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Risk of Ocular Complications in Patients with Noninfectious Intermediate Uveitis, Posterior Uveitis, or Panuveitis

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Purpose: Noninfectious uveitis results in vision loss and ocular complications without adequate treatment. We compared the risk of developing ocular complications between patients with noninfectious intermediate uveitis, posterior uveitis, or panuveitis (NIIPPU) and matched controls.

Design: Retrospective analysis of insurance claims data (OptumHealth, Eden Prairie, MN; January 1, 1998–March 31, 2012).

Participants: Cases 18 to 64 years of age with 2 or more NIIPPU diagnoses (International Classification of Diseases, 9th Revision, Clinical Modification codes) were matched 1:1 by sex, age, region, company, employment status, and index date with controls without uveitis. Patients with an ocular complication during baseline were excluded.

Methods: Continuous eligibility for 6 months or more before the first NIIPPU diagnosis date was required. Risks of ocular complications developing during patients' continuous eligibility in the study period were compared using unadjusted Kaplan-Meier survival analysis to estimate risk of and time to complications and adjusted Cox regression analysis to estimate hazard ratios (HRs).

Main Outcome Measures: Percentages of cases and controls who demonstrate ocular complications and 1-, 5-, and 10-year risks and HRs for each complication.

Results: Mean age of the 1769 cases and matched controls was 47 years and 47% were men; 302 cases had persistent NIIPPU. During the study period, NIIPPU cases had a higher risk of any ocular complication ($P < 0.001$); the 5-year risk of any ocular complication was 66% for patients versus 24% for controls. Specifically, NIIPPU patients had greater 5-year risks of glaucoma (20% vs. 9%), cataract (35% vs. 13%), visual disturbance (29% vs. 9%), blindness or low vision (5% vs. 0.5%), retinal detachment (11% vs. 0.8%), and retinal disorder (28% vs. 2%) compared with controls. Hazard ratios indicated greater risks of ocular complications in cases versus controls during the overall observation period (HR, 5.2 for any ocular complication; HR, 4.8 for visual disturbance; HR, 3.2 for cataract; and HR, 2.7 for glaucoma; all $P < 0.001$). Hazard ratios for persistent cases indicated even greater risks.

Conclusions: Noninfectious intermediate uveitis, posterior uveitis, or panuveitis, particularly persistent disease, is associated with a substantial risk of ocular complications. Optimal treatment initiatives remain imperative to reduce the ocular complication–related burden of NIIPPU. *Ophthalmology 2016;123:655-662 © 2016 by the American Academy of Ophthalmology. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).*

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Uveitis is an umbrella term that refers to infectious or noninfectious inflammation in the uveal tract and adjacent structures of the eye, depending on the anatomic site of maximum inflammation. Prevalence estimates of uveitis vary by country, race, age, and cause of the disease. Overall prevalence estimates in the United States, including both infectious and noninfectious uveitis, range from 58 to 115 cases per 100 000 persons.[1–3] Approximately 10% to 15% of preventable blindness in Western countries is caused by uveitis and associated complications.[4–7] In addition, major vision loss (defined as best-corrected visual acuity ≤20/50) has been reported in 20% to 70% of patients treated in uveitis referral centers or academic ophthalmology clinics.[5,7,8]

Uveitis is classified by the primary anatomic location of the inflammation according to the Standardization of Uveitis Nomenclature guidelines and also whether it is caused by an infectious agent or is associated with an immune-mediated disease.[9] Anterior uveitis, which refers to inflammation of the iris and ciliary body, is the most common form in Western countries,[10,11] accounting for 91% of cases in community-based clinics and more than 50% in tertiary care

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centers.[8,12–15] Although less common than anterior uveitis, noninfectious intermediate uveitis, posterior uveitis, or panuveitis (NIIPPU) typically either is idiopathic and comprises many well-defined uveitic ocular conditions or is associated with systemic underlying autoimmune disorders, both of which present with varying degrees of ocular comorbidities; these complications account for most uveitis-related visual morbidity in these patients.[5,16–18] Therefore, the goal remains to subdue inflammation and to prevent complications associated with persistent inflammation complications, where the mainstay of therapy includes corticosteroids, other immunosuppressive agents, or both.[19,20]

Vision-threatening complications in patients with NIIPPU include macular edema, cataract, glaucoma, vitreous debris, and retinopathy, with macular edema remaining the most frequently encountered structural complication of uveitis that results in central visual impairment.[5–8,15,18,21,22] In a retrospective study from 2 uveitis referral centers in the Netherlands, 41% of patients with intermediate uveitis, 28% with posterior uveitis, and 53% with panuveitis had cystoid macular edema, which accounted for 41% of visual impairment and 29% of blindness in these patients.[5] In other studies, macular edema has been estimated to be present in 85% of cases of intermediate uveitis, 35% of cases of panuveitis, and 20% of cases of posterior uveitis, causing up to 30% of permanent uveitis-related vision loss.[7,23,24] Cataract is another significant cause of vision loss in patients with uveitis, present in 18% to 35% of patients.[7,15]

Long-term corticosteroid use (systemic or local) for the treatment of uveitis can lead to glaucoma and cataract, to which significant ocular morbidity can be attributed.[25–27] Overall, the morbidity and burden associated with uveitis and these complications remain a significant cost for health care systems.[28] For the patients, there also remains a negative effect on quality of life.[28–33] To provide additional data informing the burden of disease, we aimed to assess the risk of ocular complications in a privately insured NIIPPU cohort in the United States compared with matched controls without uveitis. In addition, an analysis of persistent NIIPPU cases was conducted.

Methods

Data Source and Patient Sample

Patients were identified using the OptumHealth (Eden Prairie, MN) Reporting and Insights database from January 1998 through March 2012.[34] The OptumHealth database includes medical and drug claims for 16.4 million privately insured individuals in 69 self-insured companies and represents a diversity of industry sectors, such as financial services, manufacturing, telecommunications, energy, and the food and beverage industry. Available data include employees' benefit eligibility and medical and pharmacy service claims. The OptumHealth database is compliant with the American Health Insurance Portability and Accountability Act; ethics approval was not required for this study because the data analyzed were de-identified records from an administrative insurance database.

Patients 18 to 64 years old with a diagnosis of NIIPPU were identified using International Classification of Diseases, Ninth Revision, Clinical Modification codes for intermediate uveitis, posterior uveitis, or panuveitis (360.12 [panuveitis], 362.12 [exudative retinopathy], 362.18 [retinal vasculitis], 363.0x [focal chorioretinitis and focal retinochoroiditis], 363.10–13 and 363.15 [disseminated chorioretinitis and disseminated retinochoroiditis], 363.2x [other and unspecified forms of chorioretinitis and retinochoroiditis], and 364.24 [Vogt-Koyanagi syndrome]). A diagnosis of uveitis had to be on at least 2 medical claims to confirm the presence of the condition. These codes were modified from those used by Reeves et al[35] to exclude anterior diagnoses and those likely to be infectious. Data for the subgroup of cases with persistent NIIPPU, defined as cases with disease duration of 90 days or more and receiving standard of care such as corticosteroids, immunosuppressant therapy, biologic therapy, or a combination thereof, also were analyzed.[9]

The index date for each case was the first diagnosis of NIIPPU. Cases were required to have continuous eligibility (defined as no more than a 30-day gap between health plan enrollment segments) and no preexisting ocular complications during the baseline period (6-month period before first NIIPPU diagnosis; incident cases were identified during the 6-month baseline period). Potential controls were assigned the index date of their case match. Patients with NIIPPU with no preexisting ocular complications were matched 1:1 by sex, age, region, company, and employment status to controls without a diagnosis of uveitis. The study period spanned from the index date through the duration of continuous eligibility for each patient (Fig 1).

Ocular Outcomes and Risk Factors

Ocular complications were identified by International Classification of Diseases, 9th Revision, Clinical Modification codes and included glaucoma (365.xx); cataract (366.xx); visual disturbances (368.xx, 379.23, and 379.24), including vitreous opacities and vitreous hemorrhage; blindness or low vision (369.xx and 360.41), including blind hypotensive eye (phthisis bulbi); retinal detachment (361.xx); and retinal disorder, including cystoid macular degeneration (cystoid macular edema), retinal ischemia, retinal neovascularization, macular cyst/hole/pseudohole, macular puckering (epiretinal membrane), and retinal (macular) edema (362.53, 362.84, 362.16, 362.54, 362.56, and 362.83, respectively). The primary outcome of interest was time from the index date to the first occurrence of each of the ocular complication events. Time to any ocular complication was calculated as the time from the index date to the day of the first observed claim for any of the ocular complications under investigation. Risk factors and other causes relevant to each ocular complication were identified as potential covariates based on a literature review and were defined using International Classification of Diseases, Ninth Revision, Clinical Modification codes[36–49] (Table 1, available at www.aaojournal.org).

Statistical Analysis

Baseline characteristics were compared using univariate analyses. McNemar's tests were used for categorical variables and Wilcoxon signed-rank tests were used for continuous variables. Time to development of ocular complications during the study period was compared using unadjusted Kaplan-Meier survival analysis and log-rank tests. Patients without a claim for an ocular complication during the study period were censored at the last day of follow-up in the study period. The 1-, 5-, and 10-year risks of developing complications were estimated using Kaplan-Meier survival analysis. Adjusted Cox proportional-hazards regression models were used to estimate hazard ratios (HRs) for NIIPPU cases relative to controls, adjusting for age, sex, region, and Charlson comorbidity