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Prognostic Factors in Syphilitic Uveitis

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Purpose: To identify predictors of treatment success in syphilitic uveitis (SU).

Design: Retrospective multicentric analysis of patients treated for SU.

Participants: A total of 95 eyes (66 patients, mean [standard deviation] aged 49 [12.5] years, 31 [47%] of whom were human immunodeficiency virus [HIV]+) were analyzed.

Methods: Activity of SU was assessed at 1 week and 1 month after treatment onset, and at last follow-up. Improvement was defined by a ≥2-step decrease of both anterior chamber and vitreous haze inflammation levels, and by the size reduction in chorioretinal lesions.

Main Outcome Measures: Recovery was defined as the resolution of inflammation in all anatomic structures at 1 month.

Results: Panuveitis and posterior uveitis were the most frequent findings. Inflammatory parameters were higher in HIV+ patients. Recovery was reported in 65% and 85% of eyes at 1 month and at last follow-up, respectively. In multivariate analysis, after adjusting for initial best-corrected visual acuity and the antimicrobial treatment regimen, clinical improvement at 1 week (corrected risk ratios [cRR], 3.5 [2.3−3.8]; $P = 0.001$) was predictive of recovery at 1 month, whereas the use of periocular dexamethasone injections (cRR, 0.05 [0.02−0.6]; $P = 0.01$) and methylprednisolone pulses negatively affected the outcomes of eyes.

Conclusions: Early improvement is the strongest predictor of ophthalmological recovery in SU. *Ophthalmology 2017;■:1−9 © 2017 by the American Academy of Ophthalmology*

Supplemental material is available at www.aaojournal.org.

Although syphilis was highly endemic in the preantibiotic era,[1] it nearly disappeared in high-income countries after the discovery of penicillin and the implementation of screening and treatment programs.[2] However, similar to other sexually transmitted diseases (STDs), a resurgence of syphilis recently has been reported, particularly among human immunodeficiency virus (HIV)−infected patients and in the men having sex with men (MSM) population.[3] Between 2001 and 2014, the annual incidence of primary and secondary syphilis in the United States increased from 2.1 to 6.3 cases per 100 000 inhabitants.[4] Likewise, an outbreak of ocular syphilis occurred recently in the United States.[5]

Ocular complications (0.6%−15% of cases)[6] are more frequent during the secondary and early latent phases of syphilis, but, similar to neurosyphilis, they have been reported in all stages of the disease.[7] Although any segment of the eye can be involved, panuveitis and posterior uveitis are the most frequent ocular findings.[6] Besides superficial primary syphilis (e.g., canker of the lid or conjunctiva), it has long been hypothesized that syphilitic uveitis (SU) was closely related to neurosyphilis, and current treatment guidelines recommend treating it as such.[8] Thus, treatment with intravenous (IV) penicillin G (6 mUI 3 or 4 times per day for 10−14 days) is demanding and may extend the length of hospital stay. Moreover, cases of treatment failure have been reported.[9] Although ceftriaxone,[10] oral amoxicillin plus probenecid,[11,12] azithromycin,[13] and doxycycline[14] have been shown to be effective for early stages of syphilis, there are few data regarding the safety and efficacy of alternative treatments for neurosyphilis and SU.[15] This study aims to identify predictors of treatment success of SU and to evaluate the efficacy of alternative therapies (e.g., ceftriaxone and benzathine penicillin G [BPG]).

Methods

Patients

A retrospective multicenter study was conducted from January 2003 to April 2016 in 2 tertiary ophthalmic centers (Cochin and the Quinze-Vingts National Ophthalmology Hospital). Adult patients treated for SU were identified using the medical information system databases. All diagnoses of SU were reassessed by the investigators (F.H., S.S.). Syphilitic uveitis was defined by the

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presence of ocular inflammation compatible with the diagnosis of syphilis, the positivity of both serum *Treponema pallidum* hemagglutination assay (TPHA) and Venereal Disease Research Laboratory (VDRL) tests, and the exclusion of alternate diagnoses. Patients with optic neuritis (without any sign of intraocular inflammation) and congenital syphilis were not included. This study was approved by the local ethics committee.

Baseline Measurements

Data collection was performed using a standardized anonymous form. Baseline demographic, clinical, and paraclinical parameters were retrieved, including age, gender, socioeconomic status, sexual orientation, history of syphilis and other STDs, dermatologic and systemic clinical symptoms due to syphilis, HIV status, TPHA and VDRL levels at baseline and 3 months after onset of treatment, type, dose, and route of administration of anti-*Treponema* drugs, and use of glucocorticoids (topical or systemic). Ophthalmological findings included type and duration of ocular symptoms at presentation, best-corrected visual acuity (BCVA), slit-lamp examination (including grading of anterior segment and vitreal inflammation according to the Standardization of Uveitis Nomenclature [SUN] Guidelines),[16] laser-flare meter (when available), intraocular pressure measurement, and fundus examination. The SUN guidelines were used to classify uveitides subtypes.[16]

When available, cerebrospinal fluid (CSF) data also were collected (routine biochemical, cytologic analyses, and microbiological testing [i.e., VDRL, Fluorescent Treponemal Assay absorption test, and polymerase chain reaction]).[17] Lumbar puncture was considered abnormal in case of pleocytosis (>10 cells/mm^3), hyperproteinorrachia (>0.4 g/L), or positive CSF microbiological test results.

Outcomes

Data from ophthalmological examinations at 1 week (8±4 days), 1 month (30±12 days), and last follow-up after antimicrobial treatment onset were collected. Last follow-up was defined as month 1 examination for patients whose follow-up ended at 1 month and as the last date of follow-up for those who had additional follow-up visits. As defined by the SUN guidelines,[16] improvement was defined by a ≥2-step decrease of the levels of both anterior chamber (AC) cells and vitreous haze inflammation, and by size reduction in chorioretinal lesions. Recovery (main outcome measure) was defined as the resolution of inflammation in all anatomic ocular structures. Ocular complications included posterior synechiae, ocular hypertension, glaucoma, macular edema, serous retinal detachment, vasculitis, and optic atrophy.

Statistical Analyses

Characteristics of patients and eyes are reported as numbers and percentages for categoric variables and as mean (standard deviation) or median (interquartile range) for continuous variables. For univariate analysis, the Wilcoxon rank-sum or Kruskal–Wallis tests, and Fisher exact test were used as appropriate. Missing data for each variable were excluded from the denominator.

Patient subsets were differentiated on the basis of their HIV status and treatment regimens ("close to standard of care": group A, ≥14 days of IV penicillin G; "pragmatic approach": group B, ≥5 days of IV penicillin G followed by ceftriaxone or BPG; "non-validated treatment regimens": group C, ceftriaxone or BPG; and group D, oral doxycycline). High ocular inflammation was defined as a composite variable that was considered positive if anterior chamber cell or vitreous haze grades were >2 (when appropriate, taking into account the anatomic location of ocular inflammation).

Full details of the variables entered in model building are available in Supplementary material (available at www.aaojournal.org). Factors associated with recovery at 1 month were identified in a backward stepwise logistic regression model considering "recovery at 1 month" (positive/negative) as the dependent variable. All variables with a P value <0.2 in univariate analysis were tested in the model. To exclude variables with high collinearity from the multivariate analysis, variables significantly associated with recovery at 1 month in univariate analysis were assessed for bivariate correlation using Spearman's test. The fit of the model was tested using the Hosmer–Lemeshow goodness of fit test. Results are expressed as crude and adjusted odds ratios (ORs) and 95% confidence intervals (CIs). Because the prevalence of our outcome ("recovery at 1 month") was frequent (>10%), the ORs were corrected by the Zhang and Yu method[18] to avoid

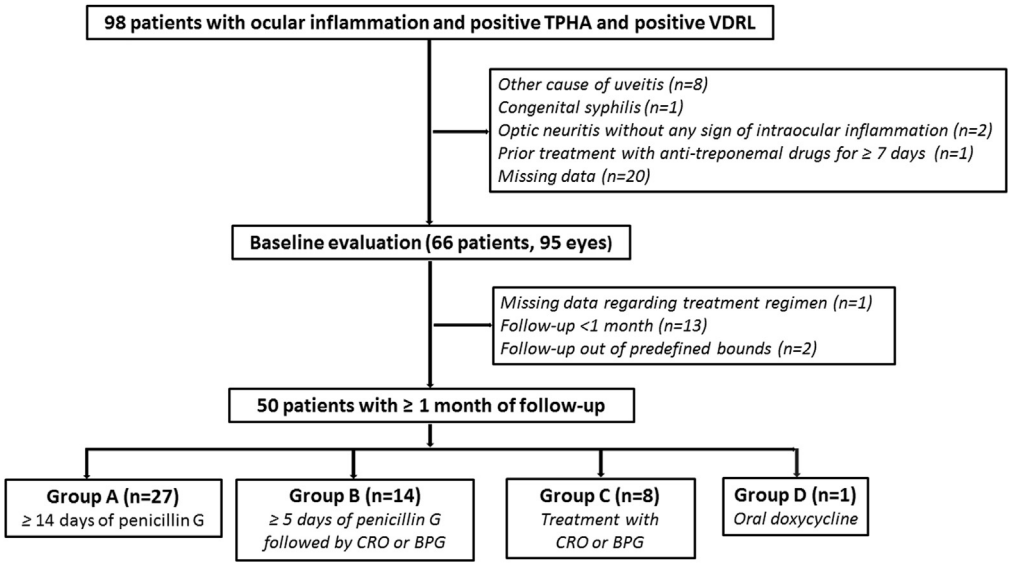

Figure 1. Flowchart showing the search strategy and inclusion/exclusion criteria for the study population.