titer on the response to pulse cyclophosphamide therapy in patients with Wegener's granulomatosis. *Arthritis Rheum* 1994;37:919–24.
  14. Rihova E, Havlikova M, Michalova K, Poch T. Diagnosis and therapy of Wegener's granulomatosis based on ocular changes [in Czech]. *Cesk Slov Oftalmol* 1997;53:223–8.
  15. Jackson CG, Williams HJ. Disease-modifying antirheumatic drugs: using their clinical pharmacological effects as a guide to their selection. *Drugs* 1998;56:337–44.
  16. Young A, Koduri G. Extra-articular manifestations and complications of rheumatoid arthritis. *Best Pract Res Clin Rheumatol* 2007;21:907–27.
  17. Colmegna I, Maldonado-Cocco JA. Polyarteritis nodosa revisited. *Curr Rheumatol Rep* 2005;7:288–96.
  18. Pagnoux C, Guilpain P, Guillevin L. Microscopic polyangiitis [in French]. *Presse Med* 2007;36:895–901.
  19. Sibilija J. Treatment of systemic lupus erythematosus in 2006. *Joint Bone Spine* 2006;73:591–8.
  20. Spertini F. New concepts for the therapy of systemic lupus erythematosus [in French]. *Rev Med Suisse* 2007;3:98–102.
  21. Kirtschig G, Murrell D, Wojnarowska F, Khumalo N. Interventions for mucous membrane pemphigoid/cicatricial pemphigoid and epidermolysis bullosa acquisita: a systematic literature review. *Arch Dermatol* 2002;138:380–4.
  22. Saw VP, Dart JK, Rauz S, et al. Immunosuppressive therapy for ocular mucous membrane pemphigoid: strategies and outcomes. *Ophthalmology* 2008;115:253–61.
  23. Elder MJ, Lightman S, Dart JK. Role of cyclophosphamide and high dose steroid in ocular cicatricial pemphigoid. *Br J Ophthalmol* 1995;79:264–6.
  24. Marx W, Reinhard T, Megahed M, Sundmacher R. Immunology-related chronic progressive cicatricial conjunctival diseases: diagnosis, therapy and prognosis [in German]. *Ophthalmologie* 2001;98:185–93.
  25. Miserocchi E, Baltatzis S, Roque MR, et al. The effect of treatment and its related side effects in patients with severe ocular cicatricial pemphigoid. *Ophthalmology* 2002;109:111–8.
  26. Musette P, Pascal F, Hoang-Xuan T, et al. Treatment of cicatricial pemphigoid with pulse intravenous cyclophosphamide [letter]. *Arch Dermatol* 2001;137:101–2.
  27. Tiev KP, Borderie VM, Briant M, et al. Severe Moorens ulcer: efficacy of monthly cyclophosphamide intravenous pulse treatment [in French]. *Rev Med Interne* 2003;24:118–22.
  28. Kazokoglu H, Saatci O, Cuhadaroglu H, Eldem B. Long-term effects of cyclophosphamide and colchicine treatment in Behcet's disease. *Ann Ophthalmol* 1991;23:148–51.
  29. Mishima S, Masuda K, Izawa Y, et al. The eighth Frederick H. Verhoeff Lecture, presented by Saiichi Mishima, MD. Behcet's disease in Japan: ophthalmologic aspects. *Trans Am Ophthalmol Soc* 1979;77:225–79.
  30. Oniki S, Kurakazu K, Kawata K. Treatment of Behcet's disease with cyclophosphamide [in Japanese]. *Nippon Ganka Gakkai Zasshi* 1973;77:508–15.
  31. Moorthy RS, Inomata H, Rao NA. Vogt-Koyanagi-Harada syndrome. *Surv Ophthalmol* 1995;39:265–92.
  32. Touitou V, Escande C, Bodaghi B, et al. Diagnostic and therapeutic management of Vogt-Koyanagi-Harada syndrome [in French]. *J Fr Ophtalmol* 2005;28:9–16.
  33. Kempen JH, Daniel E, Gangaputra S, et al. Methods for identifying long-term adverse effects of treatment in patients with eye diseases: the Systemic Immunosuppressive Therapy for Eye Diseases (SITE) Cohort Study. *Ophthalmic Epidemiol* 2008;15:47–55.
  34. Schimmer BP, Parker KL. Adrenocorticotrophic hormone; adrenocortical steroids and their synthetic analogs; inhibitors of the synthesis and actions of adrenocortical hormones. In: Brunton LL, Lazo JS, Parker KL, eds. *Goodman and Gilman's The Pharmacological Basis of Therapeutics*. 11th ed. McGraw-Hill; 2006:1587–1612.
  35. Cox DR, Oakes D. *Analysis of Survival Data*. London: Chapman & Hall; 1984:91–110. *Monographs on Statistics and Applied Probability* 21.
  36. Foster CS. Cicatricial pemphigoid. *Trans Am Ophthalmol Soc* 1986;84:527–663.
  37. Mondino BJ, Brown SI. Immunosuppressive therapy in ocular cicatricial pemphigoid. *Am J Ophthalmol* 1983;96:453–9.
  38. Thorne JE, Woreta FA, Jabs DA, Anhalt GJ. Treatment of ocular mucous membrane pemphigoid with immunosuppressive drug therapy. *Ophthalmology* 2008;115:2146–52.
  39. Durrani K, Papaliodis GN, Foster CS. Pulse IV cyclophosphamide in ocular inflammatory disease: efficacy and short-term safety. *Ophthalmology* 2004;111:960–5.
  40. Jampol LM, West C, Goldberg MF. Therapy of scleritis with cytotoxic agents. *Am J Ophthalmol* 1978;86:266–71.
  41. Rosenbaum JT. Treatment of severe refractory uveitis with intravenous cyclophosphamide. *J Rheumatol* 1994;21:123–5.
  42. Gangaputra S, Newcomb CW, Liesegang TL, et al. Methotrexate for ocular inflammatory diseases. *Ophthalmology* 2009;116:2188–98.
  43. Pasadhika S, Kempen JH, Newcomb CW, et al. Azathioprine for ocular inflammatory diseases. *Am J Ophthalmol* 2009;148:500–9.
  44. Ozyazgan Y, Yurdakul S, Yazici H, et al. Low dose cyclosporin A versus pulsed cyclophosphamide in Behcet's syndrome: a single masked trial. *Br J Ophthalmol* 1992;76:241–3.
  45. Guillevin L, Cordier JF, Lhote F, et al. A prospective, multicenter, randomized trial comparing steroids and pulse cyclo-

- phosphamide versus steroids and oral cyclophosphamide in the treatment of generalized Wegener's granulomatosis. *Arthritis Rheum* 1997;40:2187-98.
46. Martin F, Lauwerys B, Lefebvre C, et al. Side-effects of intravenous cyclophosphamide pulse therapy. *Lupus* 1997;6:254-7.
  47. Kempen JH, Gangaputra S, Daniel E, et al. Long-term risk of malignancy among patients treated with immunosuppressive agents for ocular inflammation: a critical assessment of the evidence. *Am J Ophthalmol* 2008;146:802-12.
  48. Neumann R, Foster CS. Corticosteroid-sparing strategies in the treatment of retinal vasculitis in systemic lupus erythematosus. *Retina* 1995;15:201-12.
  49. Akova YA, Jabbur NS, Foster CS. Ocular presentation of polyarteritis nodosa: clinical course and management with steroid and cytotoxic therapy. *Ophthalmology* 1993;100:1775-81.
  50. Foster CS, Forstot SL, Wilson LA. Mortality rate in rheumatoid arthritis patients developing necrotizing scleritis or peripheral ulcerative keratitis: effects of systemic immunosuppression. *Ophthalmology* 1984;91:1253-63.
  51. Messmer EM, Foster CS. Destructive corneal and scleral disease associated with rheumatoid arthritis: medical and surgical management. *Cornea* 1995;14:408-17.
  52. Fairley KF, Barrie JU, Johnson W. Sterility and testicular atrophy related to cyclophosphamide therapy. *Lancet* 1972;1:568-9.
  53. Fraunfelder FT, Meyer SM. Ocular toxicity of antineoplastic agents. *Ophthalmology* 1983;90:1-3.
  54. Gupta D, Zachariah A, Roppelt H, et al. Prophylactic antibiotic usage for *Pneumocystis jirovecii* pneumonia in patients with systemic lupus erythematosus on cyclophosphamide: a survey of US rheumatologists and the review of literature. *J Clin Rheumatol* 2008;14:267-72.
  55. Park MC, Park YB, Jung SY, et al. Risk of ovarian failure and pregnancy outcome in patients with lupus nephritis treated with intravenous cyclophosphamide pulse therapy. *Lupus* 2004;13:569-74.
  56. Asten P, Barrett J, Symmons D. Risk of developing certain malignancies is related to duration of immunosuppressive drug exposure in patients with rheumatic diseases. *J Rheumatol* 1999;26:1705-14.
  57. Kempen JH, Daniel E, Dunn JP, et al. Overall and cancer-related mortality among patients with ocular inflammation treated with immunosuppressive drugs: retrospective cohort study. *BMJ* 2009;339:b2480.
  58. Baltus JA, Boersma JW, Hartman AP, Vandenbroucke JP. The occurrence of malignancies in patients with rheumatoid arthritis treated with cyclophosphamide: a controlled retrospective follow-up. *Ann Rheum Dis* 1983;42:368-73.
  59. Baker GL, Kahl LE, Zee BC, et al. Malignancy following treatment of rheumatoid arthritis with cyclophosphamide: long-term case-control follow-up study. *Am J Med* 1987;83:1-9.
  60. Ostensen M. Treatment with immunosuppressive and disease modifying drugs during pregnancy and lactation. *Am J Reprod Immunol* 1992;28:148-52.
  61. Porter AJ, Singh SM. Transplacental teratogenesis and mutagenesis in mouse fetuses treated with cyclophosphamide. *Teratog Carcinog Mutagen* 1988;8:191-203.
  62. Rubin B, Palestine AG. Complications of corticosteroid and immunosuppressive drugs. *Int Ophthalmol Clin* 1989;29:159-71.
  63. Standardization of Uveitis Nomenclature (SUN) Working Group. Standardization of uveitis nomenclature for reporting clinical data: results of the first international workshop. *Am J Ophthalmol* 2005;140:509-16.
  64. Stegeman CA, Tervaert JW, de Jong PE, Kallenberg CG. Dutch Co-trimoxazole Wegener Study Group. Trimethoprim-sulfamethoxazole (co-trimoxazole) for the prevention of relapses of Wegener's granulomatosis. *N Engl J Med* 1996;335:16-20.
  65. Chung JB, Armstrong K, Schwartz JS, Albert D. Cost-effectiveness of prophylaxis against *Pneumocystis carinii* pneumonia in patients with Wegener's granulomatosis undergoing immunosuppressive therapy. *Arthritis Rheum* 2000;43:1841-8.

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