# Uvéites - Sclérites

UNIVERSITÉ PARIS DESCARTES

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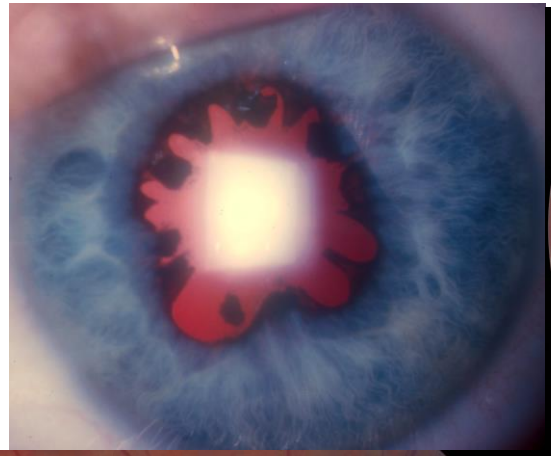
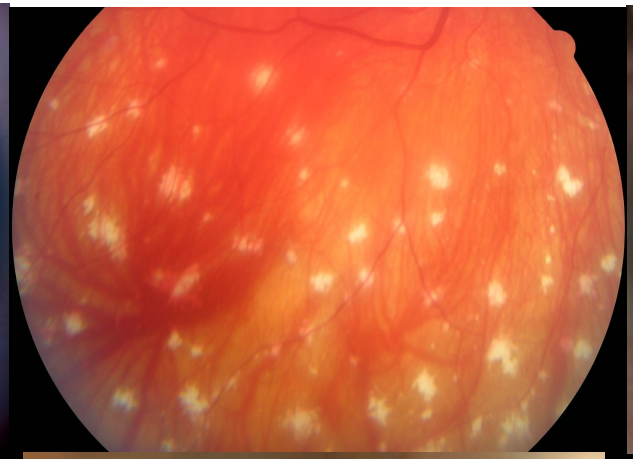
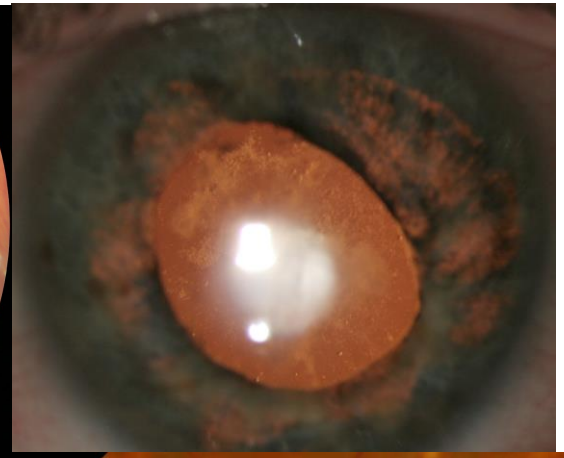
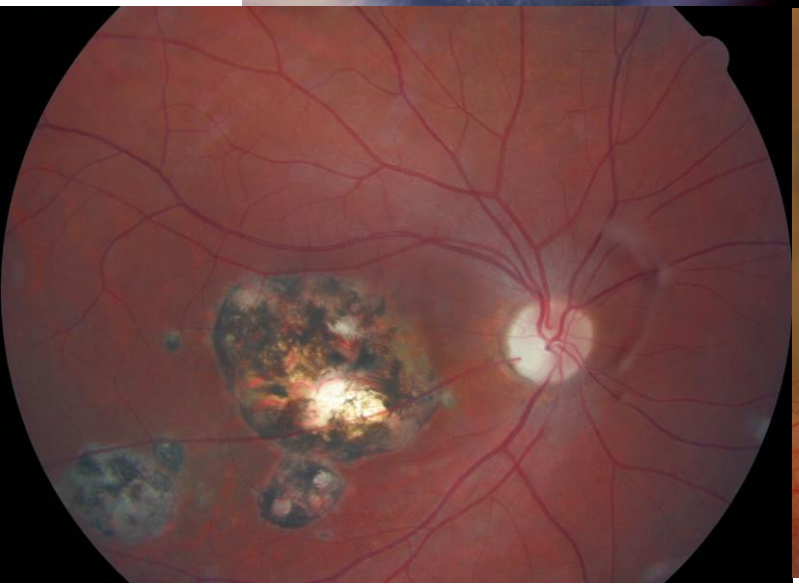
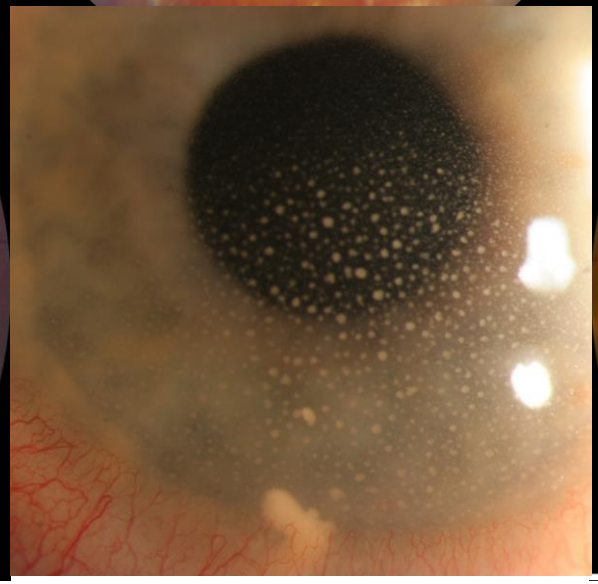
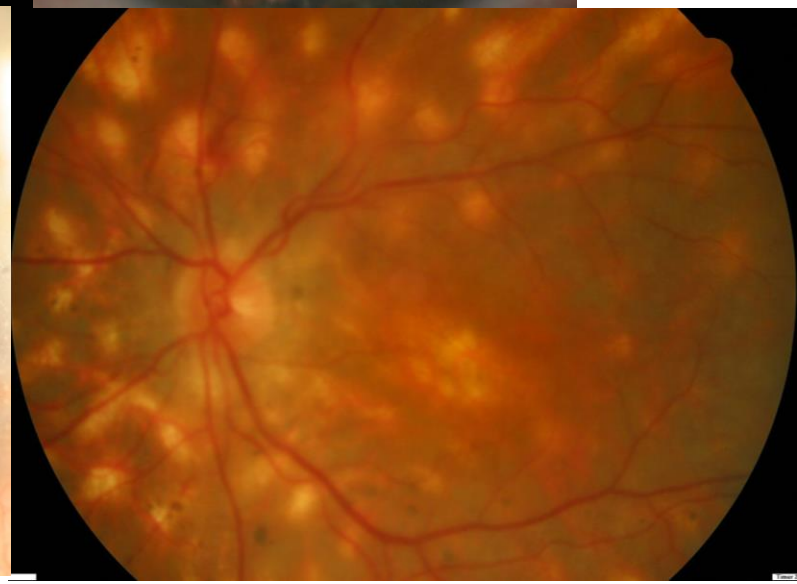
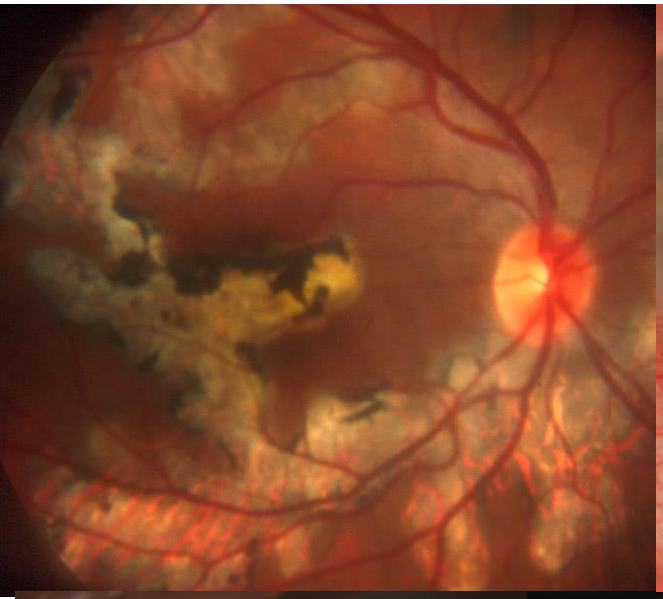
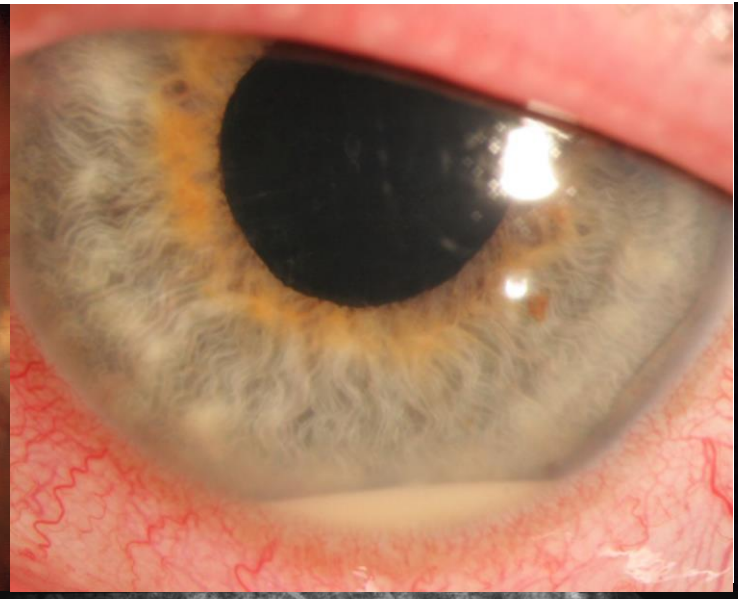
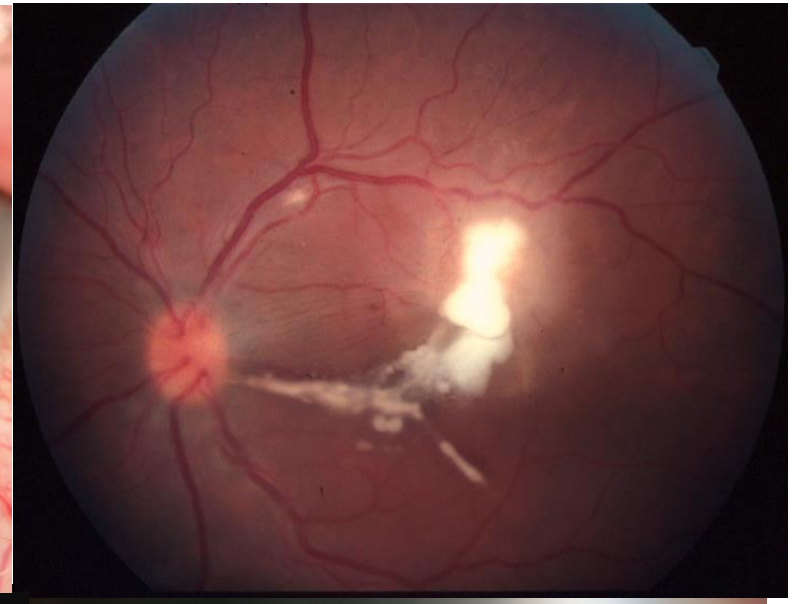
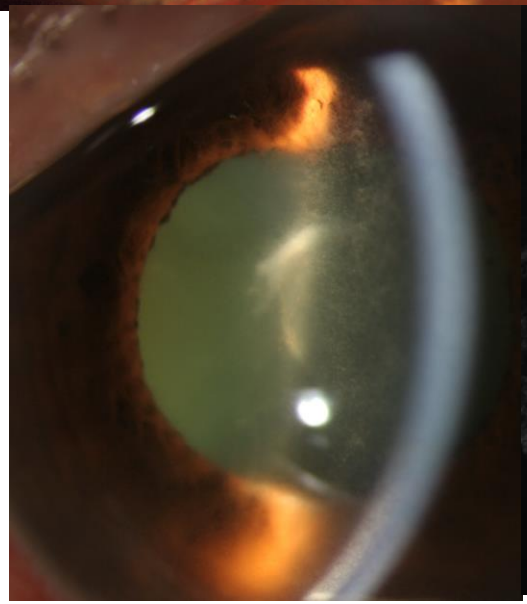
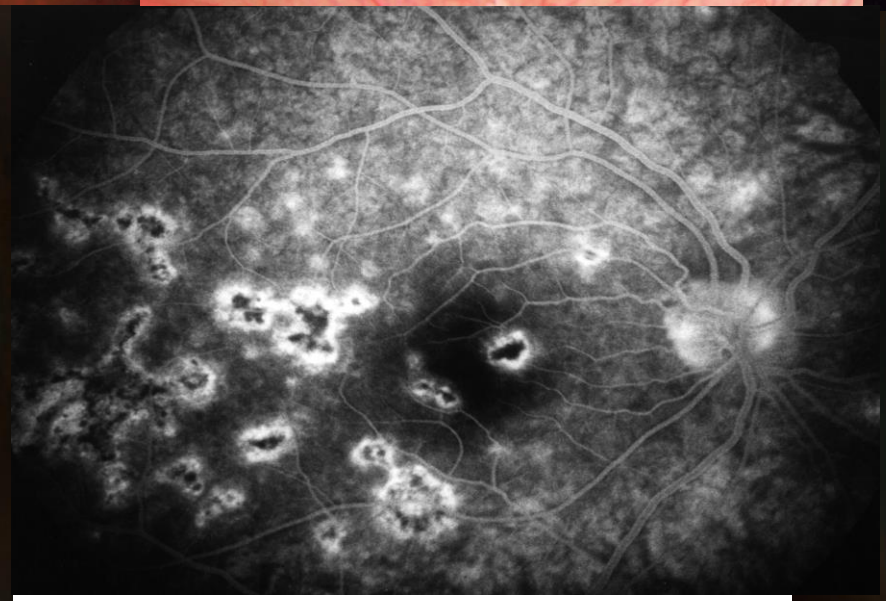
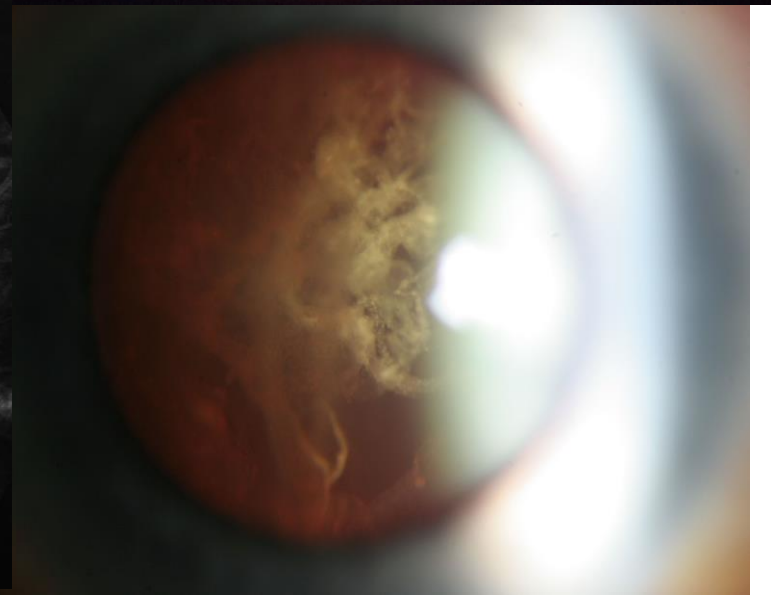
**Antoine Brézin**

# Uvéites : des maladies hétérogènes

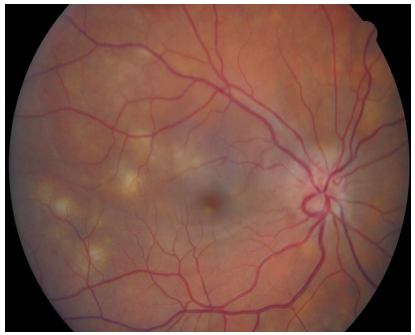







# Uvéites

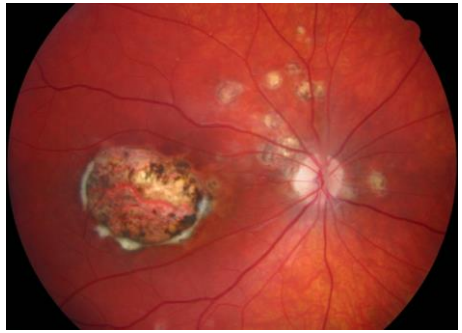
## Infectieuses

### Infections systémiques



*ex. Tuberculose*

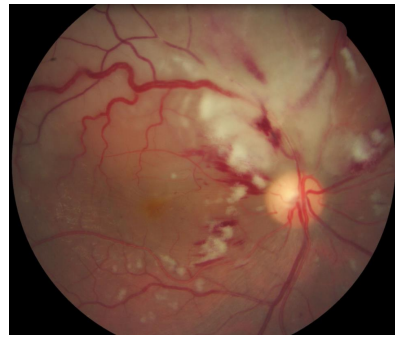
### Infections oculaires isolées



*ex. Toxoplasmose*

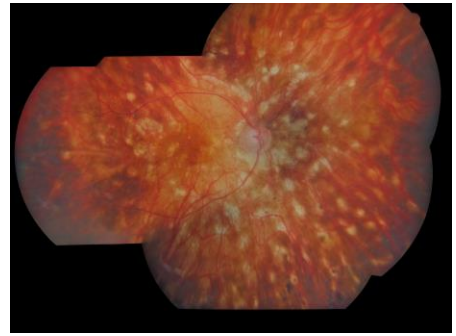
## Non infectieuses

### Maladies systémiques



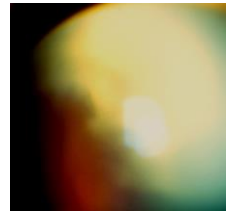
*ex. Behçet's*

### Maladies oculaires isolées



*ex. Birdshot*

*ex. Lymphome*



***Masquerade syndromes***

# Incidence and Prevalence of Uveitis in Northern California

## *The Northern California Epidemiology of Uveitis Study*

*David C. Gritz, MD, MPH,*[1,2,3] *Ira G. Wong, MD, MS*[3,4]

***Purpose:*** To determine the incidence and prevalence of uveitis in a large, well-defined population in Northern California.

***Design:*** Cross-sectional study using retrospective database and medical record review.

***Participants:*** A group of 2070 people within 6 Northern California medical center communities (N = 731 898) who had a potential diagnosis of uveitis.

***Methods:*** The patient database of a large health maintenance organization (2 805 443 members at time of the study) was searched for all patients who, during a 12-month period, had the potential diagnosis of uveitis. Detailed quarterly gender- and age-stratified population data were available. Medical records of patients who potentially had uveitis and who were members of the 6 target communities were reviewed by 2 uveitis subspecialists to confirm the diagnosis of uveitis and to establish time of onset. Demographic and clinical data were gathered for patients meeting the clinical definition of uveitis. Incidence rates were calculated by using a dynamic population model. Prevalence rates were based on the mid–study period population.

***Main Outcome Measures:*** Presence and date of onset of uveitis.

***Results:*** At midstudy, the population for the 6 communities was 731 898. During the target period, 382 new cases of uveitis were diagnosed; 462 cases of uveitis were diagnosed before the target period. These data yielded an incidence of 52.4/100 000 person-years and a period prevalence of 115.3/100 000 persons. The incidence and prevalence of disease were lowest in pediatric age groups and were highest in patients 65 years or older ($P<0.0001$). The prevalence of uveitis was higher in women than in men ($P<0.001$), but the difference in incidence between men and women was not statistically significant. Comparison between the group of patients who had onset of uveitis before the target period (ongoing uveitis) and the entire cohort of uveitis patients showed that women had a higher prevalence of ongoing uveitis than men and that this difference was largest in the older age groups ($P<0.001$).

***Conclusion:*** In this largest population-based uveitis study in the United States to date, the incidence of uveitis was approximately 3 times that of previous U.S. estimates and increased with the increasing age of patients. Women had a higher prevalence of uveitis than men, and the largest differences were in older age groups. *Ophthalmology 2004;111:491–500* 

# Prevalence of Noninfectious Uveitis in the United States
## A Claims-Based Analysis

Jennifer E. Thorne, MD, PhD; Eric Suhler, MD, MPH; Martha Skup, PhD; Samir Tari, MD, MBA; Dendy Macaulay, PhD; Jingdong Chao, PhD; Arijit Ganguli, PhD, MBA

**IMPORTANCE** Noninfectious uveitis (NIU) is a collection of intraocular inflammatory disorders that may be associated with significant visual impairment. To our knowledge, few studies have investigated NIU prevalence overall or stratified by inflammation location, severity, presence of systemic conditions, age, or sex.

**OBJECTIVE** To estimate NIU prevalence using a large, retrospective, administrative claims database.

**DESIGN, SETTING, AND PARTICIPANTS** This analysis used the OptumHealth Reporting and Insights database to estimate 2012 NIU prevalence. Analysis was conducted in September 2016. The large administrative insurance claims database includes 14 million privately insured individuals in 69 self-insured companies spanning diverse industries. Included in the study were patients with NIU with 2 or more uveitis diagnoses on separate days in 2012 and continuous enrollment in a health plan for all of 2012 and categorized by inflammation site.

**RESULTS** Of the approximately 4 million eligible adult patients, approximately 2.1 million were women, and of the 932 260 children, 475 481 were boys. The adult prevalence of NIU was 121 cases per 100 000 persons (95% CI, 117.5-124.3). The pediatric NIU prevalence was 29 cases per 100 000 (95% CI, 26.1-33.2). Anterior NIU accounted for 81% (3904 cases) of adult NIU cases (98 per 100 000; 95% CI, 94.7-100.9) and 75% (207 cases) of pediatric NIU cases (22 per 100 000; 95% CI, 19.3-25.4). The prevalences of noninfectious intermediate, posterior, and panuveitis were, for adults, 1 (95% CI, 0.8-1.5), 10 (95% CI, 9.4-11.5), and 12 (95% CI, 10.6-12.7) per 100 000, respectively, and for pediatric patients, 0 (95% CI, 0.1-1.1), 3 (95% CI, 1.8-4.1), and 4 (95% CI, 2.9-5.6) per 100 000, respectively. The prevalence of NIU increased with age and was higher among adult females than males. Application of these estimates to the US population suggests that NIU affected approximately 298 801 American adults (95% CI, 290 512-307 324) and 21 879 children (95% CI, 19 360-24 626) in 2015.

**CONCLUSIONS AND RELEVANCE** The estimated prevalence of NIU was 121 cases per 100 000 for adults (95% CI, 117.5-124.3) and 29 per 100 000 for children (95% CI, 26.1-33.2). Prevalence was estimated using administrative claims from a commercially insured population, which may have a different prevalence than other segments of the US population. A better understanding of the prevalence of NIU will help to determine the number of patients affected.

**1,21 cas /1000 adultes  0,29 cas / 1000 enfants**

*JAMA Ophthalmol. 2016;134:1237-1245*

# The possible impact of uveitis in blindness: a literature survey

M S A Suttorp-Schulten, A Rothova

*British Journal of Ophthalmology* 1996;**80**:844–848

*Table 5 Major causes of blindness in the middle age group in the Western world (adapted from Nussenblatt,[5] Thompson et al,[12] Krumpaszky and Klauss,[19] and Makabe et al[25])*

| | |
|---|---|
| 1 Tapetoretinal degeneration | 20% |
| 2 Congenital anomalies (including high myopia) | 20% |
| 3 Diabetes* | 20% |
| 4 Accidents* | 5% |
| 5 Uveitis* | 10% |

*Possibly treatable (that is, preventable).

*British Journal of Ophthalmology* 1996; **80:** 332–336

# Causes and frequency of blindness in patients with intraocular inflammatory disease

Aniki Rothova, Maria S A Suttorp-van Schulten, W Frits Treffers, Aize Kijlstra

***Aims/Background*—Uveitis, an intraocular inflammatory disease, is a significant cause of visual impairm**
**known how many patients**
**retain visual acuity and hov**
**visual impairment or even**
**aim of this study was to**
**quency of blindness in**
**uveitis and, more specifically, to identify the clinical profile of patients at risk for visual loss.**

***Methods*—A cross sectional and retrospec**
**who**
**men**
**Netherlands was performed.**

***Results*—Within the group of 582 patients, 203 (35%) exhibited blindness or visual impairment; bilateral legal blindness developed in 22 (4%) patients, 26 (4·5%) had one blind eye with visual impairment of the other, and nine (1·5%) had bilateral visual impairment. Unilateral blindness**

**ment. The most important cause of both blindness and visual impairment was cystoid macular oedema (29% and 41%, respectively). Complications of uveitis**

**surgical procedures. When the patients were subdivided according to anatomical site, those with panuveitis had the worst visual prognosis. The systemic diseases associated with a poor visual prognosis**
**tis and sar-**
**osis was the**
**ateral visual**

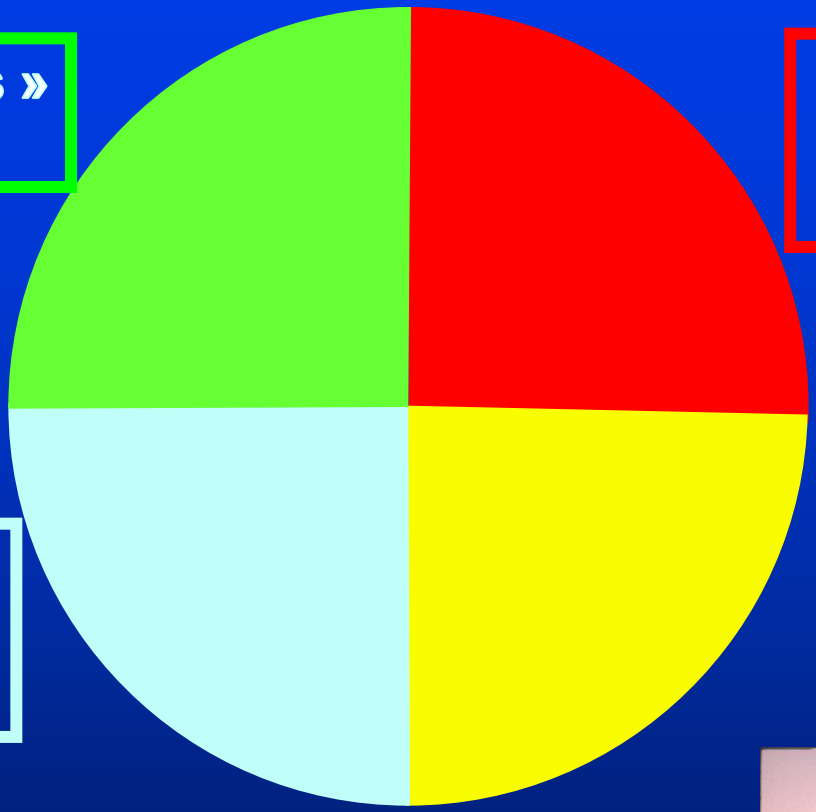
***Conclusions*—Cystoid macular oedema is the most frequent complication of uveitis and its occurrence plays a decisive role in the visual outcome of this disease.**

Œdème maculaire cystoïde : première cause de cécité et de handicap visuel au cours des uvéites

# Etiologie des uvéites

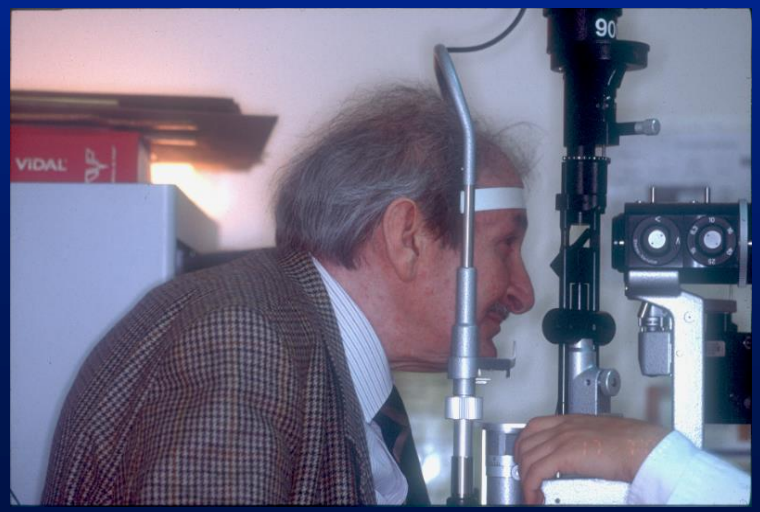
« Idiopathiques »
≈ 25%

Maladies systémiques
présumées
≈ 25%



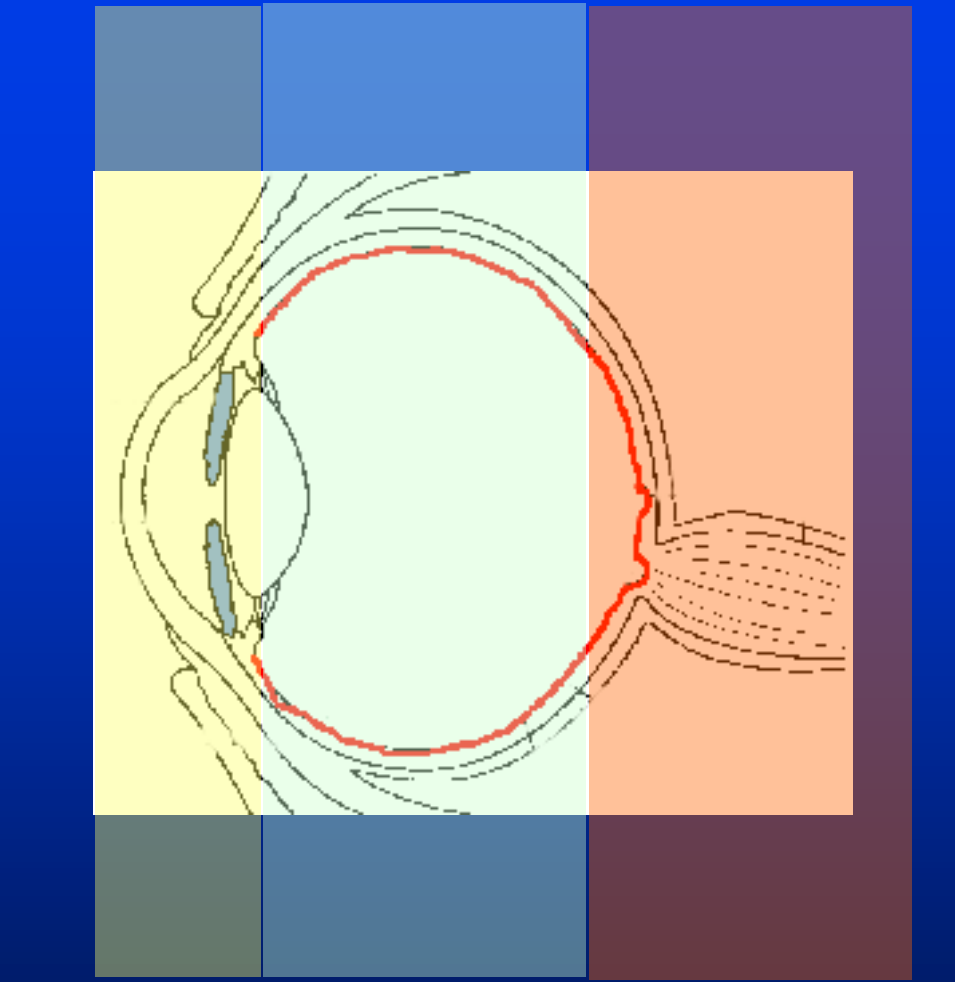
« Connues »
oculaires isolées
≈ 25%

Maladies systémiques
prouvées
≈ 25%

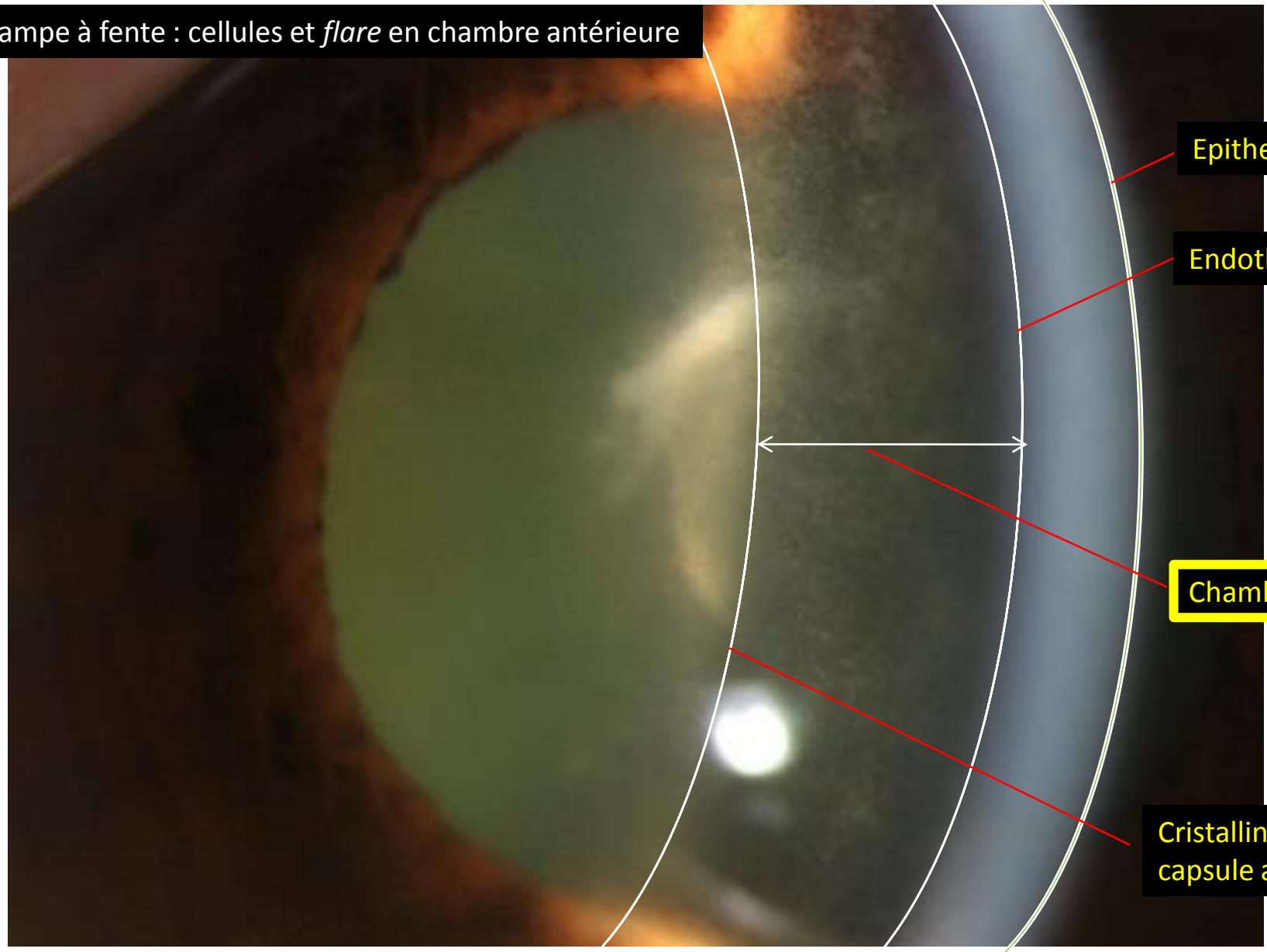


1. Standardiser l’évaluation ophtalmologique
2. Standardiser la recherche de l’étiologie
3. Standardiser la démarche thérapeutique

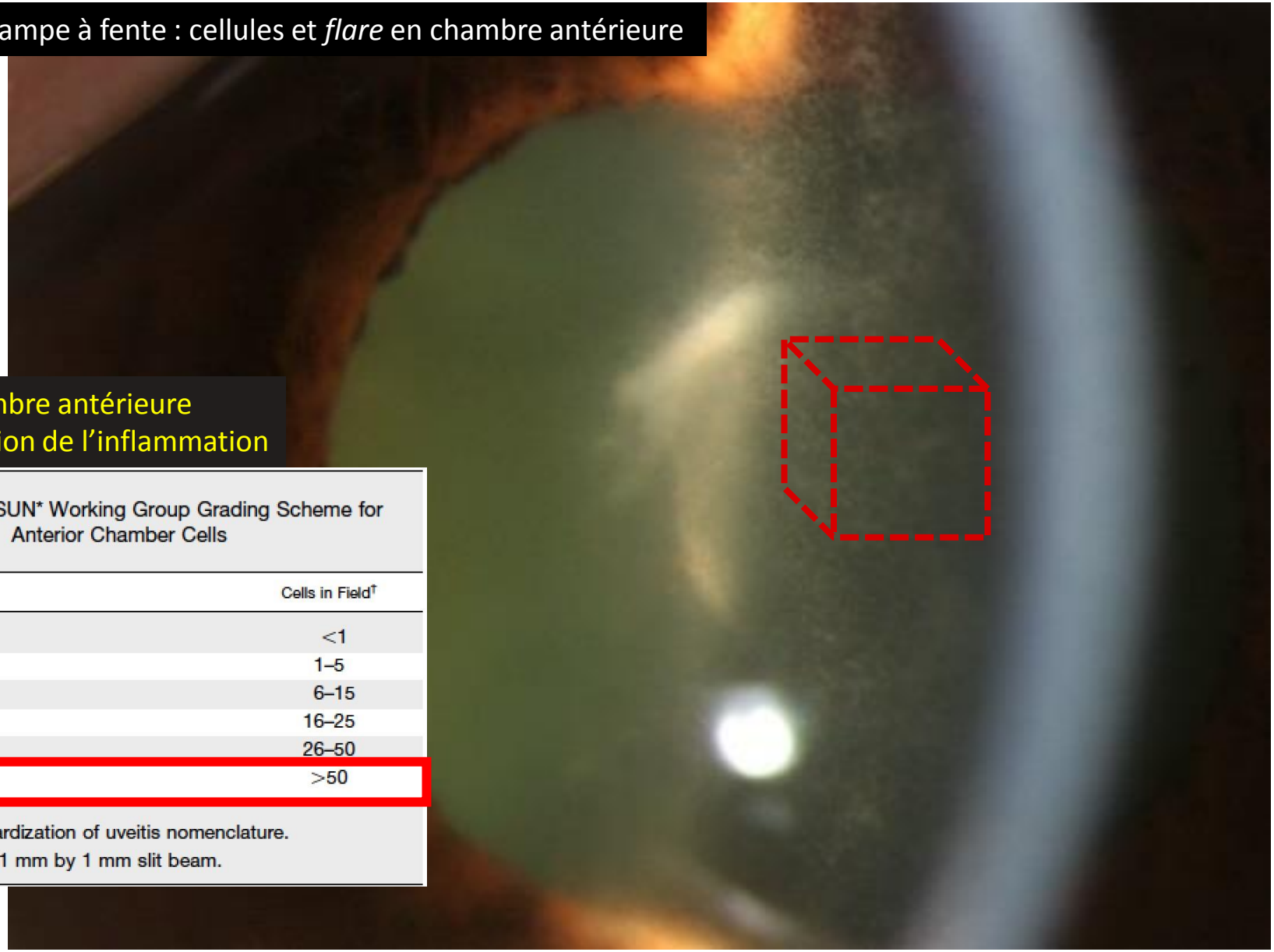
# Localisation des uvéites



Examen à la lampe à fente : cellules et *flare* en chambre antérieure



# Examen à la lampe à fente : cellules et *flare* en chambre antérieure

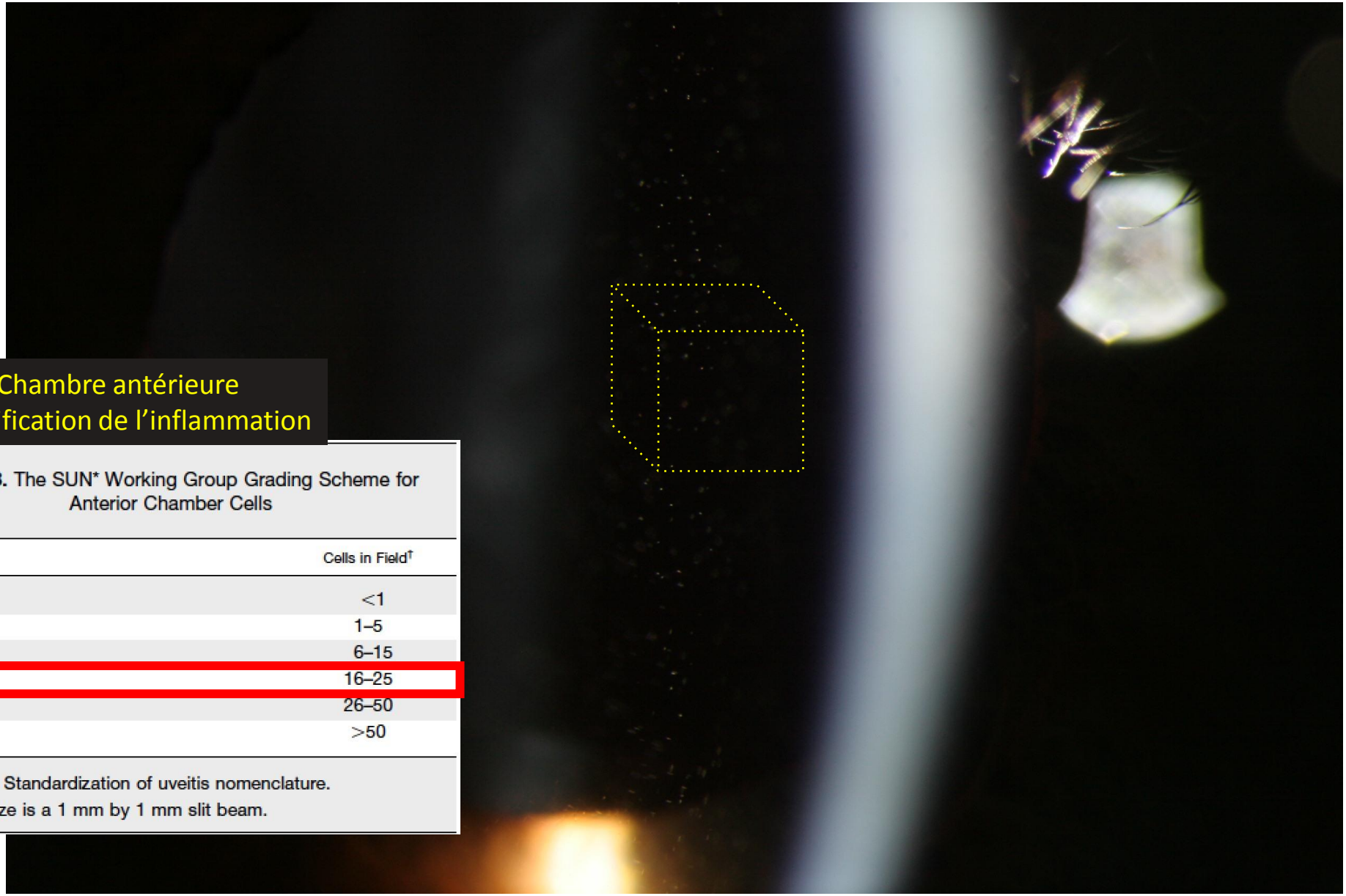


## Chambre antérieure quantification de l'inflammation

**TABLE 3.** The SUN* Working Group Grading Scheme for Anterior Chamber Cells

| Grade | Cells in Field† |
|---|---|
| 0 | <1 |
| 0.5+ | 1–5 |
| 1+ | 6–15 |
| 2+ | 16–25 |
| 3+ | 26–50 |
| 4+ | >50 |

*SUN = Standardization of uveitis nomenclature.
†Field size is a 1 mm by 1 mm slit beam.



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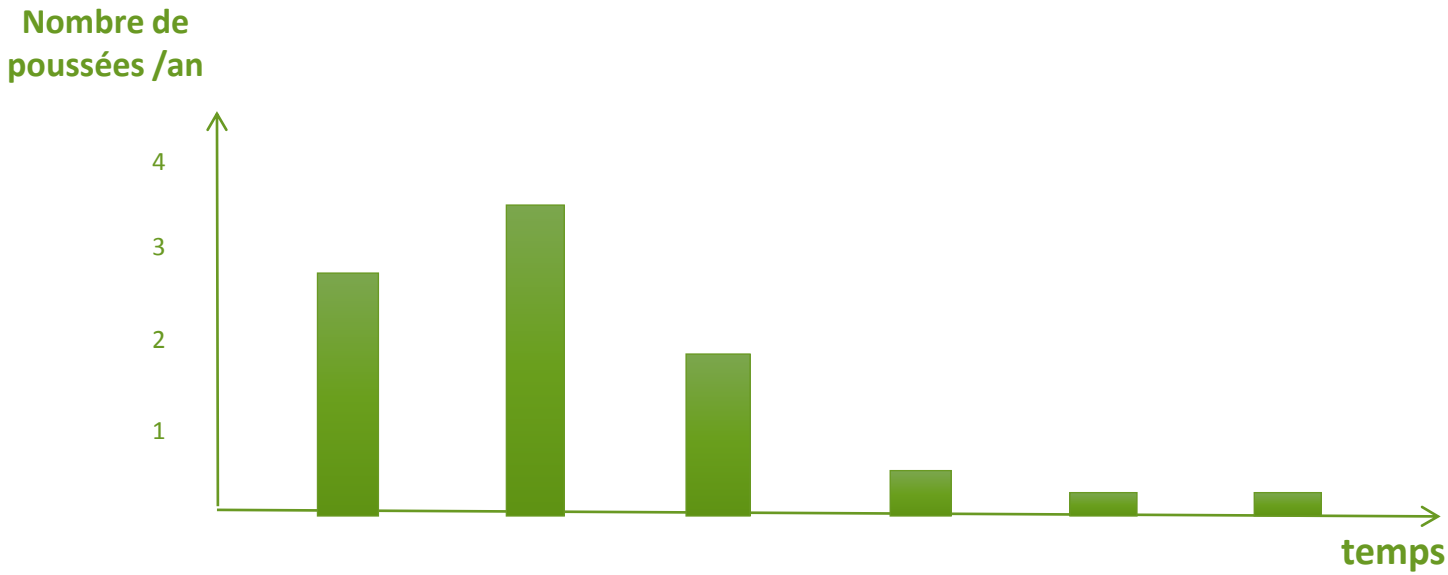
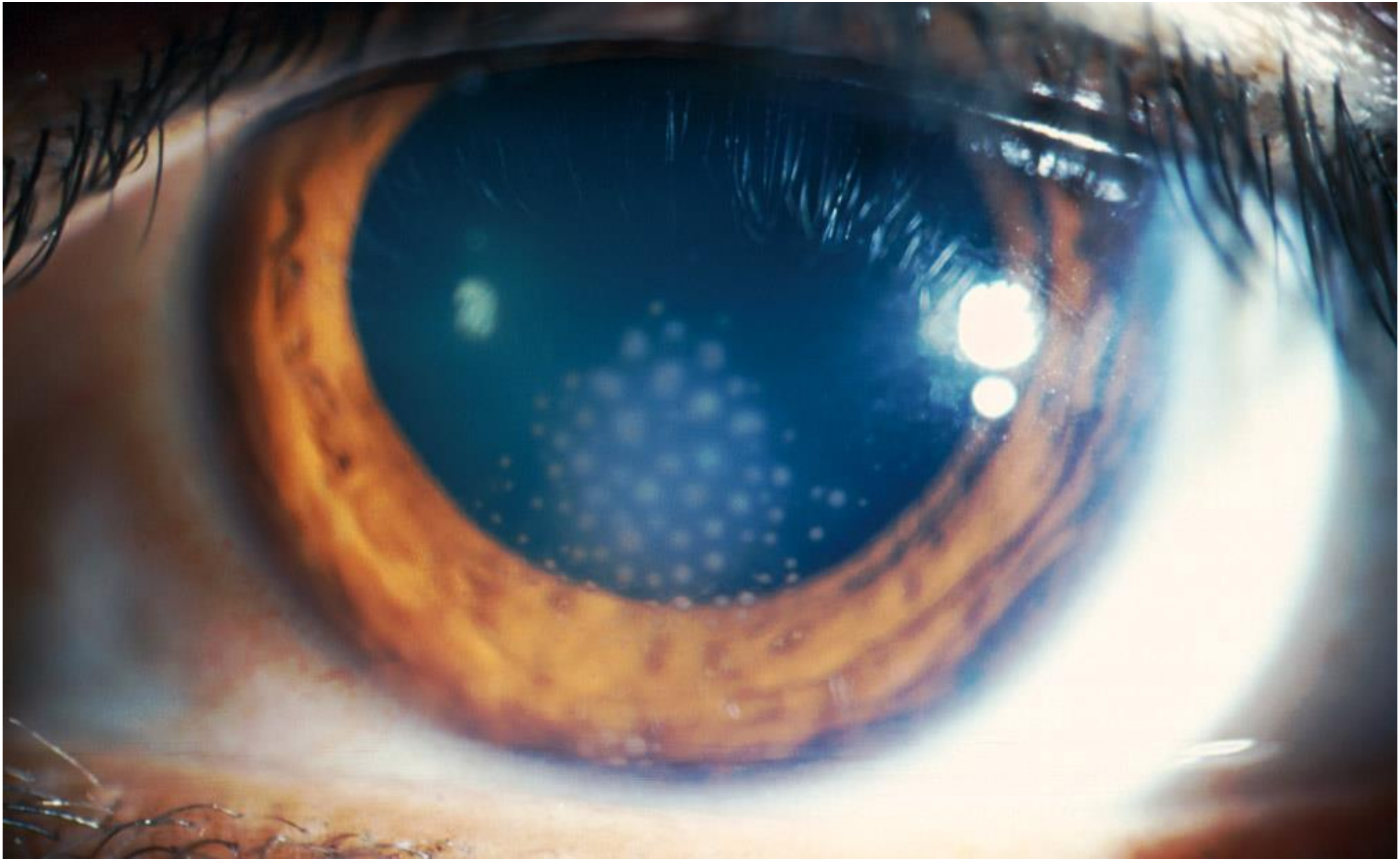
†Field size is a 1 mm by 1 mm slit beam.

Fréquence des poussées

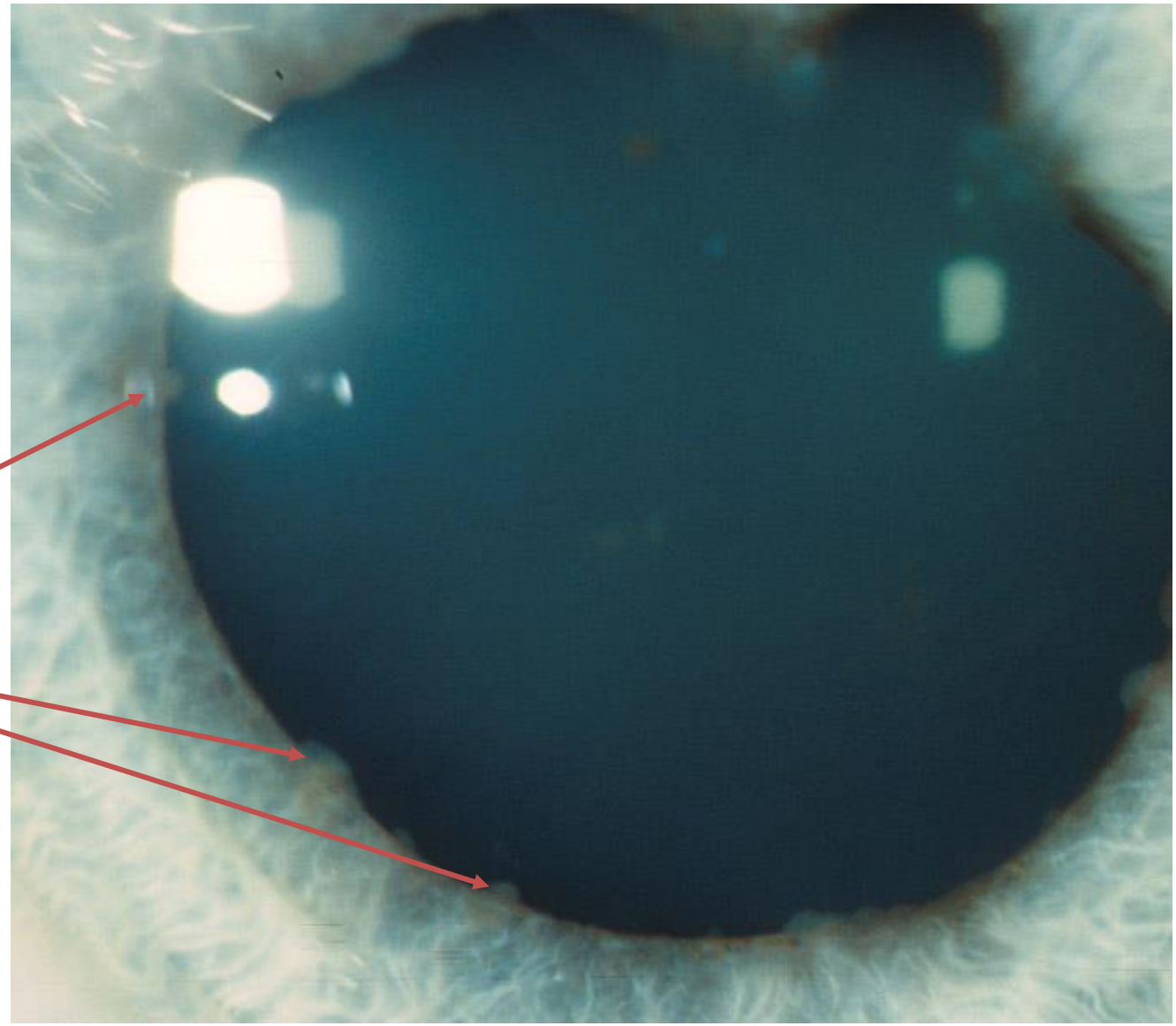


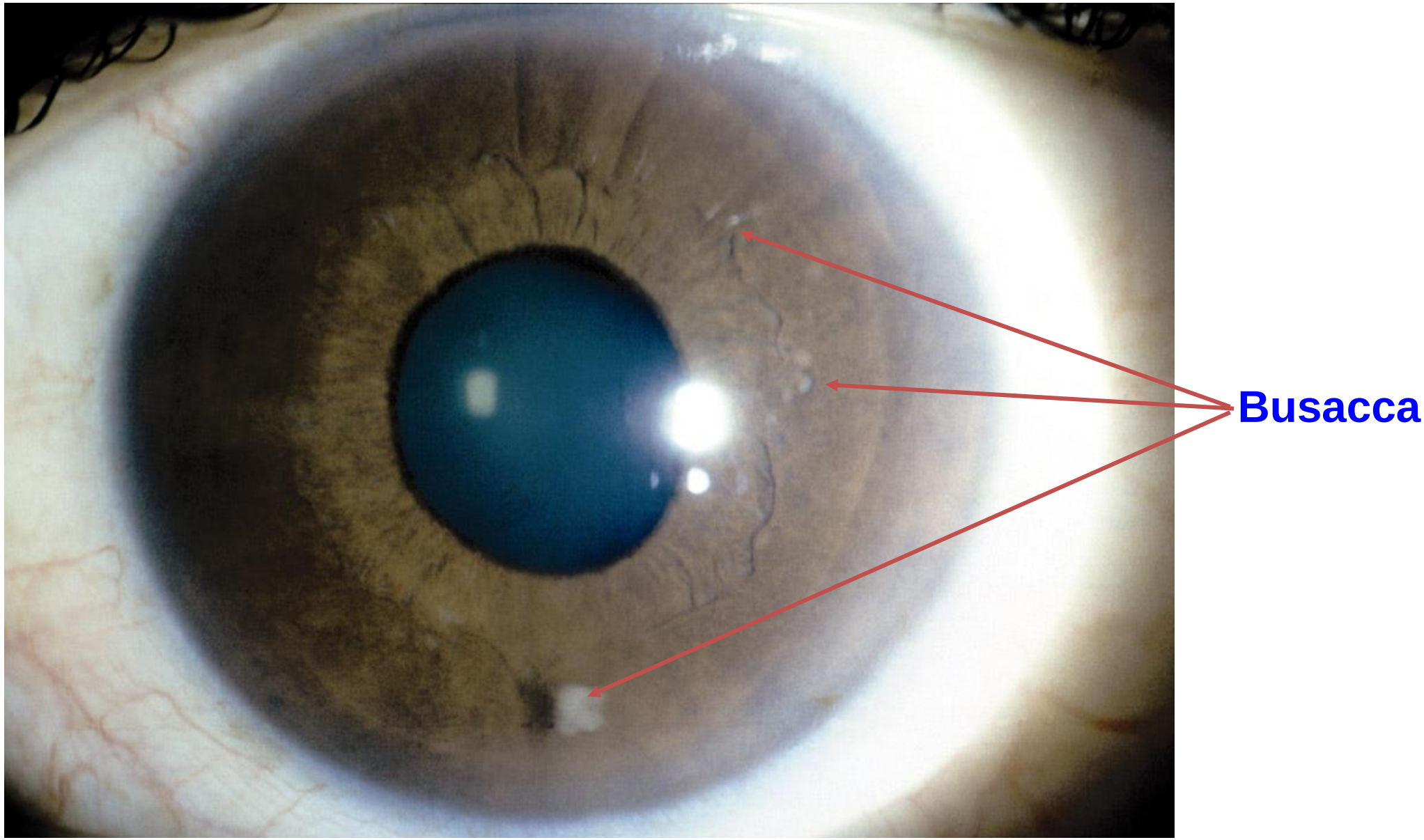


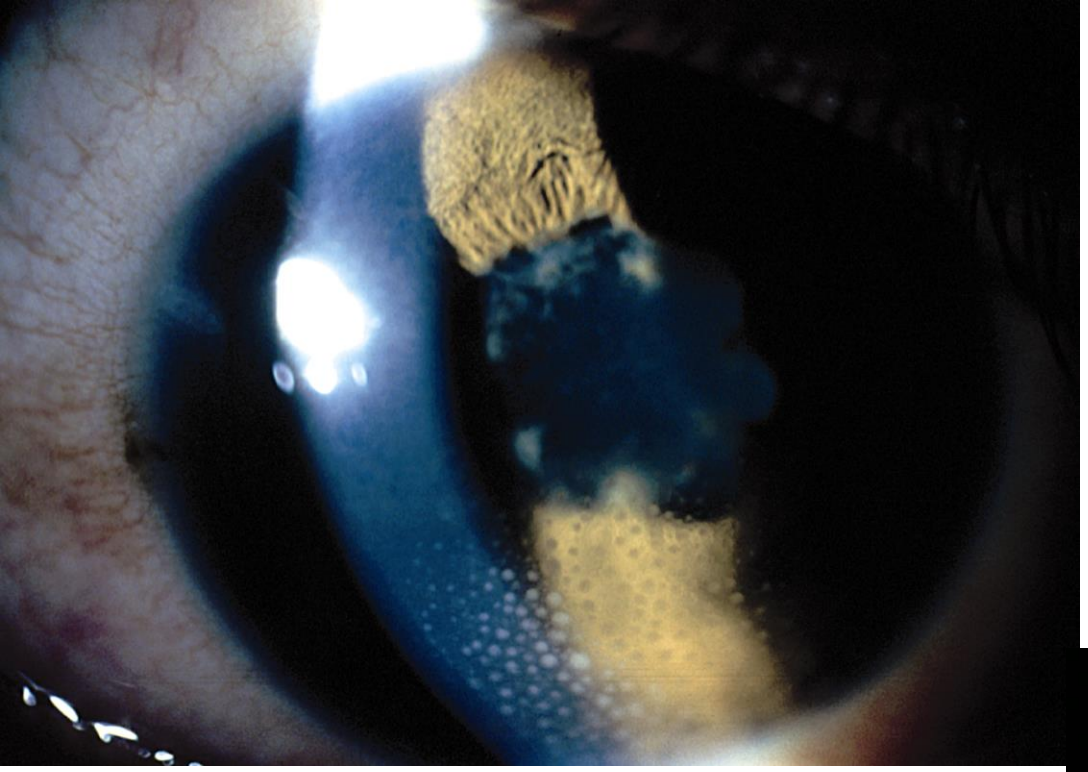
**Uvéite granulomateuse**

**Nodules Iriens**

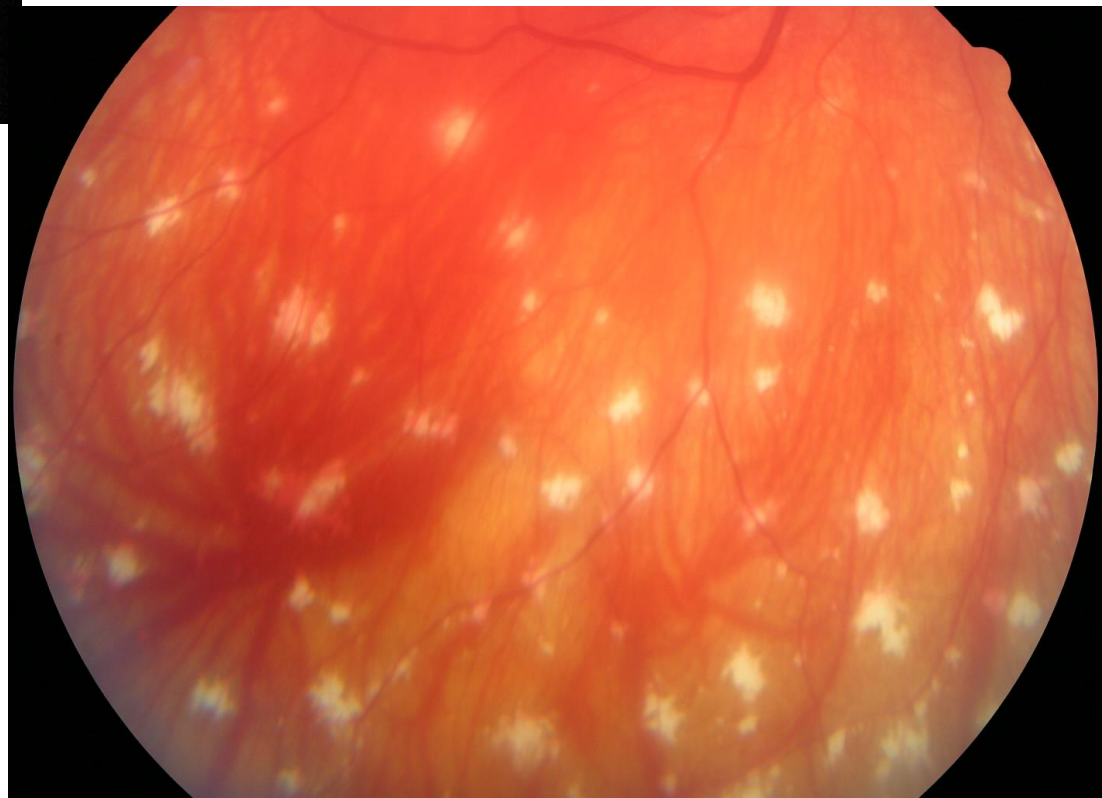
**Koeppe**




Busacca



**Sarcoïdose**



Arthritis & Rheumatism (Arthritis Care & Research)
Vol. 51, No. 6, December 15, 2004, pp 974–982
DOI 10.1002/art.20839


ORIGINAL ARTICLE

# Association of Peripheral Multifocal Choroiditis With Sarcoidosis: A Study of Thirty-Seven Patients

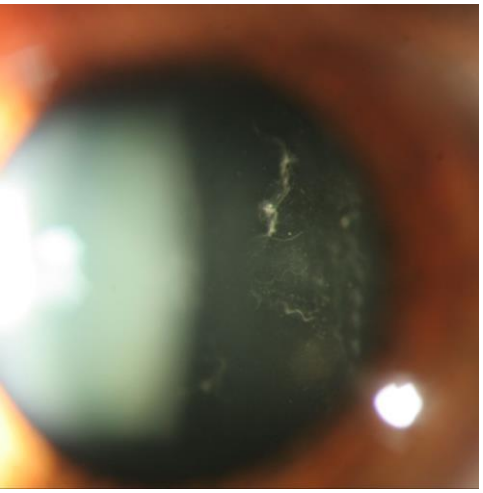
S. ABAD, V. MEYSSONIER, J. ALLALI, H. GOUYA, A. L. GIRAUDET, D. MONNET, C. PARC, F. TENENBAUM, J. L. ALBERINI, S. GRABAR, F. PESCE, F. ROLLOT, D. SICARD, R. DHOTE, P. BLANCHE, AND A. P. BRÉZIN

*Objective.* To assess the clinical spectrum of peripheral multifocal choroiditis (PMC) and its association with sarcoidosis.

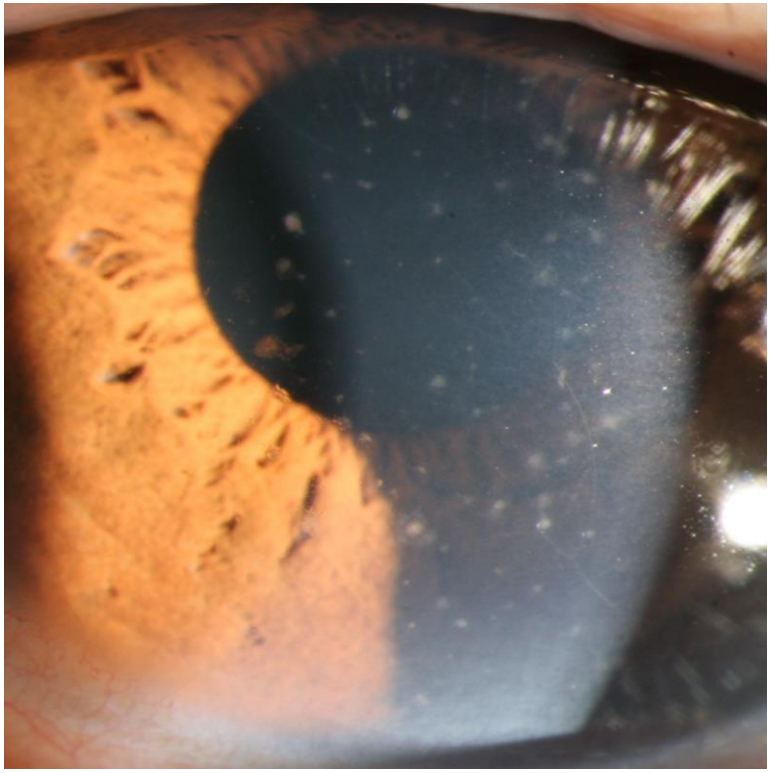
*Methods.* Thirty-seven patients examined between November 1997 and November 2001 who met all diagnostic criteria for PMC were included in this retrospective study. Patients were assessed for the following signs of sarcoidosis: typical changes on chest radiography or computed tomography; predominantly CD4 lymphocytosis in bronchoalveolar lavage fluid; elevated serum angiotensin-converting enzyme levels; elevated gallium uptake; and noncaseating granuloma on biopsy.

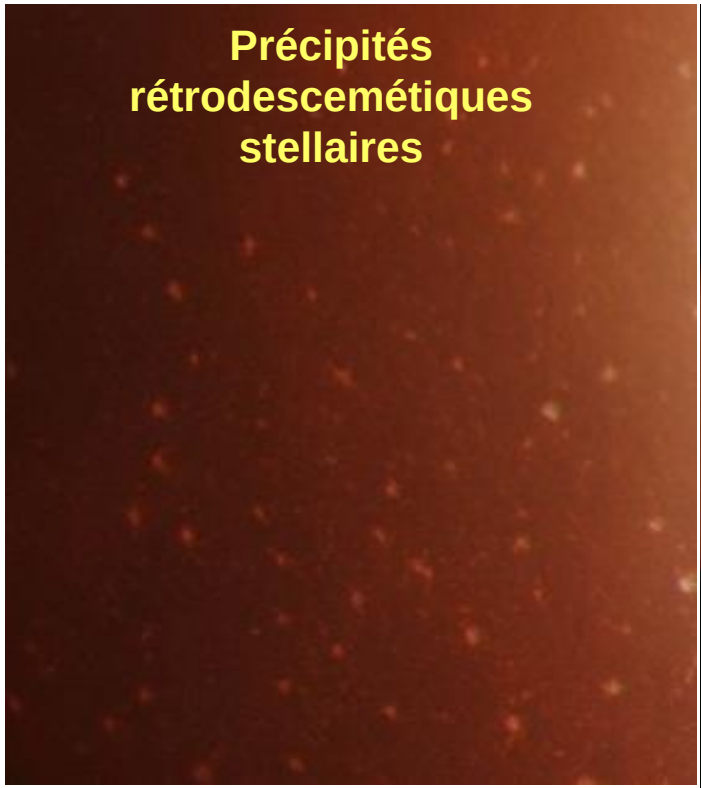
*Results.* Most of the patients were female (30 of 37; 81%) and white (30 of 37; 81%). Mean ± SD age at onset was 57.5 ± 18.7 years. Seven (19%) of the 37 patients had biopsy-proven sarcoidosis and 18 patients (49%) with presumed sarcoidosis met at least 2 of the above-mentioned criteria for sarcoidosis but had normal biopsy results. Twelve patients (32%) had an indeterminate diagnosis. Patients with presumed sarcoidosis did not differ from those with proven sarcoidosis as regards the above-mentioned criteria, except for noncaseating granuloma, implying that more than two-thirds of patients (predominantly whites) had underlying sarcoidosis. Most patients with positive gallium scintigraphy had increased mediastinal uptake, as described in sarcoidosis. Patients with underlying sarcoidosis had more severe visual impairment due to cystoid macular edema (CME). Weekly methotrexate (0.3 mg/kg) seemed to control CME.

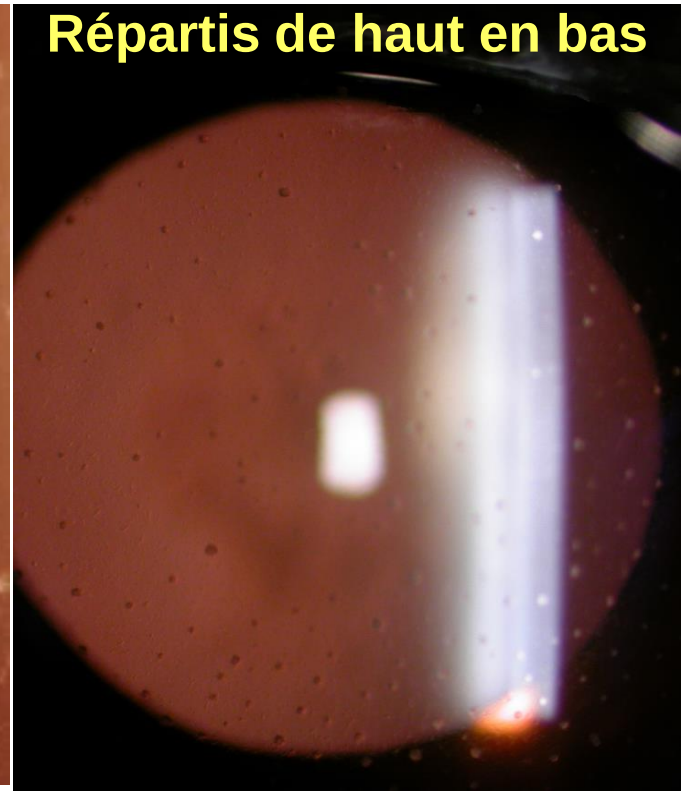
*Conclusion.* White patients with PMC should be considered to have sarcoidosi[Capture d'écran]on of sarcoidosis in patients with severe ocular disease can help with therapeutic choices.



# Cyclite hétérochromique de Fuchs




Contraste nombre de prédicipités / Tyndall et *flare* de bas grade

# The Standardization of Uveitis Nomenclature (SUN) Project*

*Trusko B. et al. Methods Inf Med 2013; 52: 259–265*

## Development of a Clinical Evidence Base Utilizing Informatics Tools and Techniques

B. Trusko[1]; J. Thorne[2]; D. Jabs[1]; R. Belfort[3]; A. Dick[4]; S. Gangaputra[5]; R. Nussenblatt[6]; A. Okada[7]; J. Rosenbaum[8]; for The Standardization of Uveitis Nomenclature (SUN) Project


### Summary

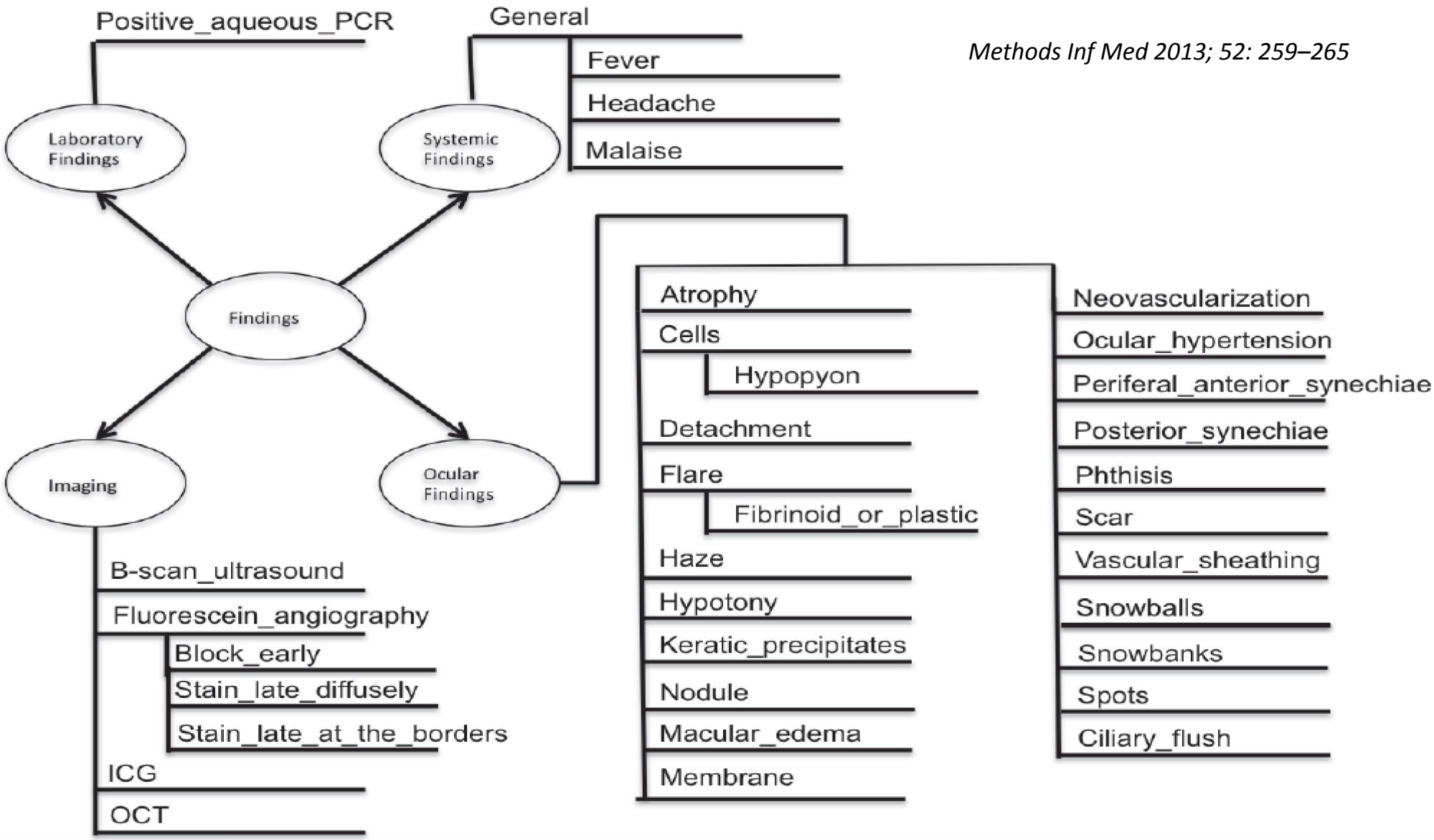
**Background:** Given the recent increased focus on evidence-based medicine, it is critical that diseases and syndromes have accurate and complete descriptions, including standardized and widely accepted terminologies. Standardizing these descriptions and terminologies is necessary to develop tools such as computerized data entry forms and classification criteria. This need is especially true for diseases that are relatively uncommon, such as uveitis.

**Objectives:** To develop a standardized and internationally accepted terminology for the field of uveitis.

**Methods:** The Standardization of Uveitis Nomenclature (SUN) Working Group (WG) is an international group of 79 uveitis experts from 18 countries and 62 clinical centers. Initial terminology was developed utilizing a "modified" green field approach, which was enhanced through web-based surveys and teleconferences via a "modified" Delphi technique. Terms were mapped provisionally into ontologic dimensions for each syndrome. The Working Group then met and utilized nominal group techniques as a formalized method of finalizing the mappings.

**Results:** Mapping of terms into dimensions to describe 28 major uveitic diseases was confirmed using nominal group techniques (achieving super-majority consensus) for each of the diseases at a meeting of the entire WG.

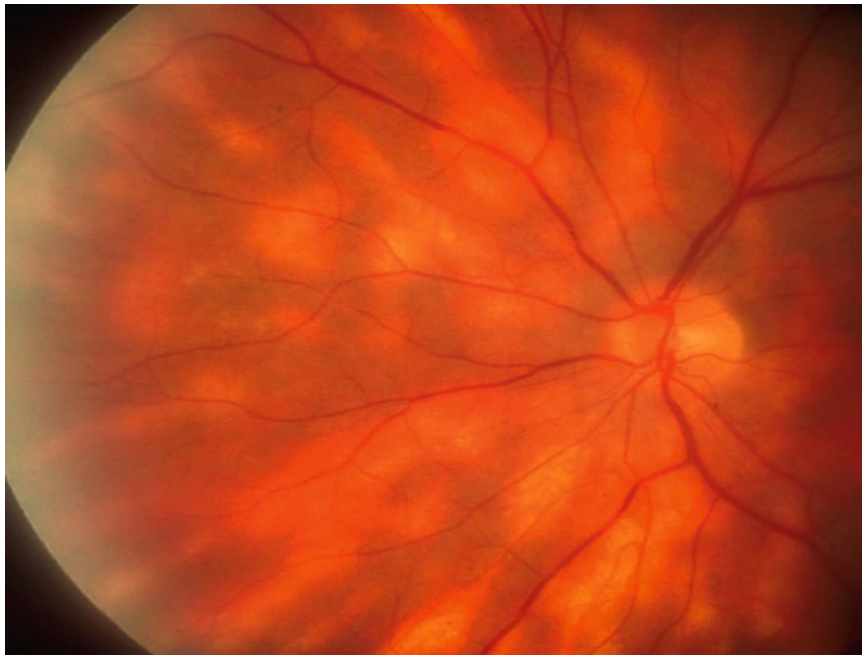
**Conclusions:** The SUN WG utilized an informatics-based approach to develop a standardized and internationally accepted terminology for the uveitides.




*Methods Inf Med 2013; 52: 259–265*

Descriptors for birdshot chorioretinopathy

*Methods Inf Med 2013; 52: 259–265*



| Dimension | Term |
|---|---|
| Onset | Insidious |
| Duration | Persistent |
| Course | Chronic |
| Laterality | Bilateral, simultaneous |
| Location | Posterior uveitis |
| Primary site of inflammation | Choroid |
| Morphology | Multifocal spots |
| Descriptors of spots – shape and size | Ovoid indistinct, 50–250 µm |
| Descriptors of spots – color | Yellow-orange or cream-colored |
| Fundus location (2-dimensional) | Posterior pole and mid periphery |
| Other findings | Vitreous cells |
| Imaging – fluorescein angiogram | Vascular leakage; spots not visible to faint hyperfluorescent |

# Interobserver Agreement Among Uveitis Experts on Uveitic Diagnoses: The Standardization of Uveitis Nomenclature Experience

DOUGLAS A. JABS, ANDREW DICK, JOHN T. DOUCETTE, AMOD GUPTA, SUSAN LIGHTMAN, PETER MCCLUSKEY, ANNABELLE A. OKADA, ALAN G. PALESTINE, JAMES T. ROSENBAUM, SOPHIA M. SALEEM, JENNIFER THORNE, AND BRETT TRUSKO, FOR THE STANDARDIZATION OF UVEITIS NOMENCLATURE WORKING GROUP

*Am J Ophthalmol 2018;186:19–24*

K = -1.00 jamais en accord

K= 0 hasard

K= 1.00 toujours en accord

Pairwise (k) agreement statistic (36 k/disease)

**TABLE.** Interobserver Agreement Among Uveitis Experts on Uveitic Diagnosis

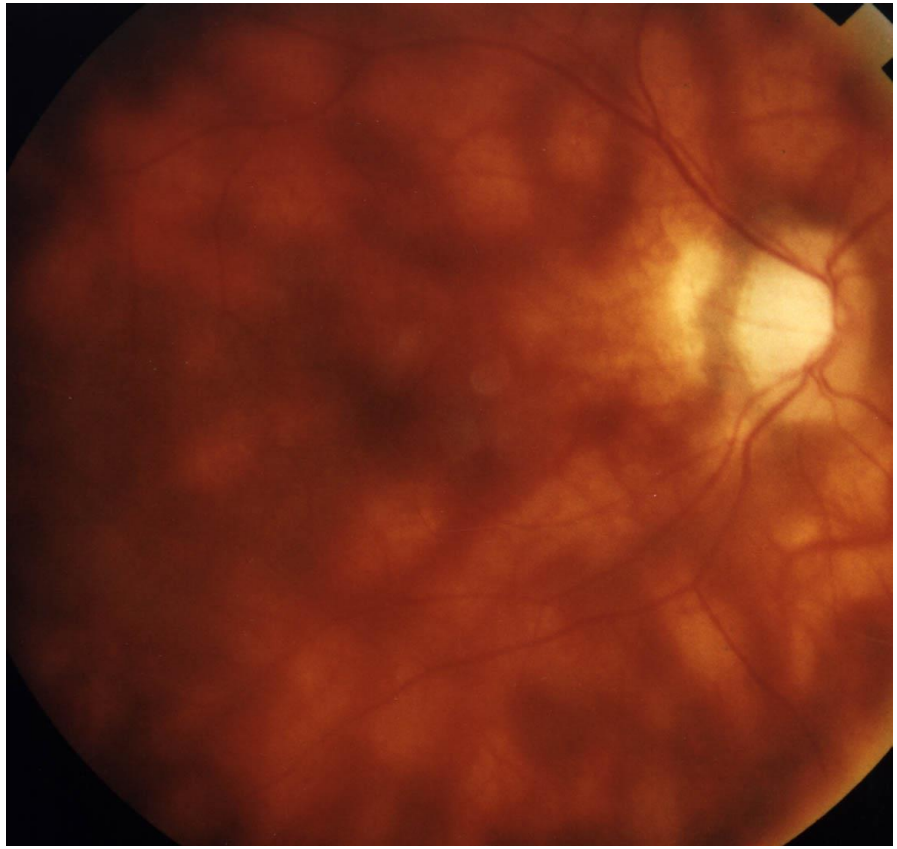
| Disease | No. of Cases Submitted | Online Voting Results | | | Final Results After Consensus Conference (% Cases) | | |
|---|---|---|---|---|---|---|---|
| | | Mean κ | SD | Range κs[a] | Accepted | Rejected | Tabled |
| Cytomegalovirus anterior uveitis | 112 | 0.79 | 0.15 | 0.51–1.00 | 82 | 17 | 1 |
| Herpes simplex anterior uveitis | 250 | 0.32 | 0.14 | 0.00–0.56 | 42 | 56 | 2 |
| Varicella zoster anterior uveitis | 163 | 0.58 | 0.10 | 0.35–0.87 | 76 | 23 | 1 |
| Fuchs uveitis syndrome | 249 | 0.44 | 0.13 | 0.16–0.65 | 59 | 41 | <1 |
| Juvenile idiopathic arthritis chronic uveitis | 251 | 0.29 | 0.16 | −0.02 to 0.64 | 80 | 19 | 1 |
| Spondylitis/human leukocyte antigen-B27–associated uveitis | 251 | 0.47 | 0.11 | 0.27–0.71 | 74 | 22 | 4 |
| Tubulointerstitial nephritis with uveitis | 125 | 0.54 | 0.22 | 0.16–0.87 | 76 | 24 | 0 |
| Pars planitis | 308 | 0.32 | 0.15 | −0.04 to 0.63 | 74 | 25 | 1 |
| Intermediate uveitis, non–pars planitis type | 209 | 0.49 | 0.09 | 0.27–0.67 | 55 | 45 | 0 |
| Multiple sclerosis associated uveitis | 183 | 0.44 | 0.08 | 0.31–0.62 | 62 | 38 | <1 |
| Acute posterior multifocal placoid pigment epitheliopathy | 149 | 0.44 | 0.12 | 0.17–0.84 | 52 | 48 | 0 |
| Birdshot chorioretinitis | 257 | 0.36 | 0.09 | 0.20–0.57 | 81 | 18 | 1 |
| Multiple evanescent white dot syndrome | 95 | 0.39 | 0.12 | 0.10–0.75 | 54 | 44 | 2 |
| Multifocal choroiditis with panuveitis | 251 | 0.30 | 0.13 | 0.02–0.58 | 57 | 42 | 1 |
| Punctate inner choroiditis | 250 | 0.52 | 0.08 | 0.32–0.70 | 58 | 42 | 0 |
| Serpiginous choroiditis | 157 | 0.37 | 0.19 | −0.02 to 0.69 | 78 | 22 | <1 |
| Serpiginous-like tuberculous choroiditis | 104 | 0.28 | 0.15 | −0.02 to 0.55 | 92 | 8 | 0 |
| Acute retinal necrosis | 252 | 0.43 | 0.18 | 0.13–0.61 | 75 | 25 | <1 |
| Cytomegalovirus retinitis | 251 | 0.27 | 0.16 | 0.07–0.65 | 84 | 16 | 0 |
| Syphilitic uveitis | 250 | 0.47 | 0.12 | 0.15–0.68 | 86 | 14 | 0 |
| Toxoplasmic retinitis | 213 | 0.23 | 0.14 | 0.03–0.53 | 82 | 17 | 1 |
| Tuberculous uveitis | 254 | 0.24 | 0.16 | 0.01–0.58 | 71 | 27 | 2 |
| Behçet disease | 248 | 0.36 | 0.13 | 0.15–0.61 | 80 | 18 | 2 |
| Sarcoid uveitis | 383 | 0.56 | 0.15 | 0.23–0.86 | 72 | 28 | 0 |
| Sympathetic ophthalmia | 149 | 0.31 | 0.12 | 0.07–0.51 | 75 | 25 | <1 |
| Vogt-Koyanagi-Harada disease, early | 224 | 0.45 | 0.14 | 0.16–0.72 | 69 | 30 | 1 |
| Vogt-Koyanagi-Harada disease, late | 177 | 0.42 | 0.14 | 0.13–0.68 | 58 | 41 | 1 |
| Overall | 5766 | 0.39 | 0.14 | −0.04 to 1.00 | 71 | 28 | 1 |

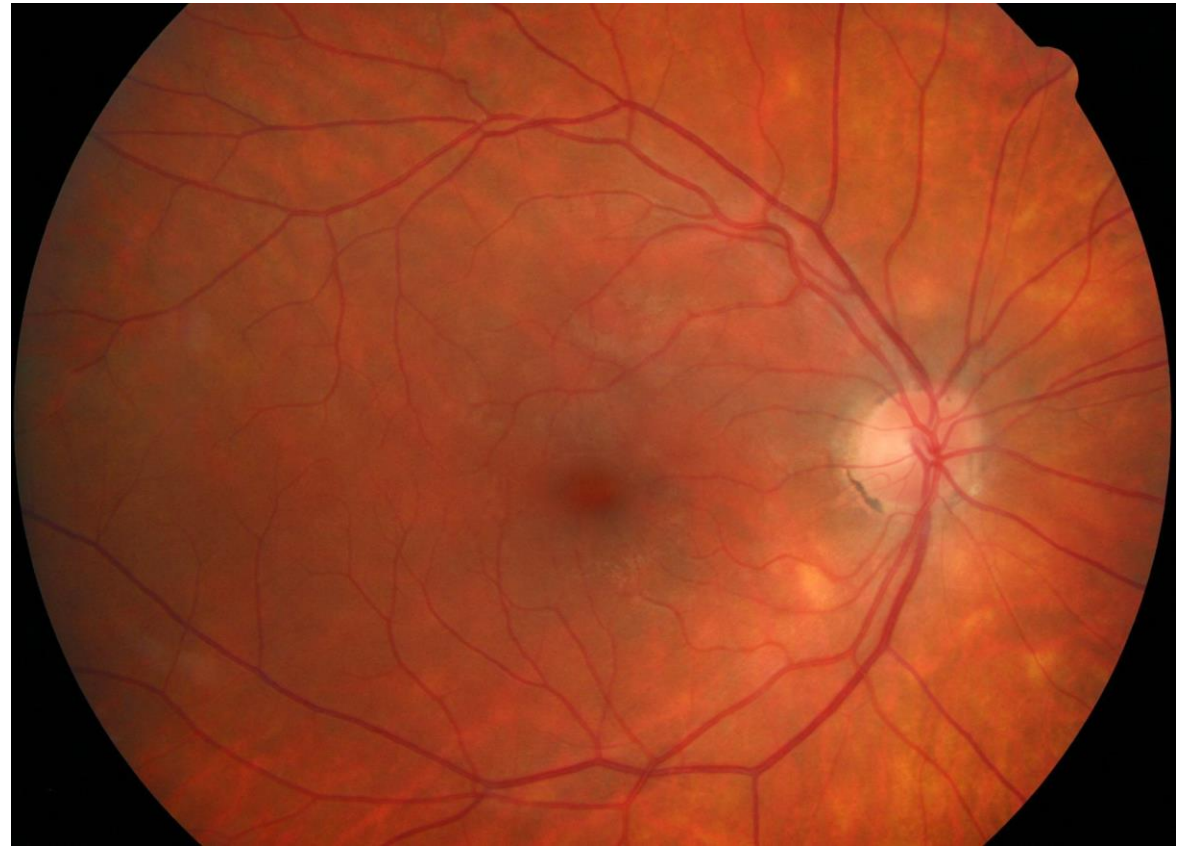
SD = standard deviation.

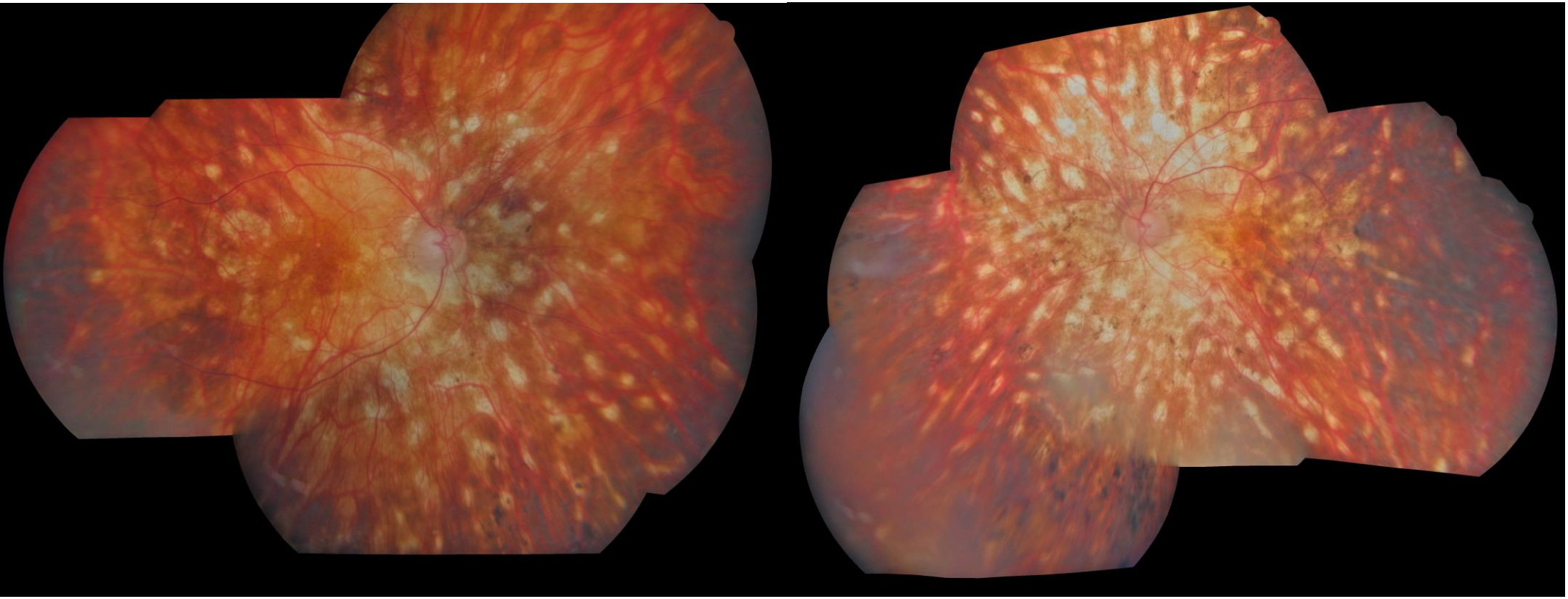
[a]Range of the κs for the pairwise comparisons within a disease.

*Jabs et al. Am J Ophthalmol 2018;186:19–24*

**Birdshot** k  Moyenne : 0.36 ± 0.09  Range 0.20–0.57

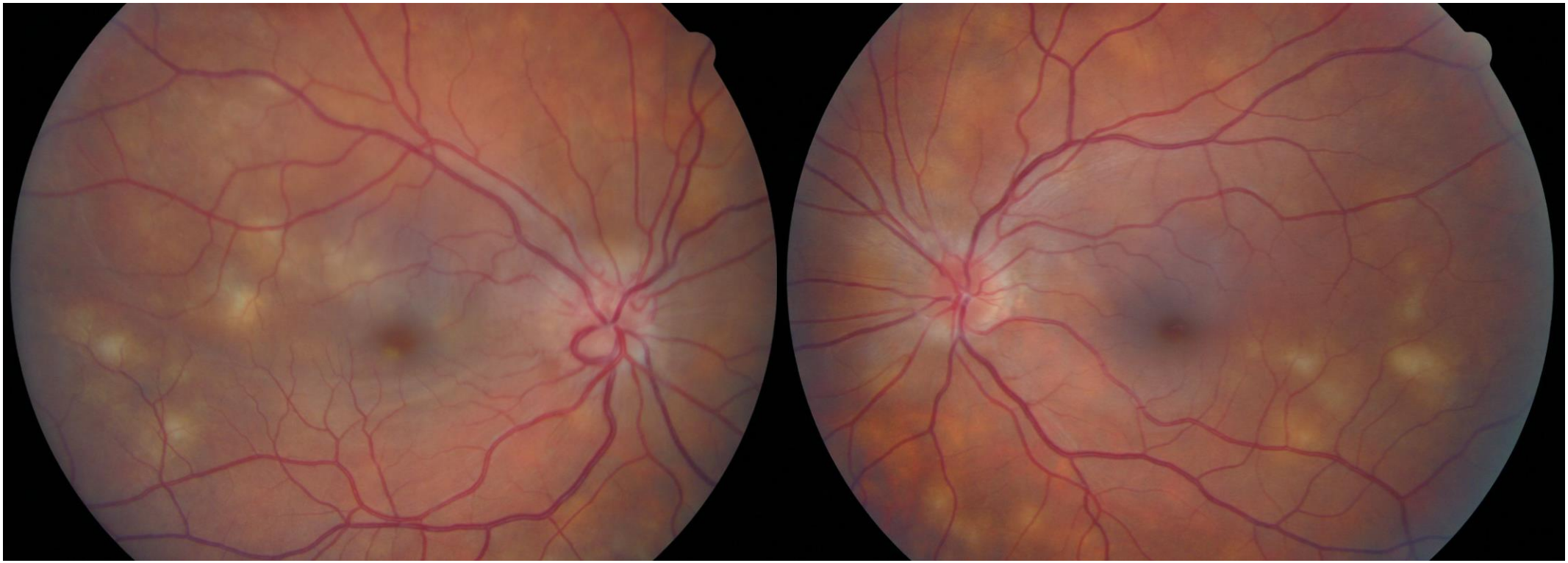




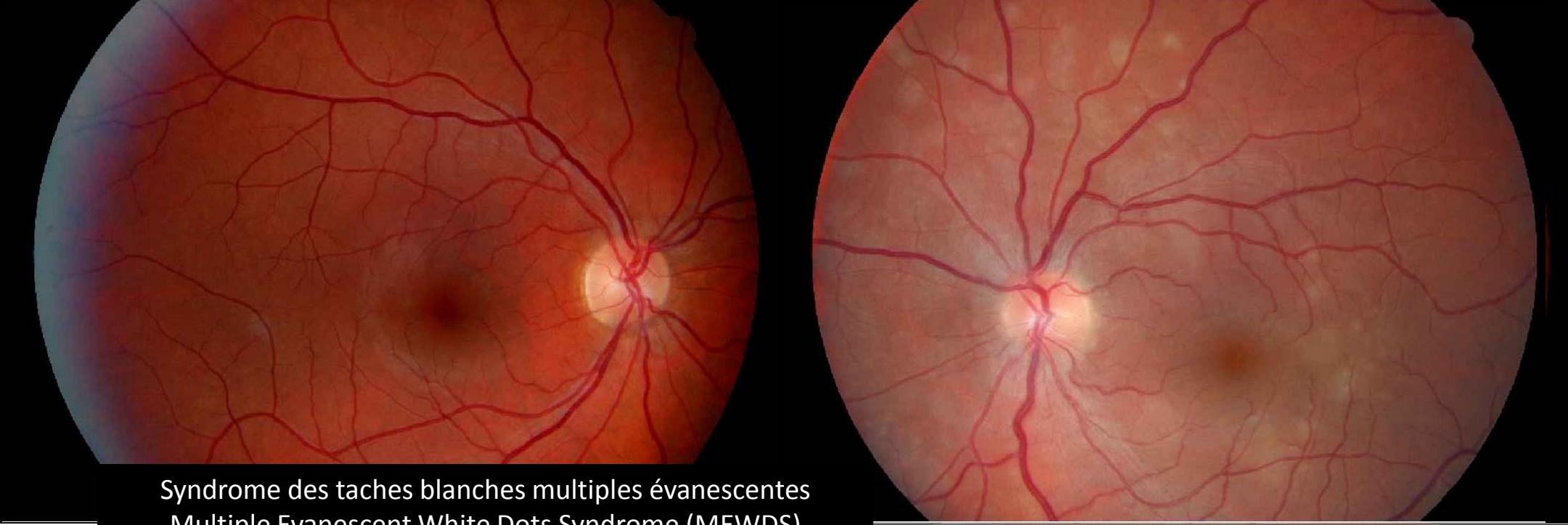


Late stage birdshot chorioretinopathy

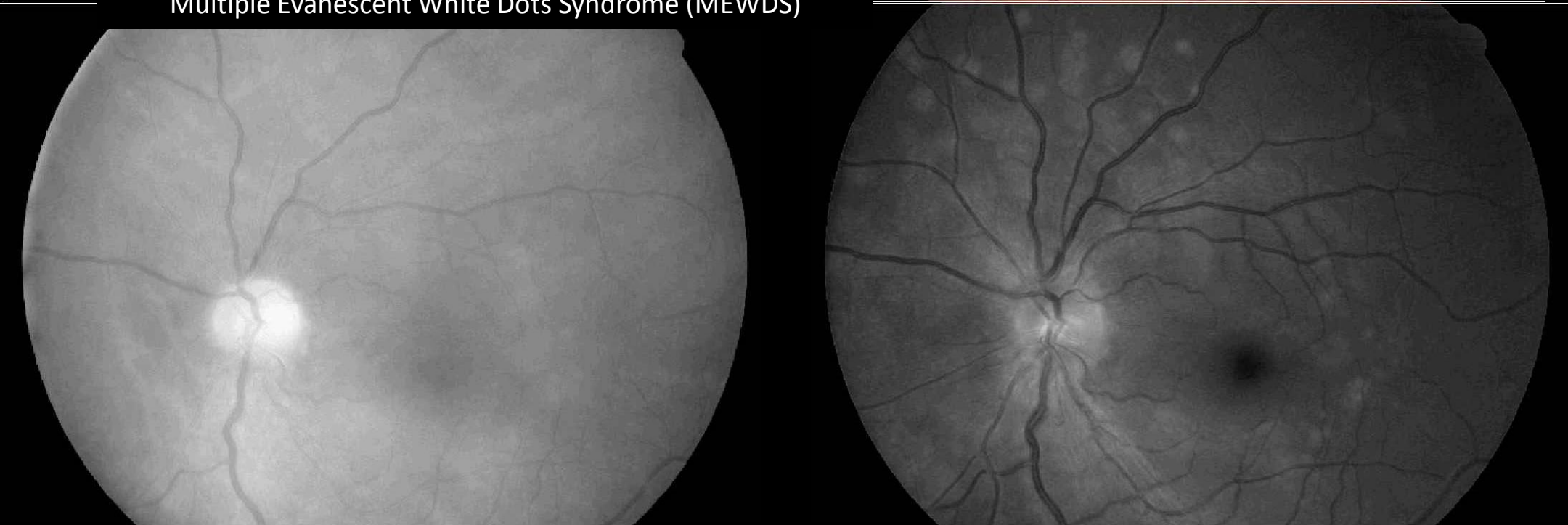
# D’autres taches blanches

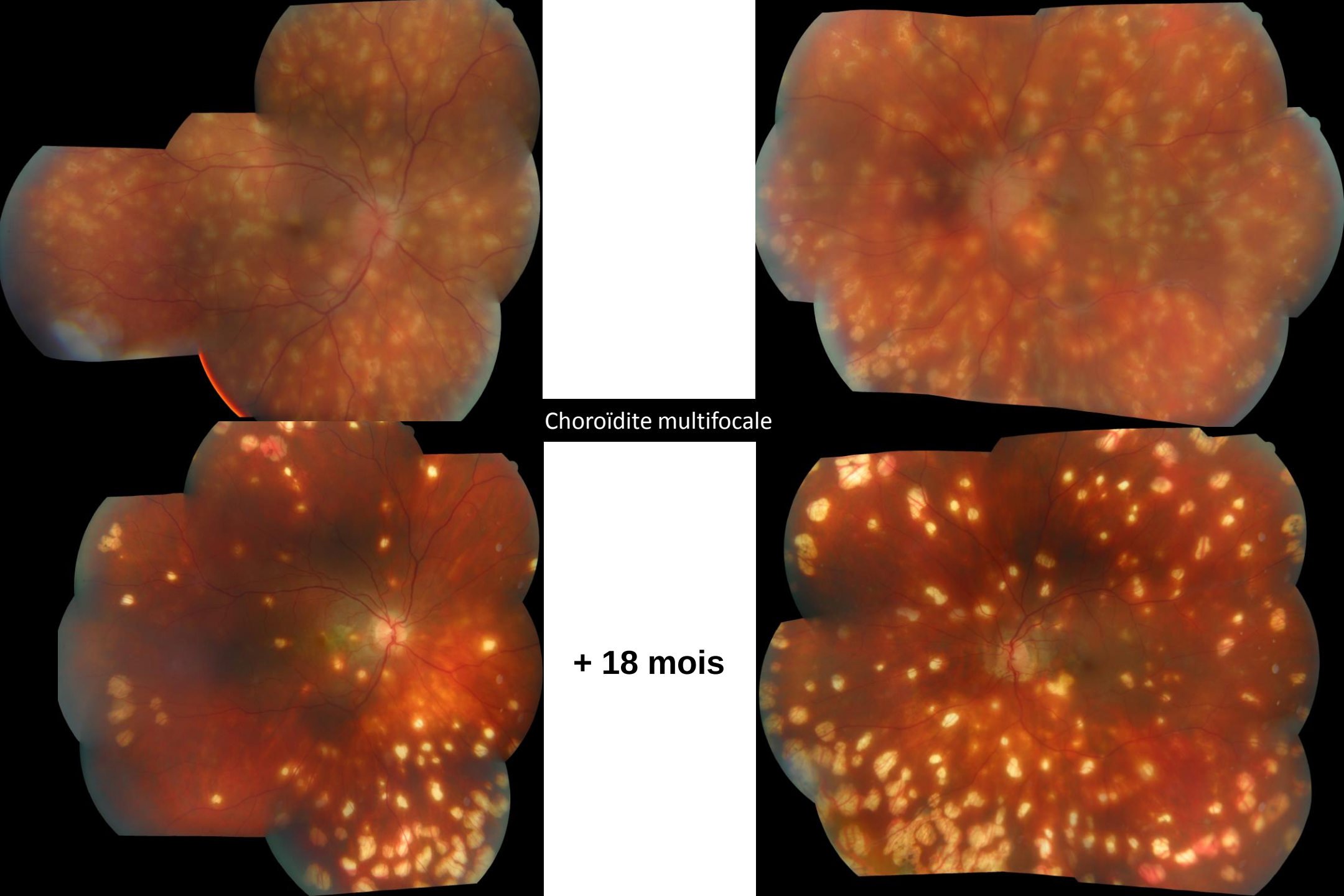


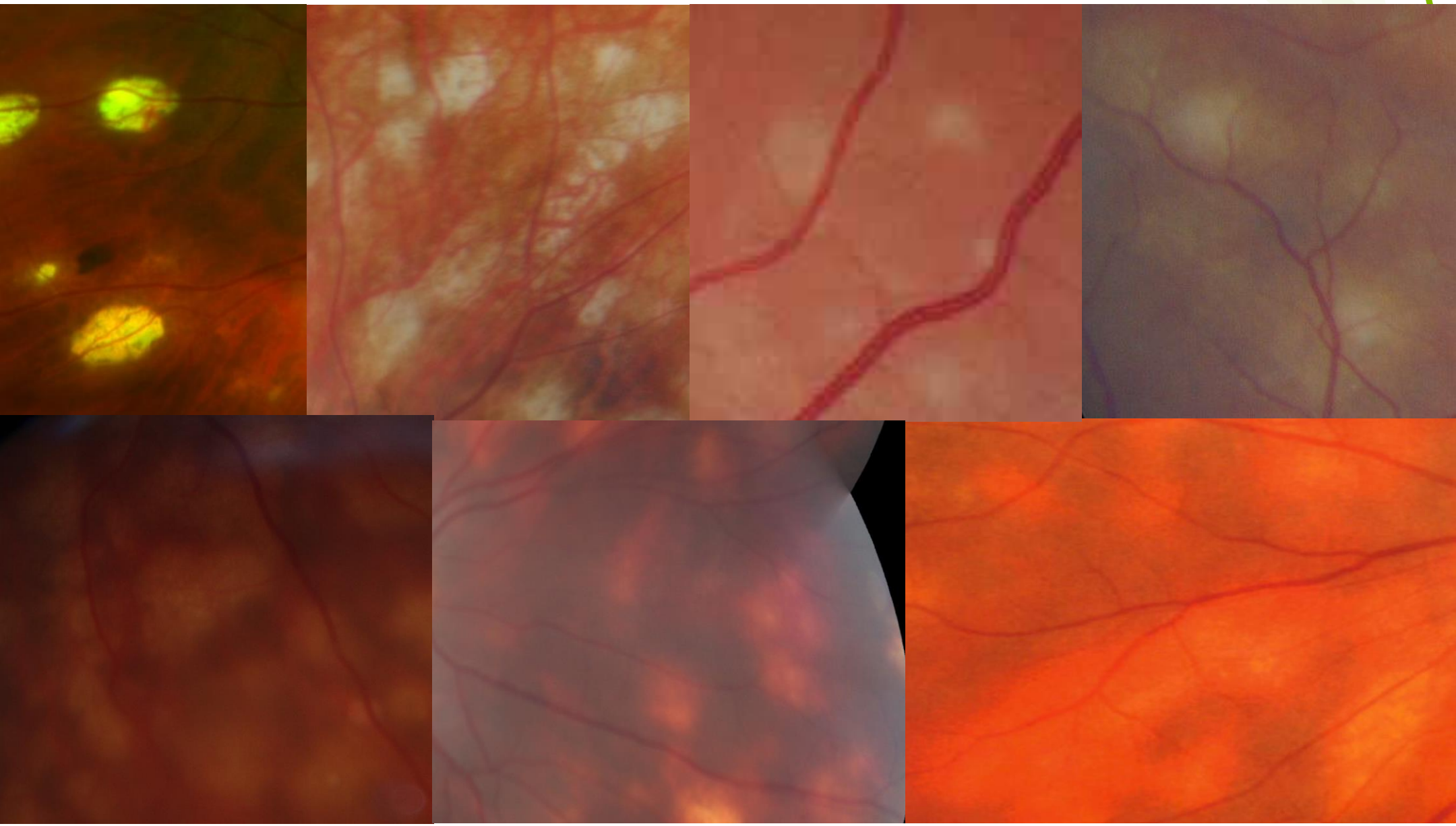
Tuberculose



Syndrome des taches blanches multiples évanescentes
Multiple Evanescent White Dots Syndrome (MEWDS)



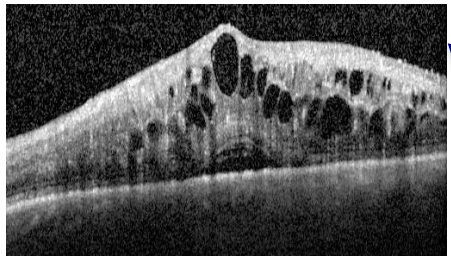

Choroïdite multifocale
+ 18 mois



# Evaluer le retentissement

## Œdème maculaire

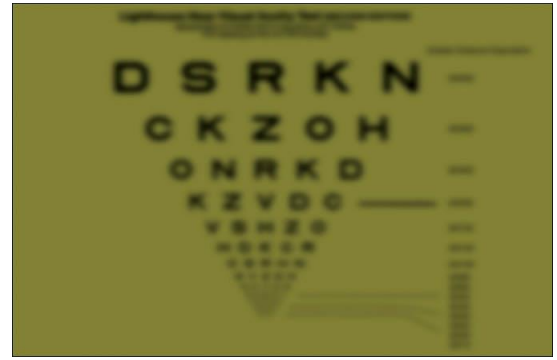
(µm)



250µm

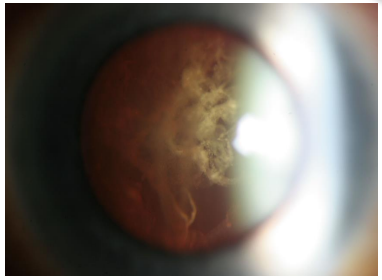
1000µm

## Acuité visuelle




20/20

## Inflammation en chambre antérieure et dans le vitré

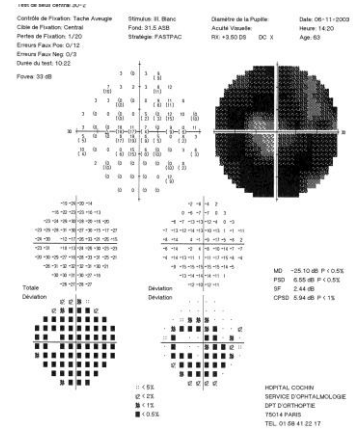


0 1+ 2+ 3+ 4+

NLP

## Champ visuel

(MD)



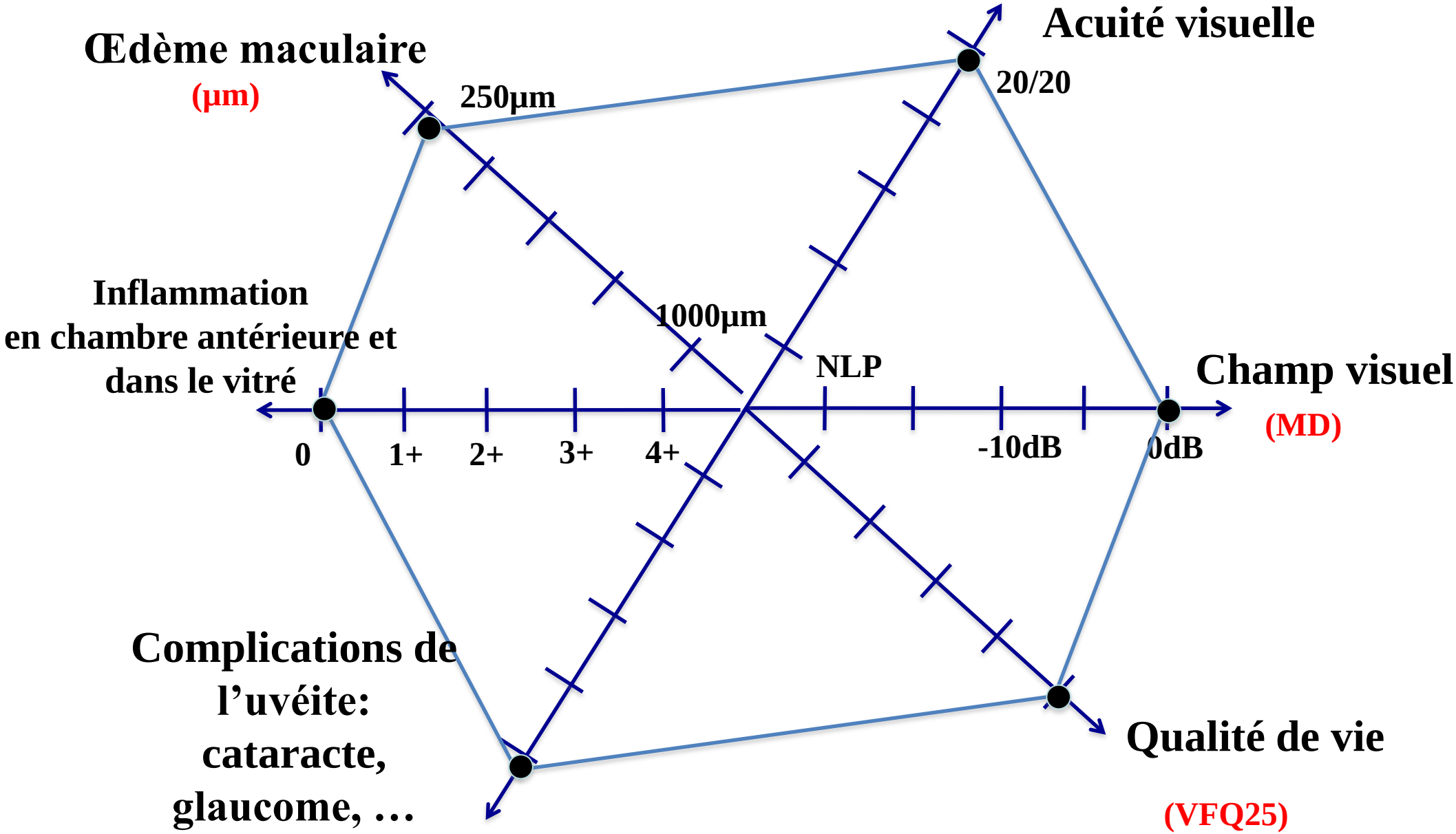
-10dB 0dB

## Complications de l'uvéite: cataracte, glaucome

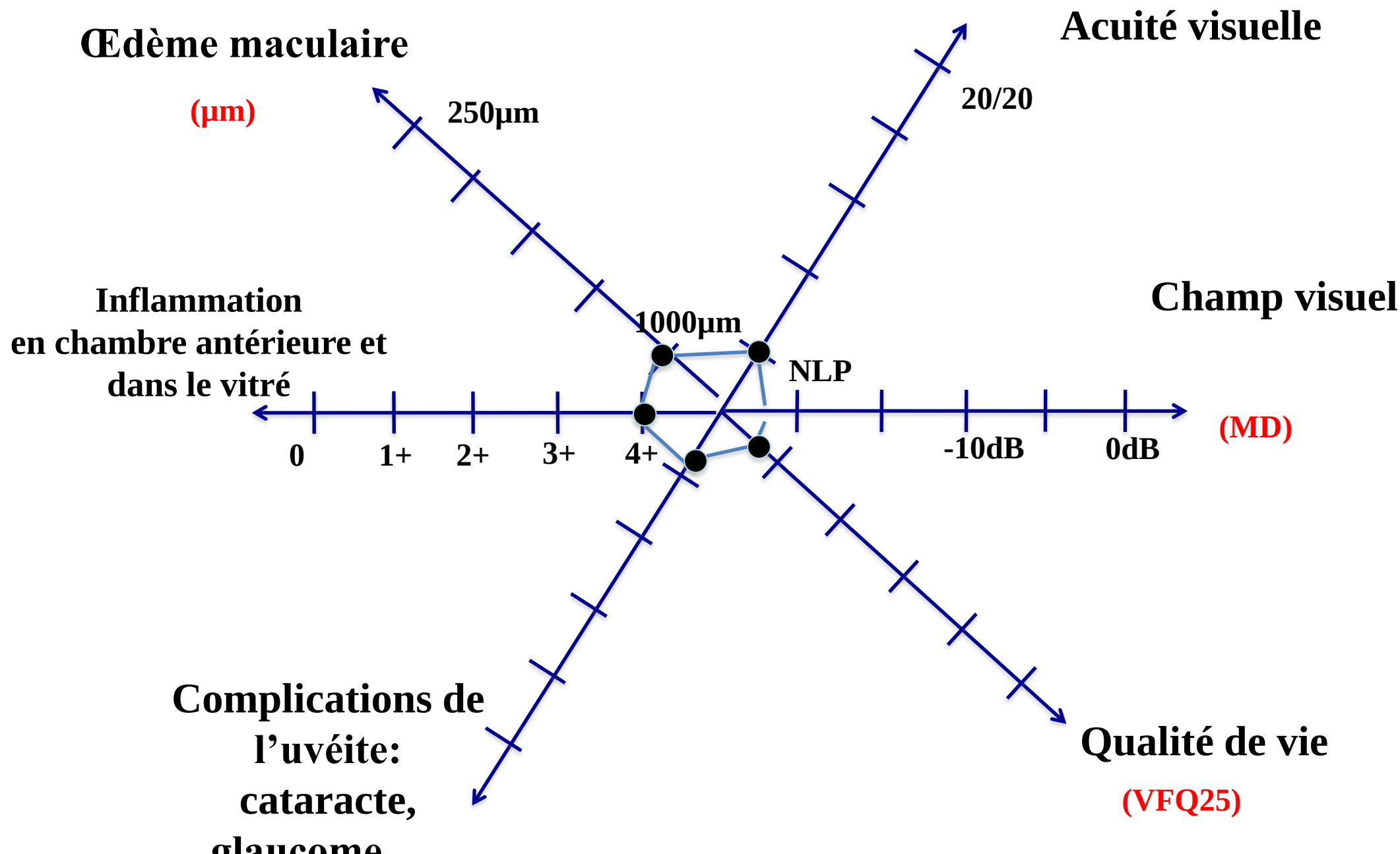
## Qualité de vie

(VFQ25)

# Quiescence et absence de lésion oculaire irréversible



# Uvéite active “catastrophique”



1. Standardiser l’évaluation ophtalmologique
2. Standardiser la recherche de l’étiologie
3. Standardiser la démarche thérapeutique

# Relevance of diagnostic investigations in patients with uveitis: Retrospective cohort study on 300 patients☆

Jérôme Hadjadj [a], Agnès Dechartres [b,c,d], Thibaut Chapron [e], Manal Assala [a], Sawsen Salah [b,e], Bertrand Dunogué [a,b], Lucile Musset [f], Bruno Baudin [g], Matthieu Groh [a,b], Philippe Blanche [a,b], Luc Mouthon [a,b], Dominique Monnet [b,e], Claire Le Jeunne [a,b], Antoine Brézin [b,e], Benjamin Terrier [a,b,*]

[a] Department of Internal Medicine, National Referral Center for Rare Systemic Autoimmune Diseases, Hôpital Cochin, Assistance Publique-Hôpitaux de Paris (AP-HP), Paris, France
[b] Faculté de Médecine, Université Paris Descartes, Sorbonne Paris Cité, Paris, France
[c] Centre de Recherche Epidémiologie et Statistique, INSERM U1153, Paris, France
[d] Centre d'Epidémiologie Clinique, Hôpital Hôtel-Dieu, AP-HP, Paris, France
[e] Department of Ophthalmology, Hôpital Cochin, AP-HP, Paris, France
[f] Department of Immunology, Immunochemistry & Autoimmunity Laboratory, Hôpital Pitié-Salpêtrière, AP-HP, Paris, France
[g] Department of Biochemistry, Hôpital Saint-Antoine, AP-HP, Paris, France

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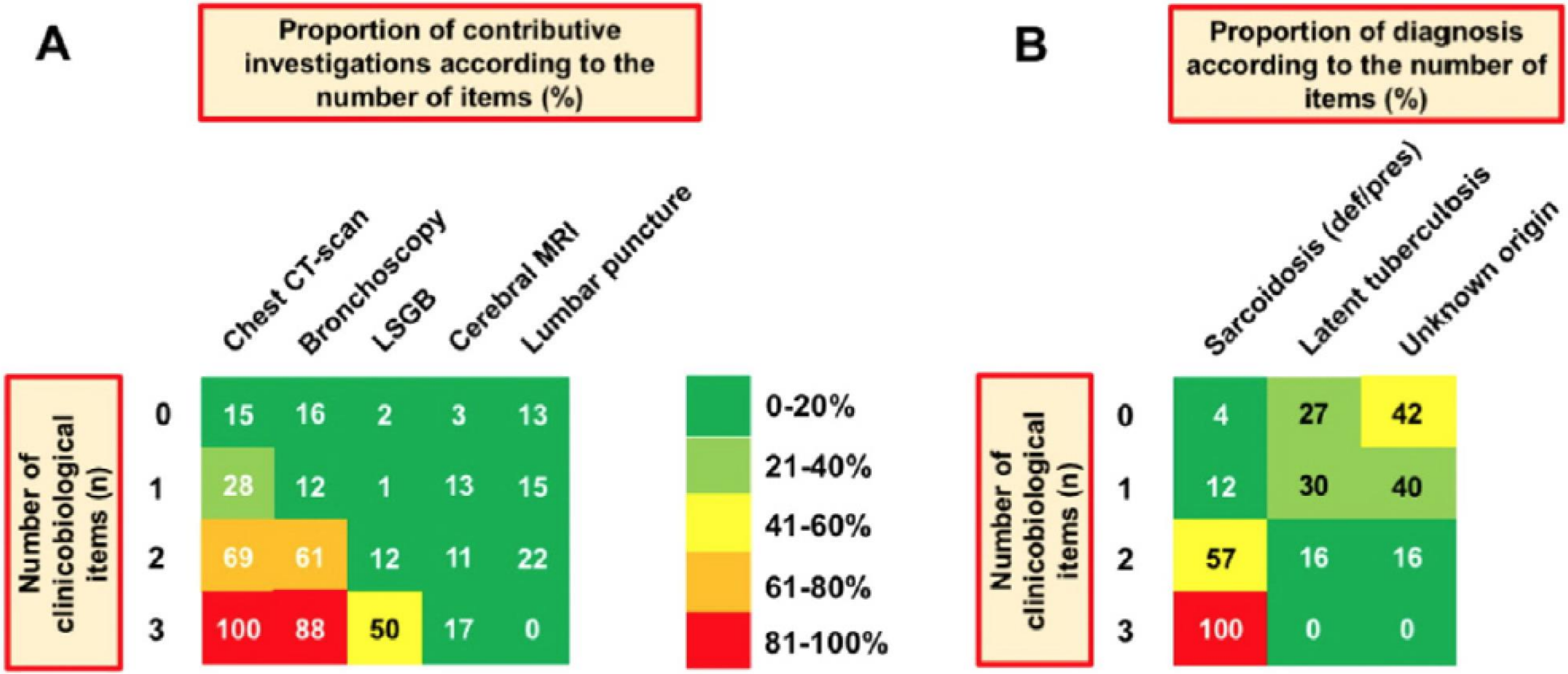
ABSTRACT

*Objective:* The diagnostic workup of uveitis is a challenge due to the wide range of diagnoses and the lack of a well-codified diagnostic procedure. We aimed to evaluate the relevance of diagnostic investigations for the etiological diagnosis of uveitis.

*Methods:* Retrospective cohort study of patients referred for etiological diagnosis of uveitis. Uveitis related to ophthalmological diseases or occurring during the course of previously diagnosed diseases were not included.

*Results:* Three hundred patients were included. Chest CT-scan was suggestive of sarcoidosis in 83 (29%). Features associated with abnormal CT-scan were: snowballs and/or peripheral multifocal choroiditis (PMC) upon ocular examination ($P = 0.004$), blood lymphopenia ($P < 0.0001$), angiotensin converting enzyme (ACE) level > 1.5 ULN ($P = 0.0003$). Bronchoscopy showed granuloma in 18 (11%) while alveolar lymphocytosis suggestive of sarcoidosis was reported in 45 (27%). Presence of granuloma on bronchial biopsies was always associated with chest CT-scan abnormalities, whereas 31% of patients with alveolar lymphocytosis had normal CT-scans. Features associated with contributive bronchoscopy were: snowballs and/or PMC ($P = 0.003$), ACE > 1.5 ULN ($P = 0.007$), abnormal chest-CT scan ($P < 0.0001$). Salivary gland biopsy revealed granuloma in 12 patients (5%). Cerebral MRI was abnormal in 15 patients (9%) who mostly presented with snowballs and/or retinal vasculitis. Finally, the main causes of uveitis were latent tuberculosis (25%) and sarcoidosis (22%), but 34% remained of undetermined origin. Uveitis relapses were observed in 31% and did not differ between patients with an identified diagnosis and those with idiopathic uveitis.

*Conclusion:* Identification of factors associated with abnormal investigations might improve the optimal diagnostic workup adapted to each patient.




**Figures indicated the proportion of contributive investigations or of specific diagnosis according to the number of the following features:**

1) **Presence of snowballs and/or PMC upon ocular examination**
2) **Lymphopenia**
3) **ACE level >1.5 ULN**

Fig. 2. Performance of clinicobiological features to predict contribution of investigations and uveitis diagnoses.

# Randomized Controlled Trial Evaluating a Standardized Strategy for Uveitis Etiologic Diagnosis (ULISSE)

AUDREY DE PARISOT, LAURENT KODJIKIAN, MARIE-HÉLÈNE ERRERA, NEILA SEDIRA, EMMANUEL HERON, LAURENT PÉRARD, PIERRE-LOÏC CORNUT, CHRISTELLE SCHNEIDER, SOPHIE RIVIÈRE, PRISCILLE OLLÉ, GRÉGORY PUGNET, PASCAL CATHÉBRAS, PIERRE MANOLI, BAHRAM BODAGHI, DAVID SAADOUN, STÉPHANIE BAILLIF, NATHALIE TIEULIE, MARC ANDRE, FRÉDÉRIC CHIAMBARETTA, NICOLAS BONIN, PHILIP BIELEFELD, ALAIN BRON, FRÉDÉRIC MOURIAUX, BORIS BIENVENU, STÉPHANIE VICENTE, SYLVIE BIN, CHRISTIANE BROUSSOLLE, EVELYNE DECULLIER, PASCAL SÈVE, AND THE ULISSE GROUP

• PURPOSE: To prospectively assess the efficiency of a standardized diagnostic approach, compared to an open strategy, for the etiologic diagnosis of uveitis.

• DESIGN: Noninferiority, prospective, multicenter, clustered randomized controlled trial.

• METHODS: Consecutive patients with uveitis, who visited 1 of the participating departments of ophthalmology, were included. In the standardized group, all patients had a minimal evaluation regardless of the type of uveitis (complete blood count, erythrocyte sedimentation rate, C-reactive protein, tuberculin skin test, syphilis serology, and chest radiograph) followed by more complex investigations according to ophthalmologic findings. In the open group, the ophthalmologist could order any type of investigation. Main outcome was the percentage of etiologic diagnoses at 6 months.

• RESULTS: Nine hundred and three patients with uveitis were included from January 2010 to May 2013 and the per-protocol population comprised 676 patients (open 373; standardized 303). Mean age at diagnosis was 46 years. Anatomic distribution of uveitis was as follows: anterior (60.8% and 72.3%, $P = .0017$), intermediate (11.7% and 12.3%, $P = .8028$), posterior (17.8% and 8.2%, $P = .0004$), and panuveitis (15.3% and 15.2%, $P = .9596$). An etiologic diagnosis was established in 54.4% of cases in the open group and 49.5% in the standardized group ($P = .2029$). The difference between both strategies (standardized minus open) was −4.9% (95% CI [−12.5%; 2.6%]). There were more investigations in the open group than in the standardized group (5371 vs 3759, $P < .0001$).

• CONCLUSION: The standardized strategy appears to be an efficient diagnostic approach for the etiologic diagnosis of uveitis, although its noninferiority cannot be proved. 

EXTENDED REPORT

# A novel evidence-based detection of undiagnosed spondyloarthritis in patients presenting with acute anterior uveitis: the DUET (Dublin Uveitis Evaluation Tool)

Muhammad Haroon,[1] Michael O'Rourke,[2] Pathma Ramasamy,[3] Conor C Murphy,[3] Oliver FitzGerald[1]

*Ann Rheum Dis 2015;74:1990–1995*

## ABSTRACT

**Background** To date, there are no formal guidelines or referral pathways for acute anterior uveitis (AAU) patients developed or endorsed by any international or national societies. The objective of our study was to develop and validate an assessment algorithm for referral from ophthalmologists of appropriate AAU patients to rheumatology that will aid the early diagnosis of the spondyloarthropathy (SpA).

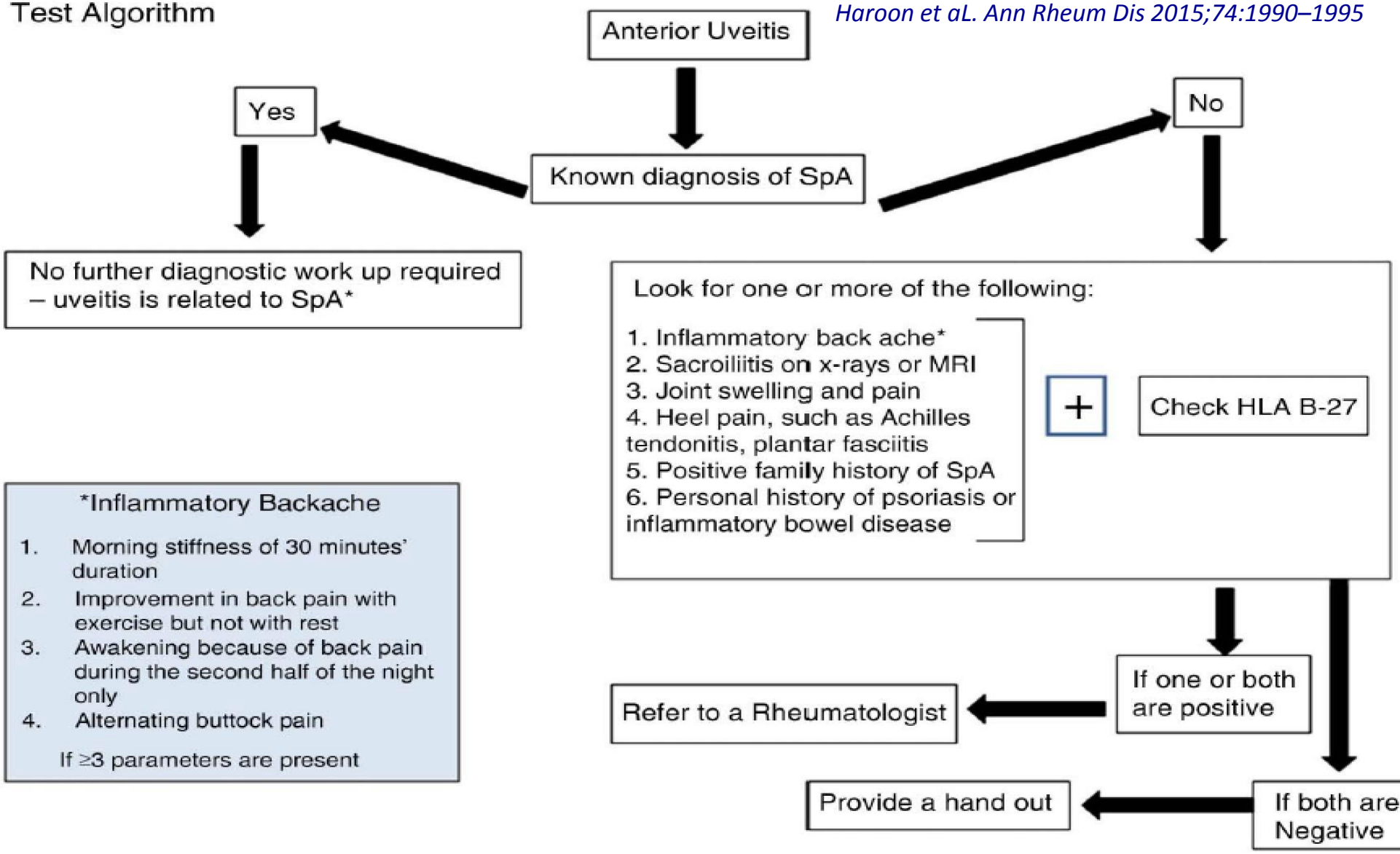
**Methods** All consecutive patients attending the emergency department of local ophthalmology hospital with AAU, but who did not have a known diagnosis of SpA, were eligible to participate in this study. Patients with any other known cause of AAU were excluded. Two independent cohorts were enrolled. Test algorithm and Dublin Uveitis Evaluation Tool (DUET) algorithm (revised form of test algorithm) were used in these cohorts to identify patients as SpA suspects and non-SpA controls, respectively.

**Results** STUDY PHASE-1. ALGORITHM DEVELOPMENT COHORT (n=101): After rheumatologic evaluation of the entire cohort, 41.6% (n=42) had undiagnosed SpA. Our test algorithm was noted to have: sensitivity 100% and specificity 53.5%. Further regression analysis resulted in the development of the DUET algorithm which made the following improvements: sensitivity 95%, specificity 98%, positive likelihood ratio (LR) 56.19, and negative LR 0.04. STUDY PHASE-2. DUET ALGORITHM VALIDATION COHORT (n=72): After rheumatologic evaluation of the cohort, 40% (n=29) were diagnosed with SpA, with the following performance of DUET algorithm—sensitivity 96%, specificity 97%, positive LR 41.5 and negative LR 0.03.

**Conclusions** Approximately 40% of patients presenting with idiopathic AAU have undiagnosed SpA. A simple to apply algorithm is described with excellent sensitivity and specificity.

Test Algorithm

*Haroon et aL. Ann Rheum Dis 2015;74:1990–1995*



# Ophthalmic Findings and Frequency of Extraocular Manifestations in Patients with HLA-B27 Uveitis

## *A Study of 175 Cases*

*Dominique Monnet, MD,[1] Maxime Breban, MD, PhD,[2] Christophe Hudry, MD,[2] Maxime Dougados, MD,[2] Antoine P. Brézin, MD, PhD[1]*

***Objective:*** To analyze ocular and extraocular manifestations in patients with HLA-B27–associated uveitis.

***Design:*** Large, observational case series.

***Participants:*** One hundred seventy-five consecutive patients with HLA-B27–associated uveitis seen in a single center between January 1996 and March 2001.

***Methods:*** Features of uveitis were noted and patients were referred systematically to rheumatologists. The history of previous uveitis attacks and extraocular manifestations of spondyloarthropathy was recorded. Assessments of spondyloarthropathies were based on criteria established by the European Spondyloarthropathy Study.

***Main Outcome Measures:*** Percentage of patients with extraocular manifestations. The time between the first episode of uveitis and symptoms or diagnosis of extraocular disease was estimated. Characteristics of uveitis were analyzed.

***Results:*** The male-to-female ratio was 1.3 to 1, and the median age at the time of the first attack of uveitis was 31 years. An HLA-B27–associated extraocular disorder was seen in 136 cases (77.7%). Of these, ankylosing spondylitis was diagnosed in 81 patients (46.3%) and presumed in 17 (9.7%). Undifferentiated spondyloarthropathy was observed in 21 patients (12%) and other HLA-B27–associated diseases in 17 patients (9.7%). The onset of extraocular symptoms occurred at a younger age (mean±standard deviation [SD], 26.4±11.1 years) than the first attack of uveitis (mean±SD, 34.0±14.1 years; $P<0.0001$). The diagnosis of an extraocular disease was made only after the appearance of ophthalmic manifestations in 88 of 136 patients. Among 117 patients (66.9%) with more than 1 episode of uveitis, same eye attacks were observed in 48 of 117 patients (41.0%), more than the expected percentage than attacks of a random eye ($P<0.0001$). The median ± SD frequency of active episodes of uveitis was 0.8±0.6 per year and decreased as the duration of the disease lengthened ($P<0.0001$). Patients with extraocular disease had a greater total number of attacks of uveitis ($P = 0.02$), but other ophthalmic findings did not differ between patients with and without an extraocular disorder.

***Conclusions:*** Uveitis is frequently the first indication of a previously undiagnosed HLA-B27–associated extraocular disease. The most common of these diseases are spondyloarthropathies. *Ophthalmology 2004;111: 802–809 © 2004 by the American Academy of Ophthalmology.*

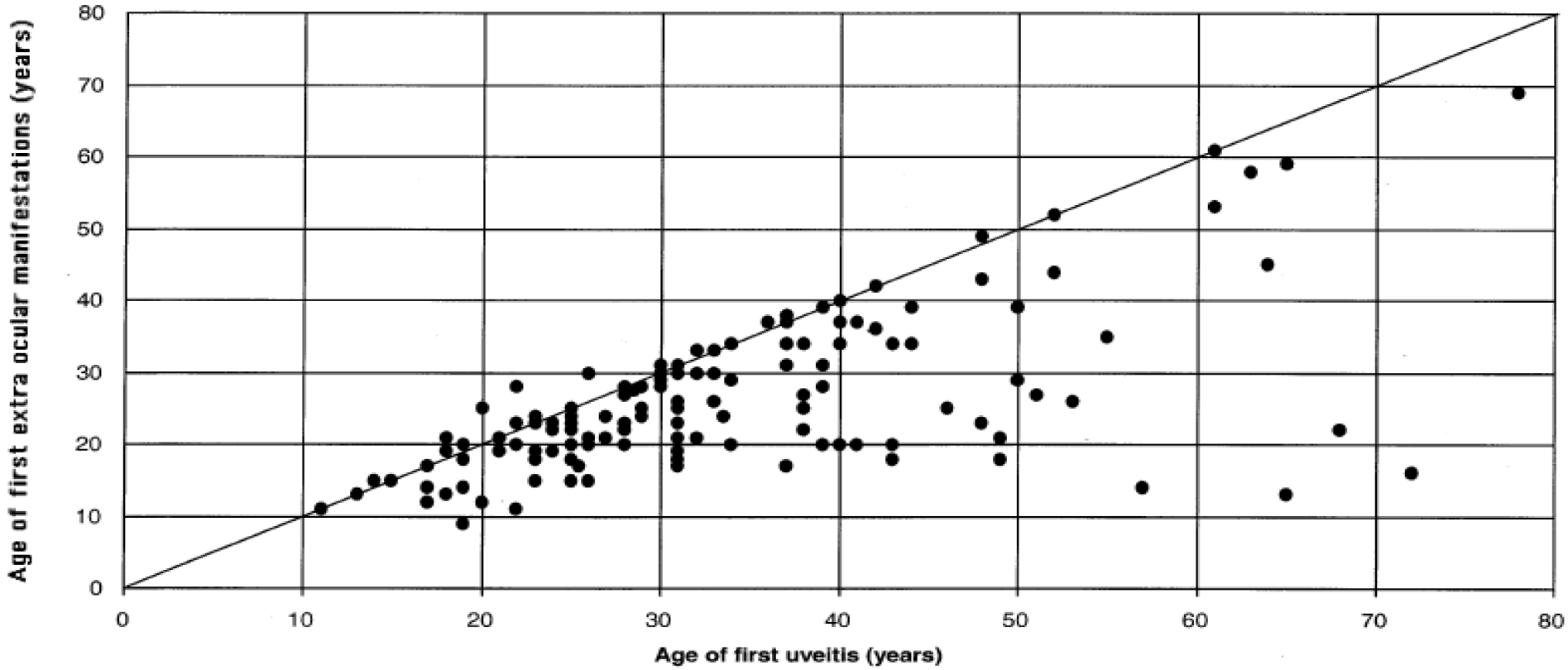



**Figure 2.** Comparison between age at the time of initial uveitis and initial extraocular manifestations.

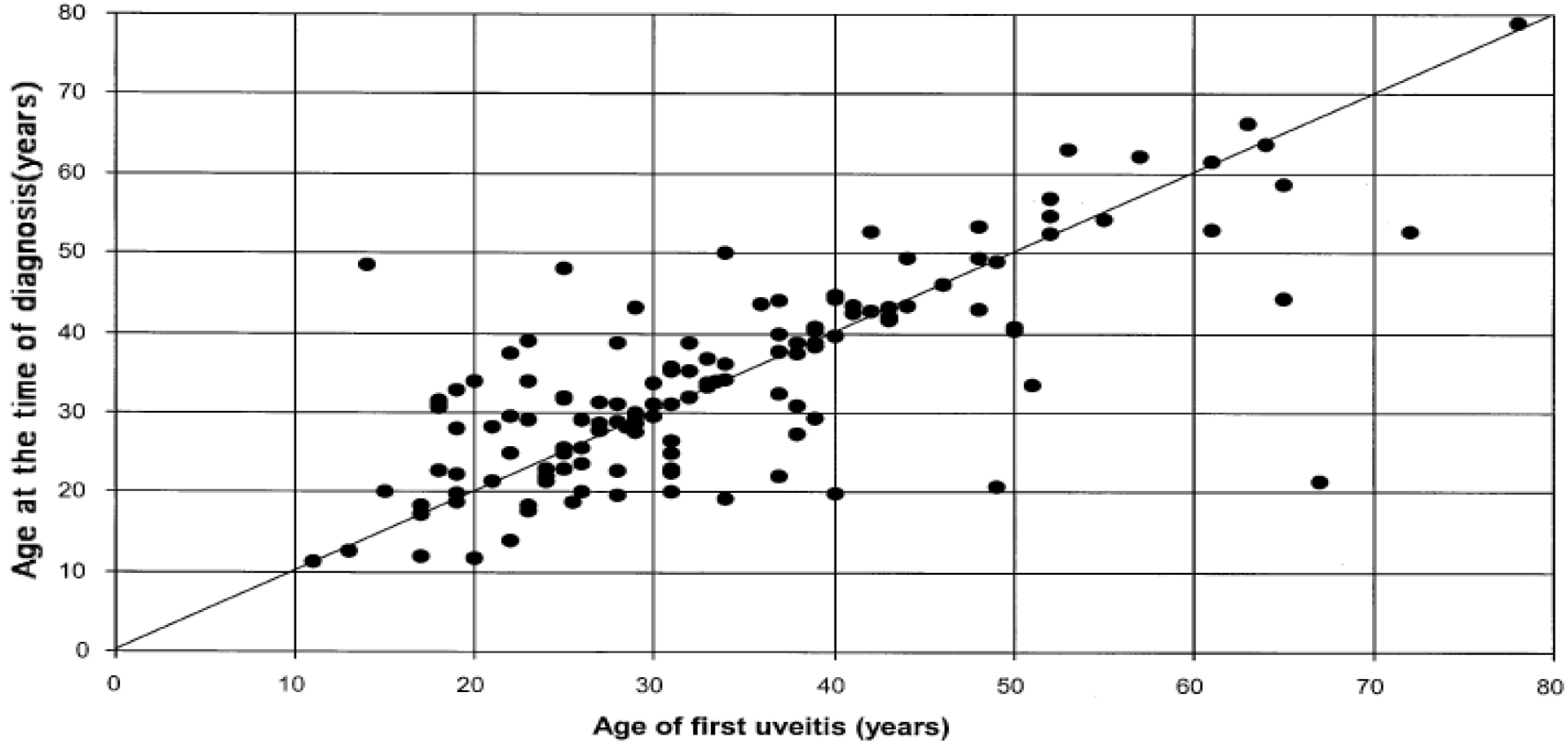



**Figure 3.** Comparison between age at time of initial uveitis and age at time of diagnosis of spondyloarthropathy.

# Description and Prevalence of Spondyloarthritis in Patients with Anterior Uveitis

## *The SENTINEL Interdisciplinary Collaborative Project*

*Xavier Juanola, MD, PhD,[1] Estíbaliz Loza Santamaría, MD,[2] Miguel Cordero-Coma, MD, PhD,[3,4] for the SENTINEL Working Group**

***Purpose:*** To describe and analyze the prevalence of spondyloarthritis (SpA) in patients with anterior uveitis (AU).

***Design:*** Multicentric, observational, prospective study.

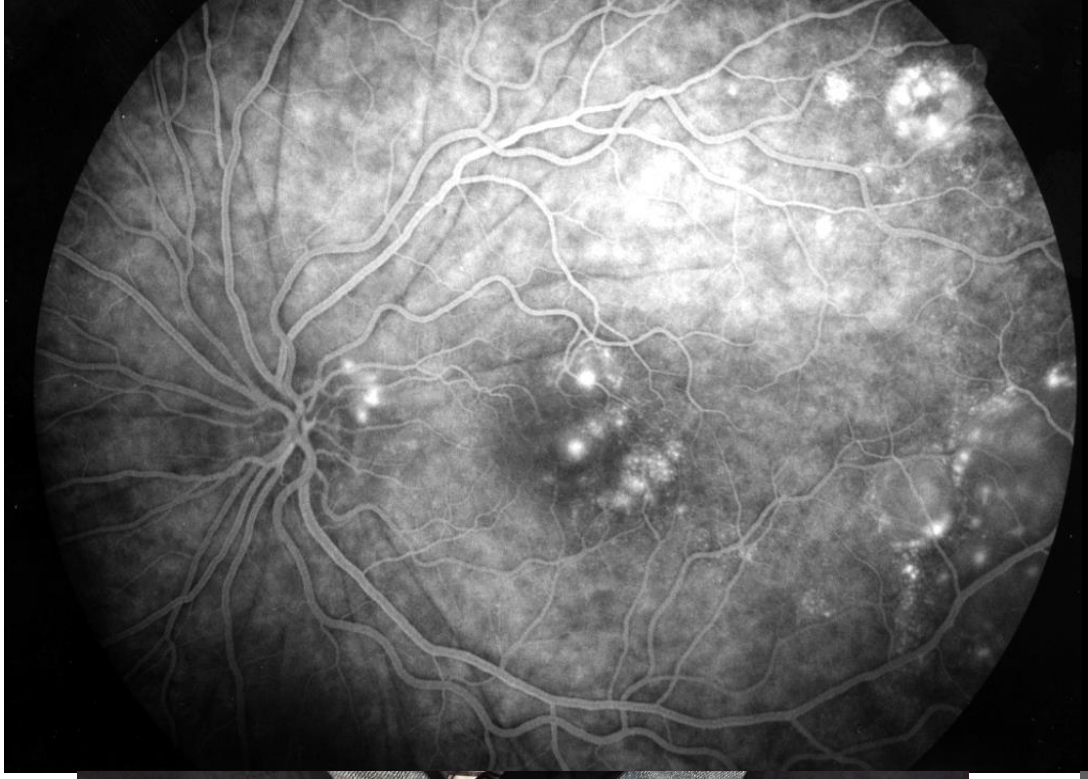
***Participants:*** Consecutive patients with AU who were human leukocyte antigen (HLA)-B27 positive or HLA-B27 negative with more than 1 episode of AU separated by at least 3 months were selected. Patients with a previous diagnosis of SpA were excluded.

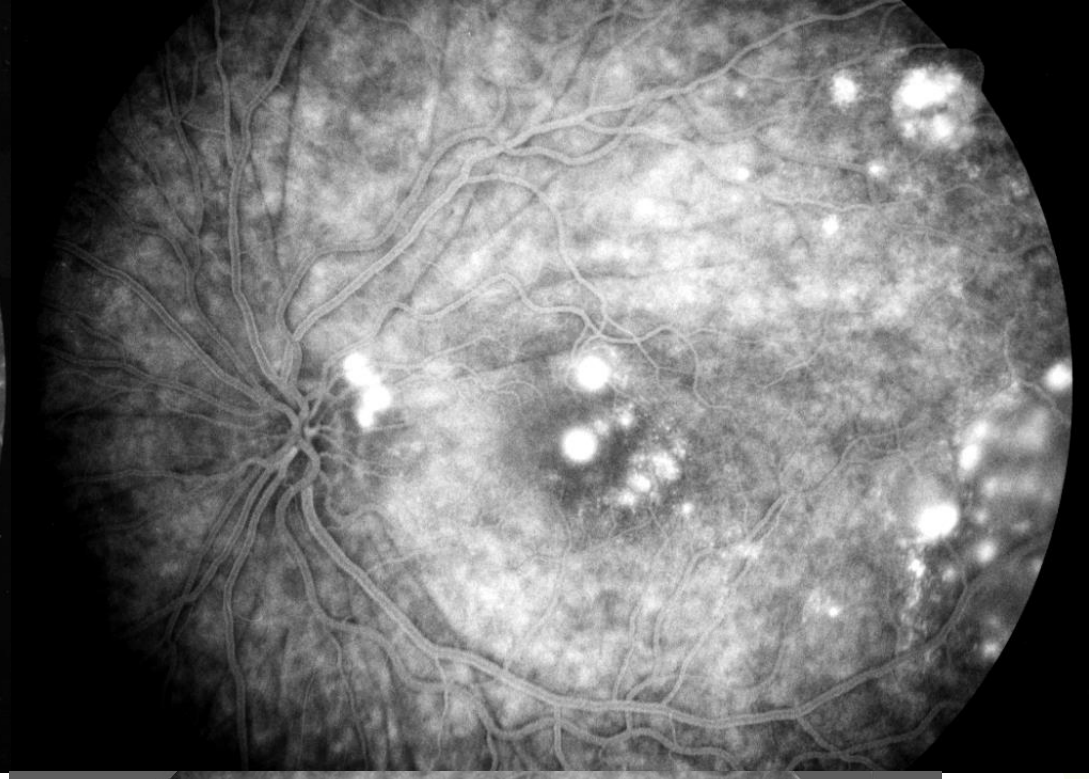
***Methods:*** Included patients were evaluated by an ophthalmologist and a rheumatologist following a predefined visit schedule.

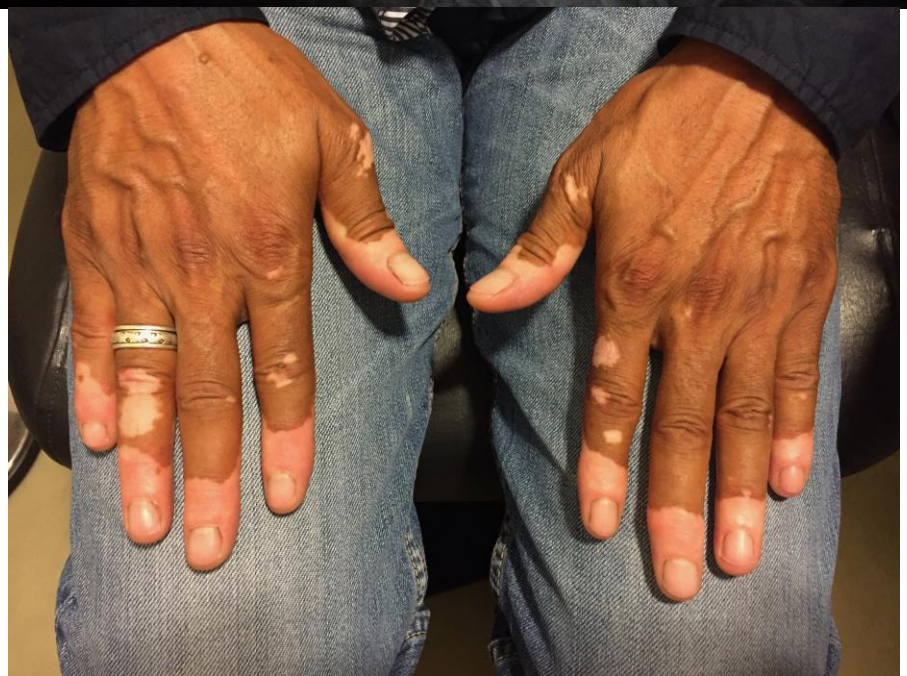
***Main Outcome Measures:*** Sociodemographic and clinical variables including the diagnosis of SpA according to Assessment of SpondyloArthritis International Society (ASAS) criteria and an exhaustive ophthalmological examination (best-corrected visual acuity, intraocular pressure, biomicroscopic examination of the anterior and posterior segment of the eye, cataract evaluation, optical coherence tomography evaluating both the 1-mm central retina thickness and the optic nerve head and retinal nerve fiber layer, and visual field in a dark room with 1 eye patched) were collected. Baseline descriptive, bivariate, and concordance analyses were performed.

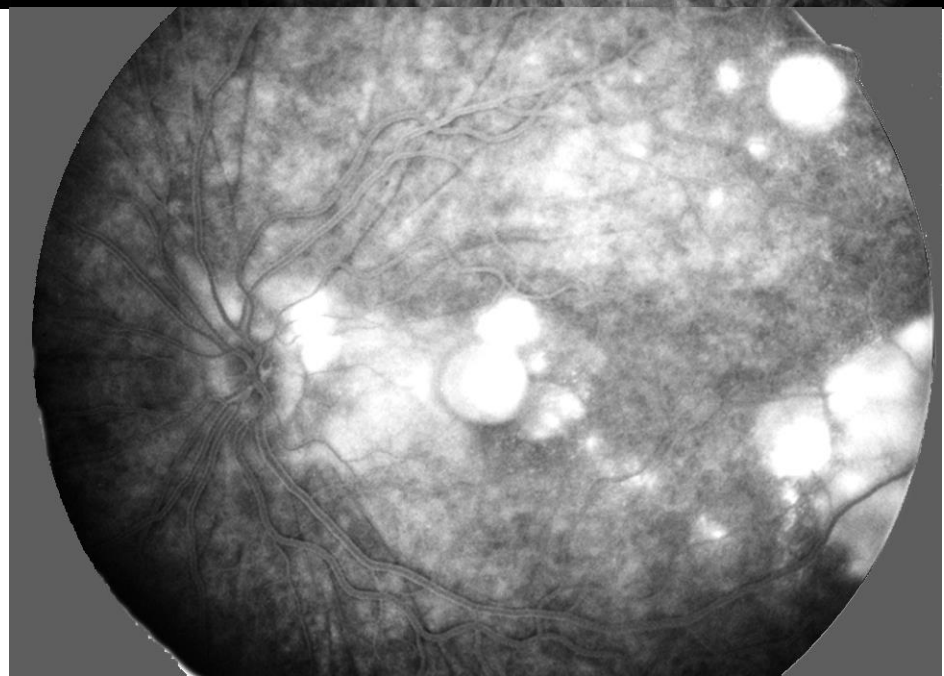
***Results:*** We included 798 patients, mostly men (59%) with a mean age of 45 years; 60% were AU HLA-B27 positive, and 40% had recurrent negative AU HLA-B27. A total of 50.2% and 17.5% of patients presented axial and peripheral SpA according to ASAS criteria, respectively. Patients with AU who were HLA-B27 positive were more frequently diagnosed with axial (69.8% vs. 27.3%, $P < 0.0001$) and peripheral SpA (21.9% vs. 11.1%, $P < 0.0001$) than patients with recurrent negative AU HLA-B27. In general, we did not detect important differences between groups in the ophthalmologic variables.

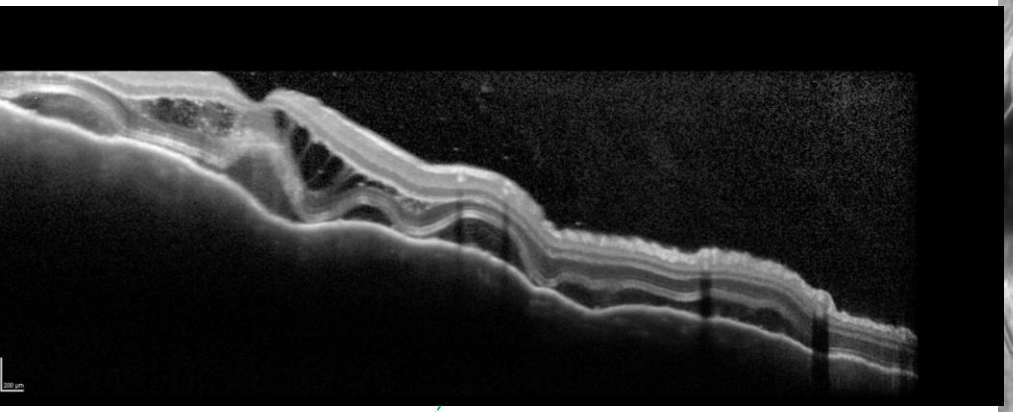
***Conclusions:*** A large percentage of patients with clinically significant AU have an undiagnosed SpA. This percentage is even higher if the HLA-B27 haplotype is positive. *Ophthalmology 2016;123:1632-1636 © 2016 by the American Academy of Ophthalmology.*

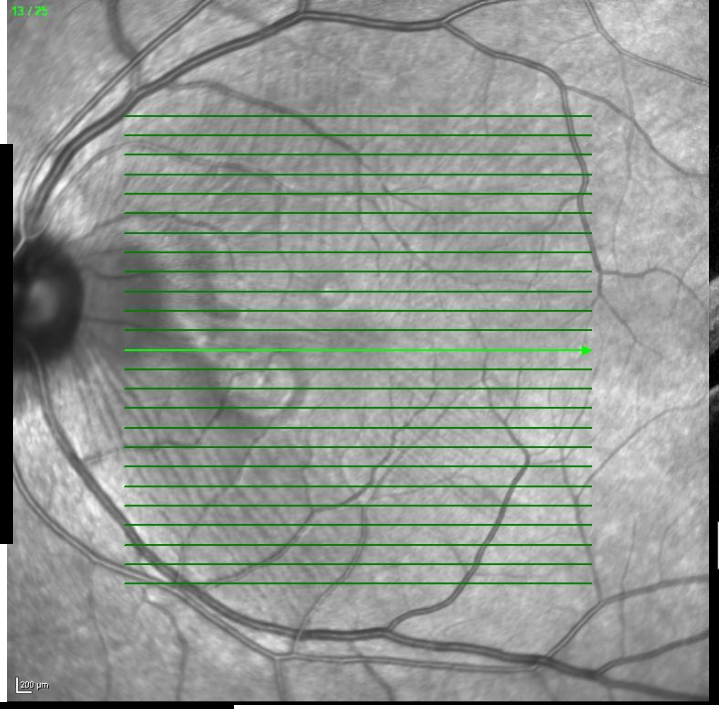








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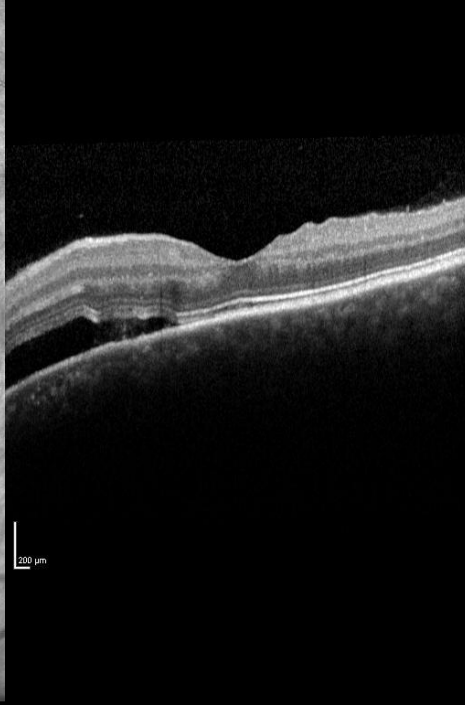
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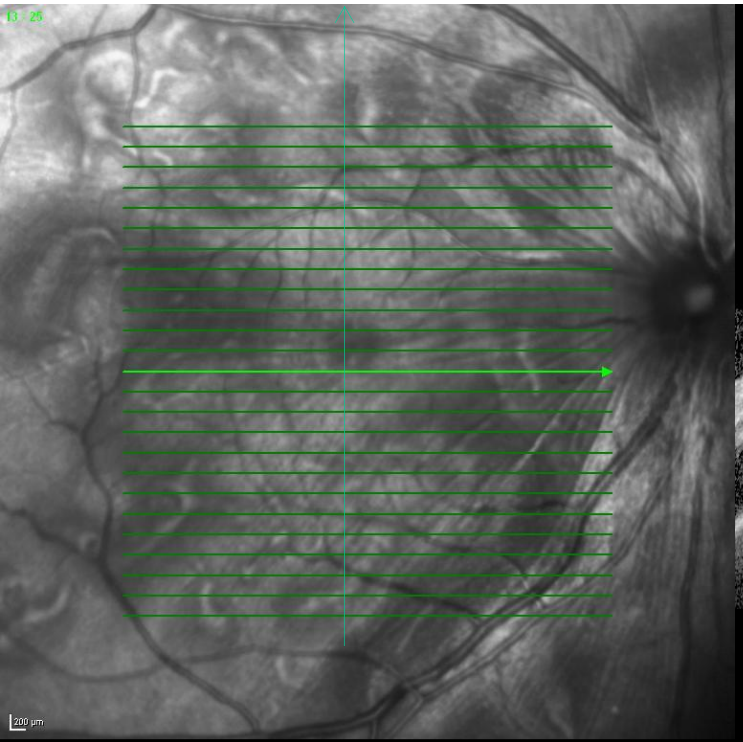
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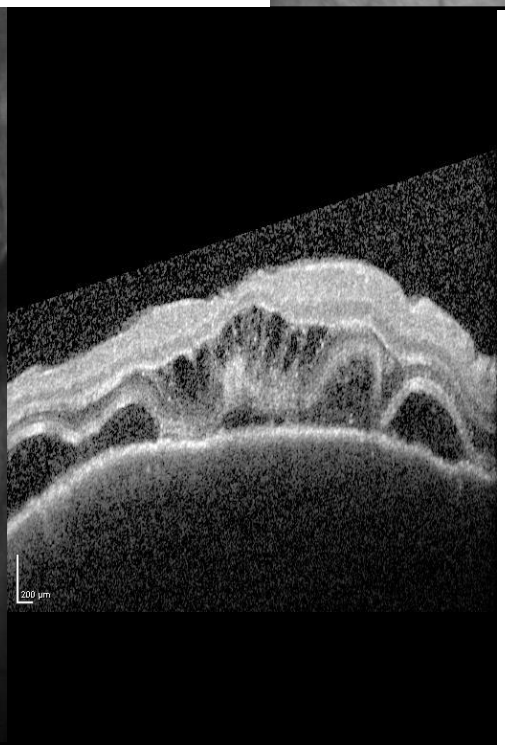

200 µm

# Characteristics of Vogt-Koyanagi-Harada Disease in a French Cohort: Ethnicity, Systemic Manifestations, and HLA Genotype Data

**S. Abad**
Service de Médecine Interne, Laboratoire de recherche clinique et thérapeutique UPRES EA3409, Université Paris XIII, Faculté Léonard de Vinci, Hôpital Avicenne, Assistance Publique-Hôpitaux de Paris, Paris, France

**D. Monnet**
Service d'Ophtalmologie, Université Paris Descartes, Faculté de Médecine, Hôpital Cochin, Paris, France

**S. Caillat-Zucman**
Laboratoire d'Immunologie, Université Paris Descartes, Faculté de Médecine, Hôpital Necker, Paris, France

**S. Mrejen**
Service d'Ophtalmologie, Université Paris Descartes, Faculté de Médecine, Hôpital Cochin, Paris, France

**P. Blanche**
Service de Médecine Interne, Université Paris Descartes, Faculté de Médecine, Hôpital Cochin, Paris, France

**M. Chalumeau**
Service de Pédiatrie, Université Paris Descartes, Faculté de Médecine, Hôpital St-Vincent de Paul, Paris, France

**L. Mouthon**
Service de Médecine Interne, Université Paris Descartes, Faculté de Médecine, Hôpital Cochin, Paris, France

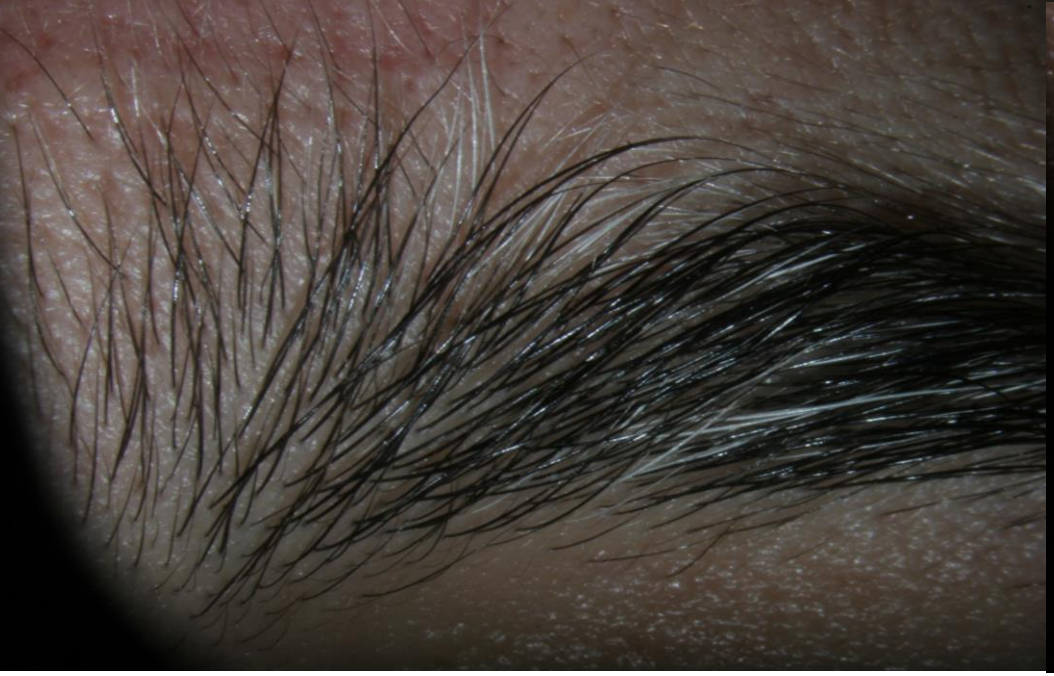
**R. Dhote**
Service de Médecine Interne, Laboratoire de recherche clinique et thérapeutique UPRES EA3409, Université Paris XIII, Faculté Léonard de Vinci, Hôpital Avicenne, Assistance Publique-Hôpitaux de Paris, Paris, France

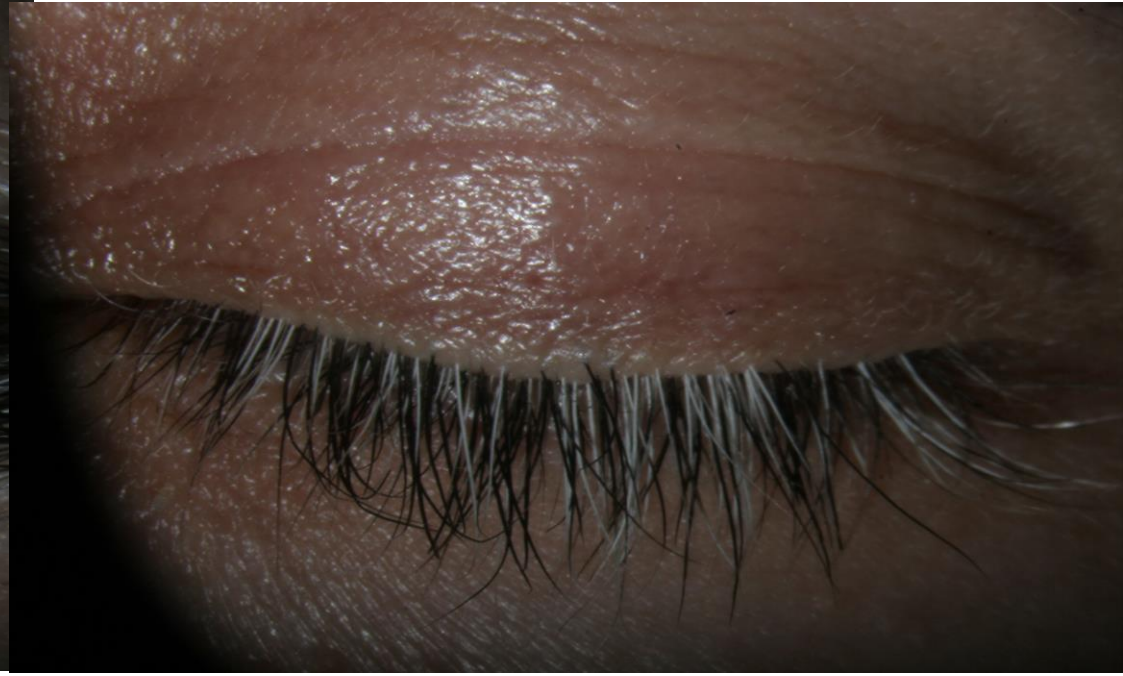
**A. P. Brézin**
Service d'Ophtalmologie, Université Paris Descartes, Faculté de Médecine, Hôpital Cochin, Paris, France

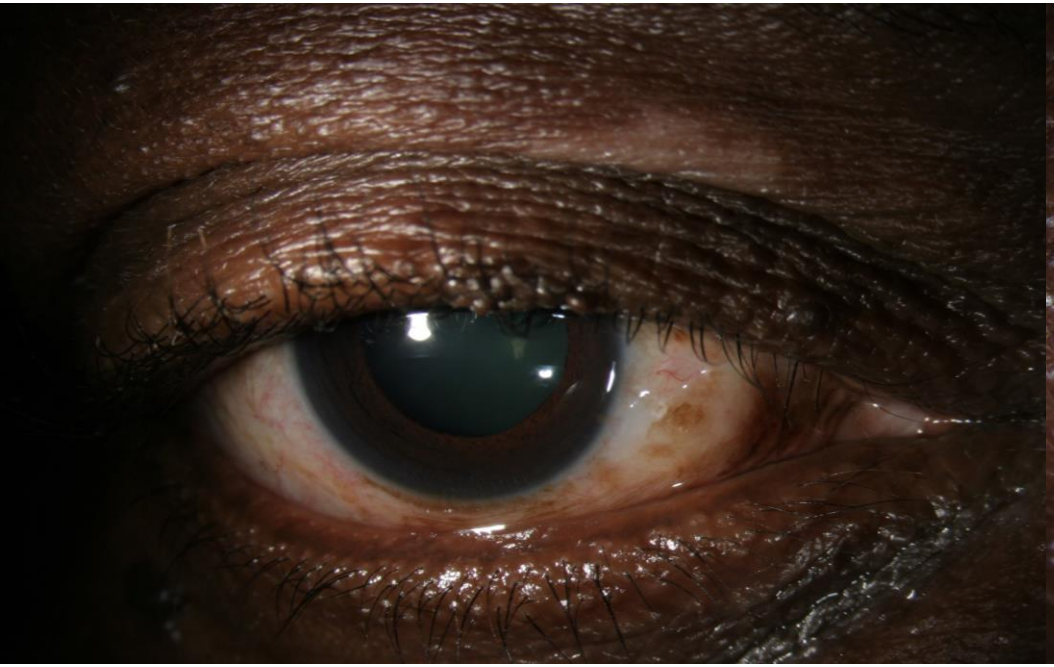
**ABSTRACT** *Purpose*: To assess in patients followed in a French referral center the clinical spectrum of Vogt-Koyanagi-Harada (VKH) disease and the HLA-DRB1*04 genotype. *Methods*: Patients previously diagnosed as having VKH disease were re-evaluated in a cross-sectional study using the VKH Committee's revised criteria. High-resolution HLA-DRB1 genotyping was performed. *Results*: Eleven white patients satisfied ophthalmologic diagnostic criteria. All originated from Mediterranean countries. Nine and 3 patients had neurologic and/or cutaneous abnormalities, respectively. Among DRB1*04-positive patients, the HLA-DRB1*0405 subtype was 71%. *Conclusion*: These VKH patients predominantly had an incomplete form. The HLA-DRB1*0405 subtype allele was enriched in a group of Mediterranean stock.

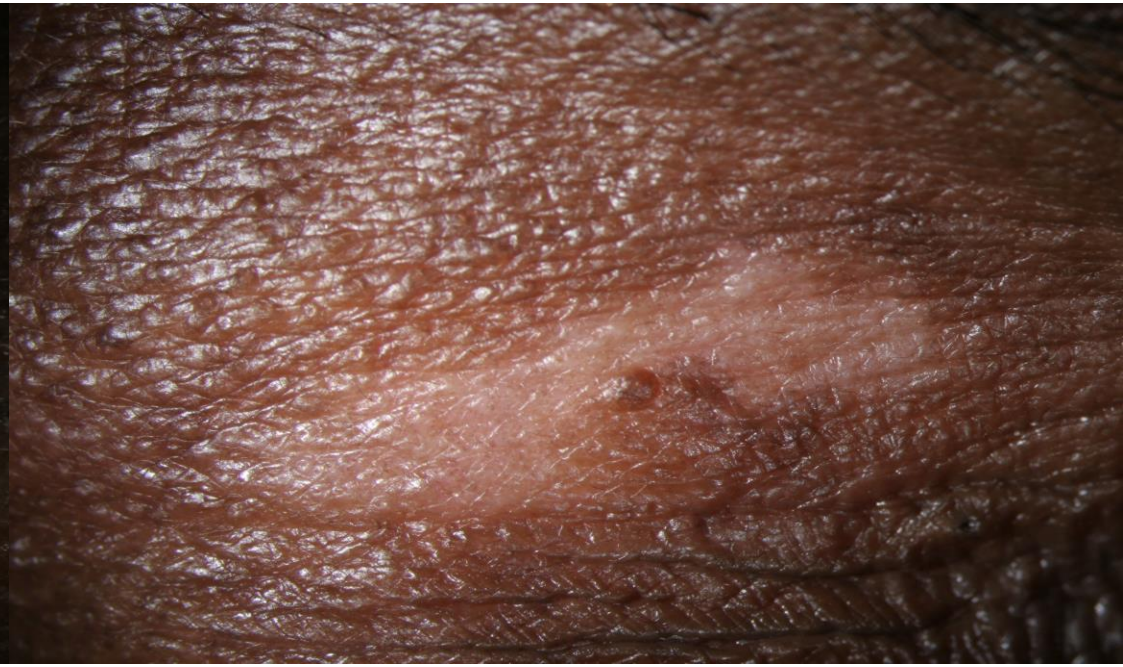
**Formes incomplètes : 80%**

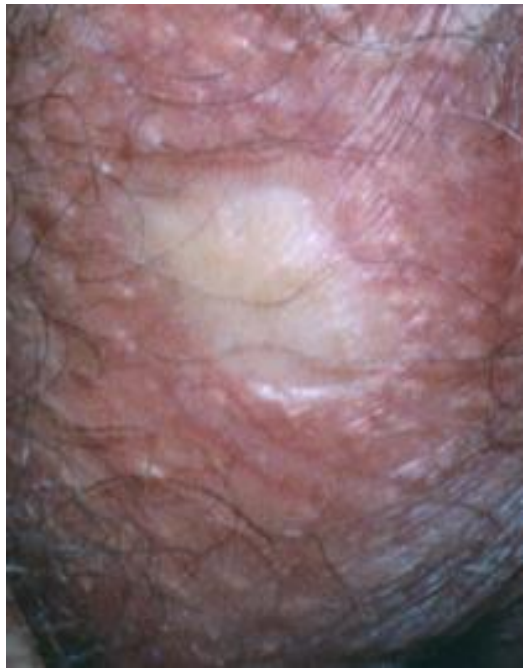
***Ocular Immunology and Inflammation, 16:3–8, 2008***











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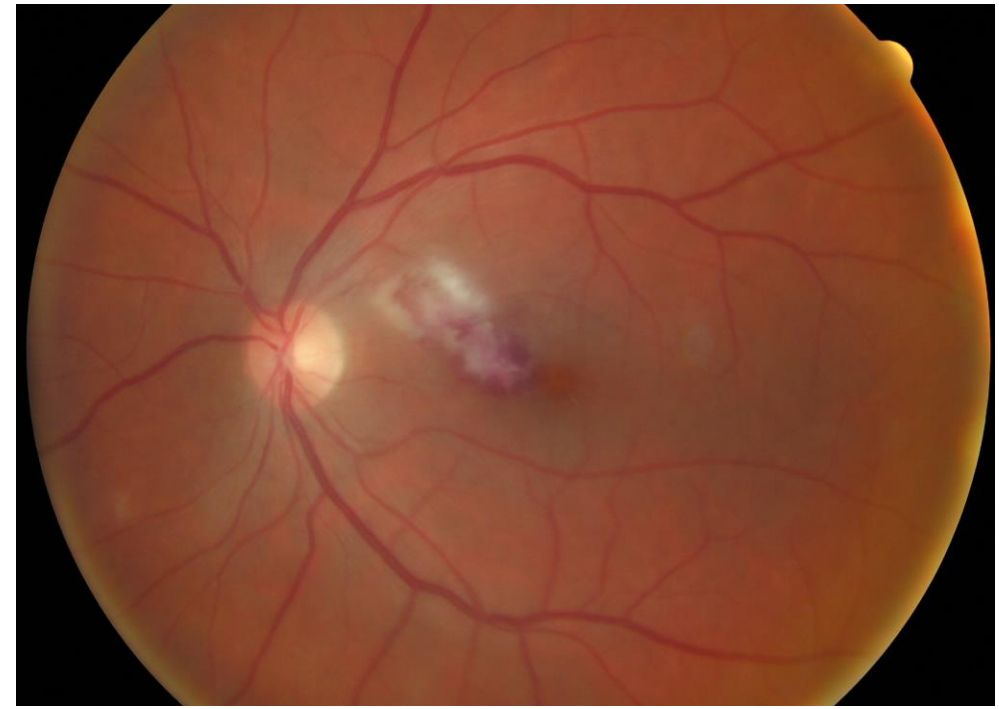
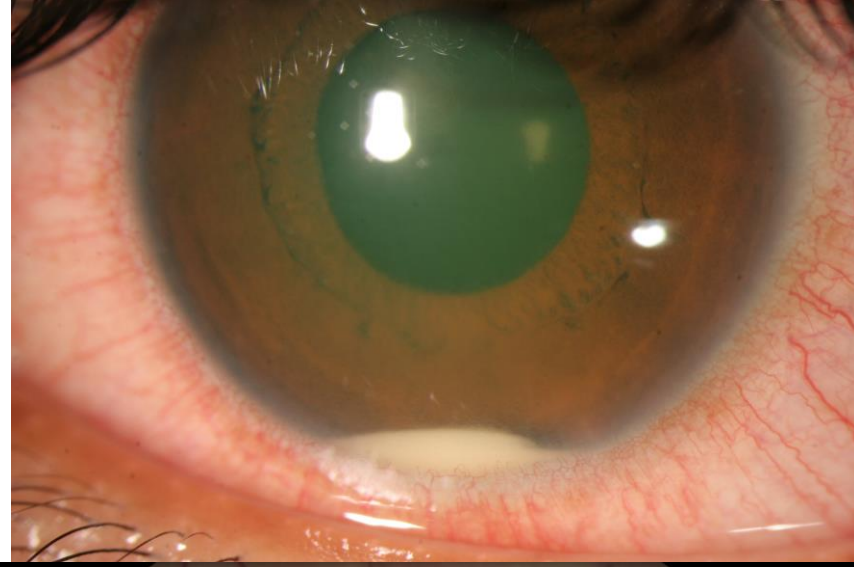
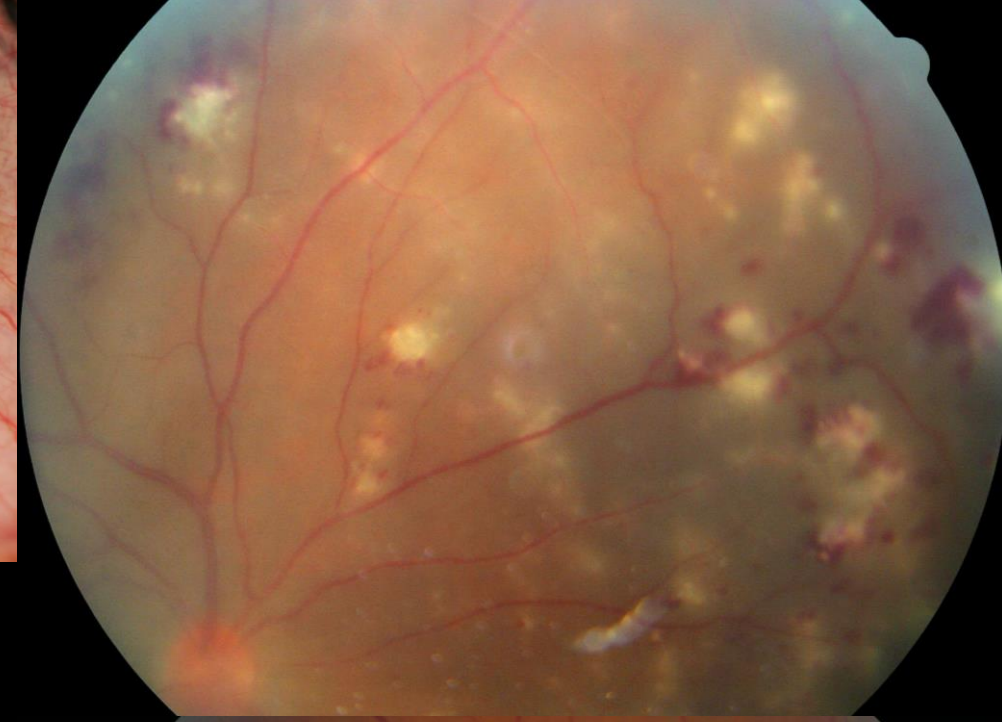
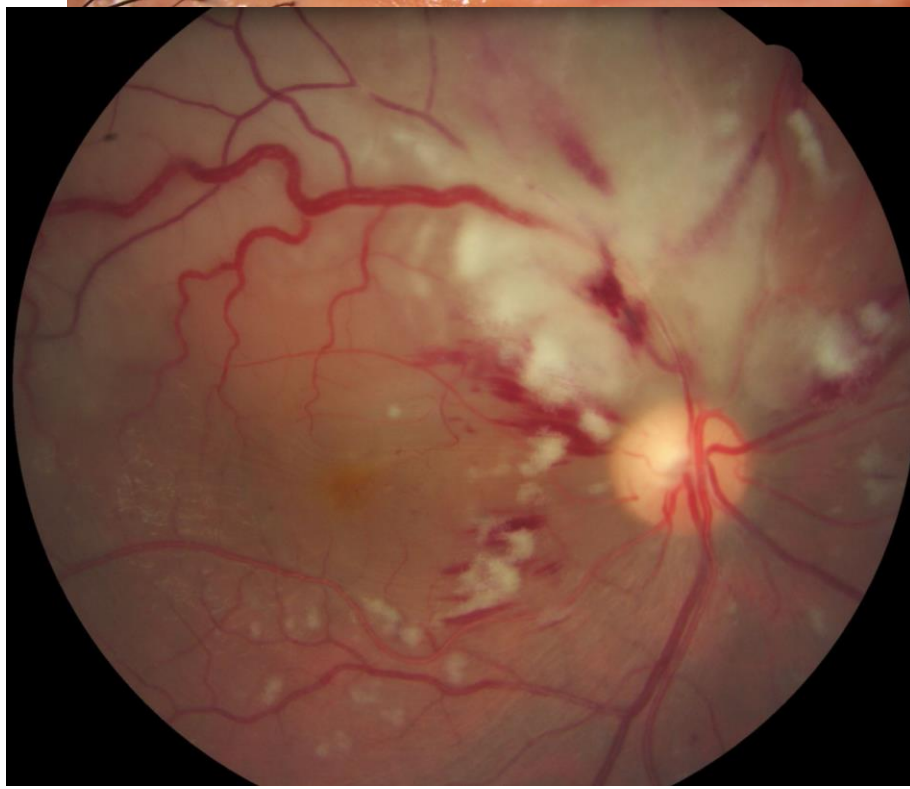
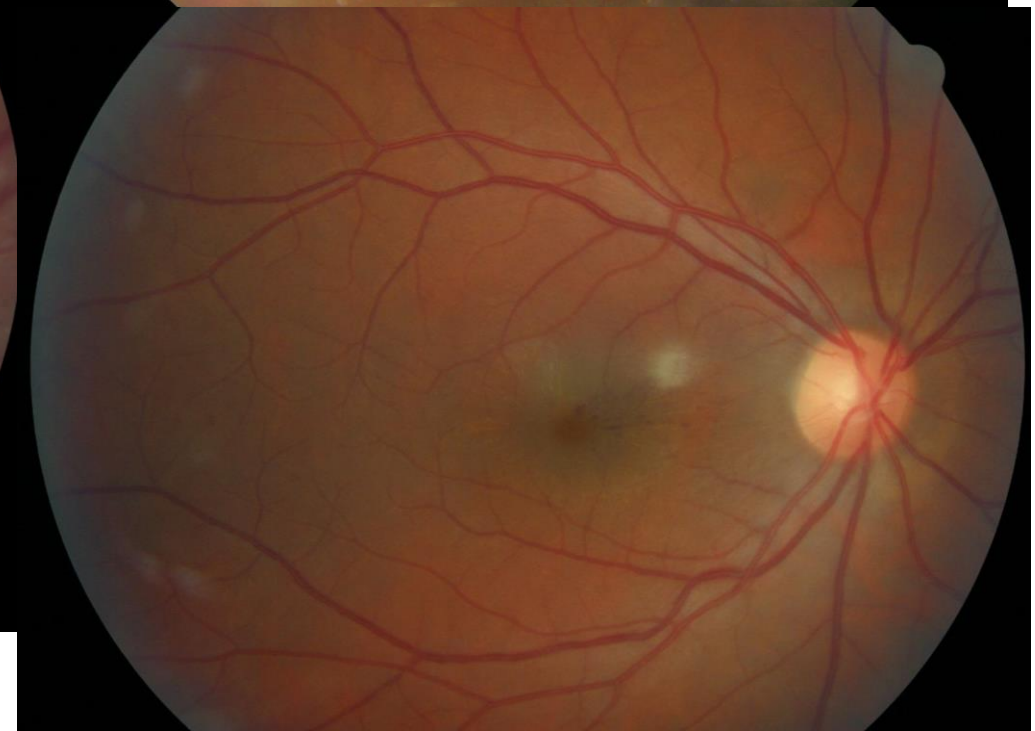


# Maladie de Behçet





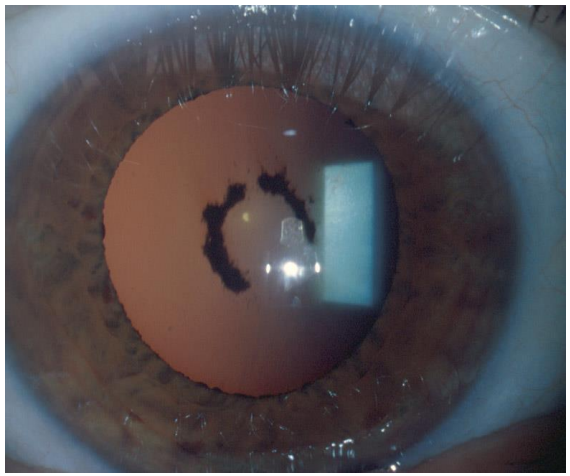


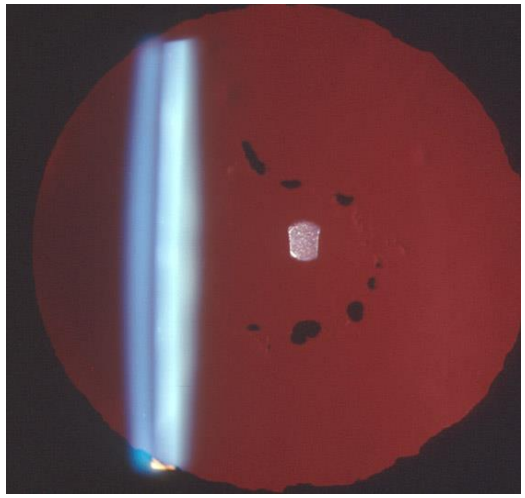


Maladie de Behçet

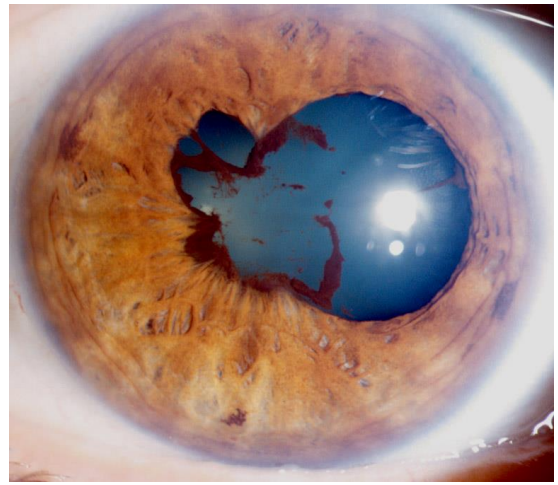
1. Standardiser l’évaluation ophtalmologique
2. Standardiser la recherche de l’étiologie
3. Standardiser la démarche thérapeutique

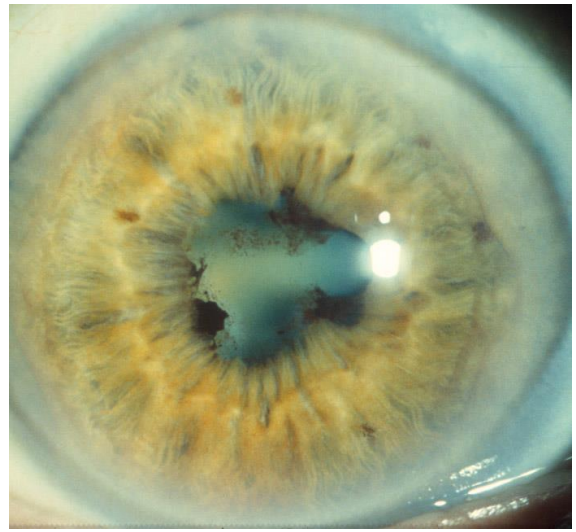
Succès





A temps



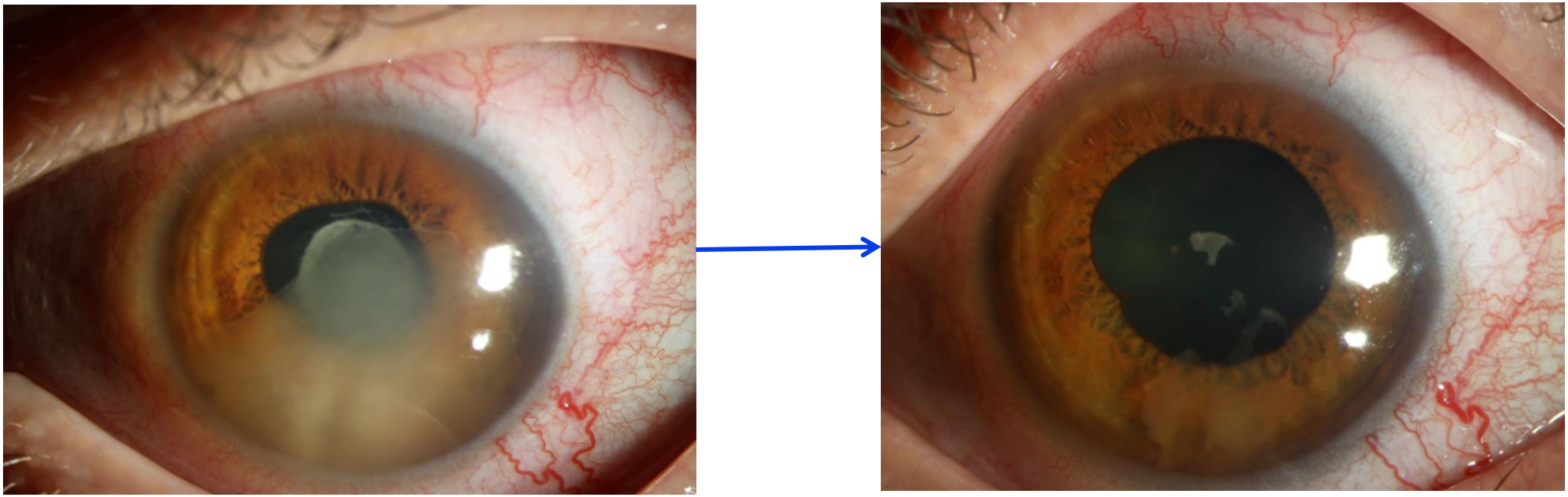


Trop tard

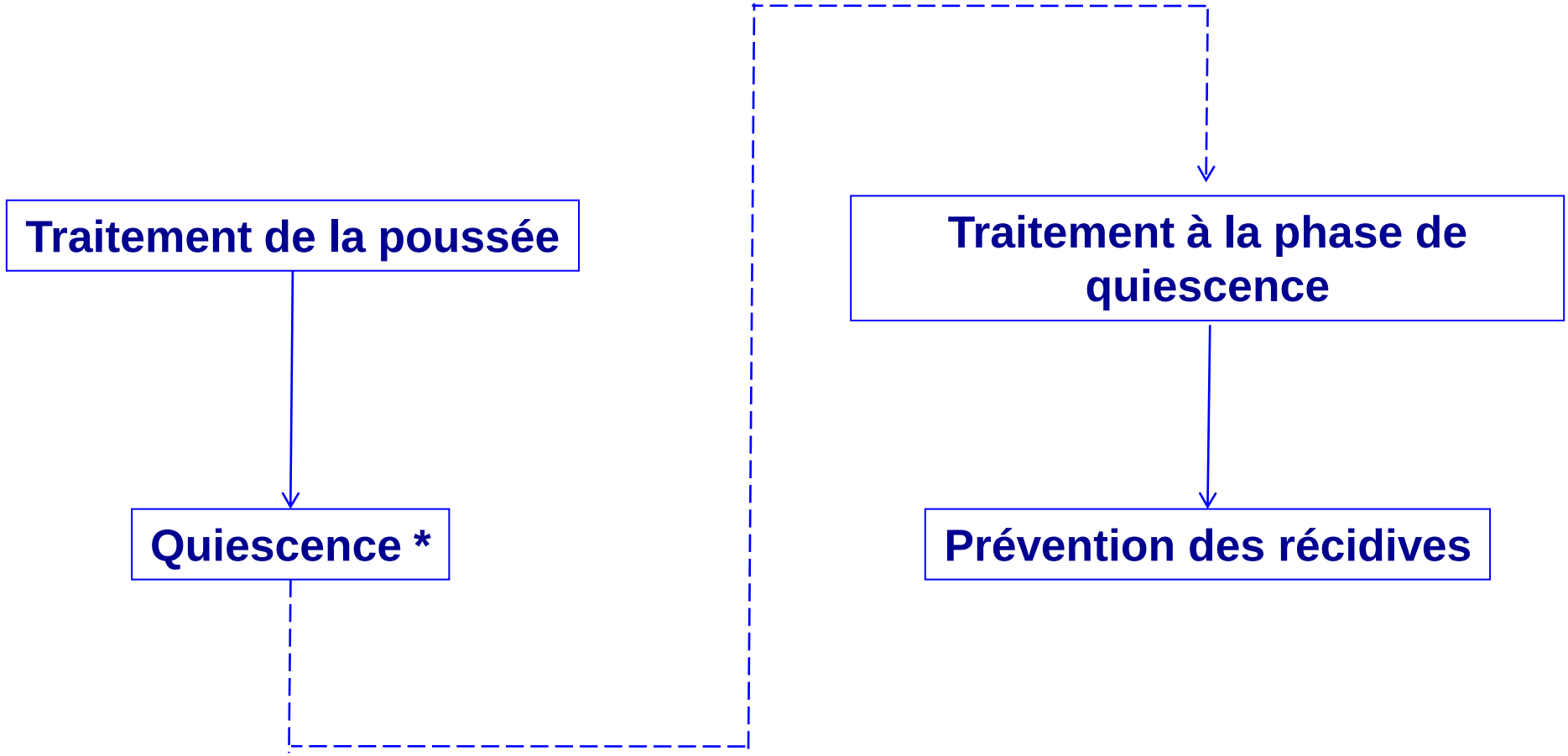
Échec

# Uvéite antérieure

## Traitement topique généralement efficace

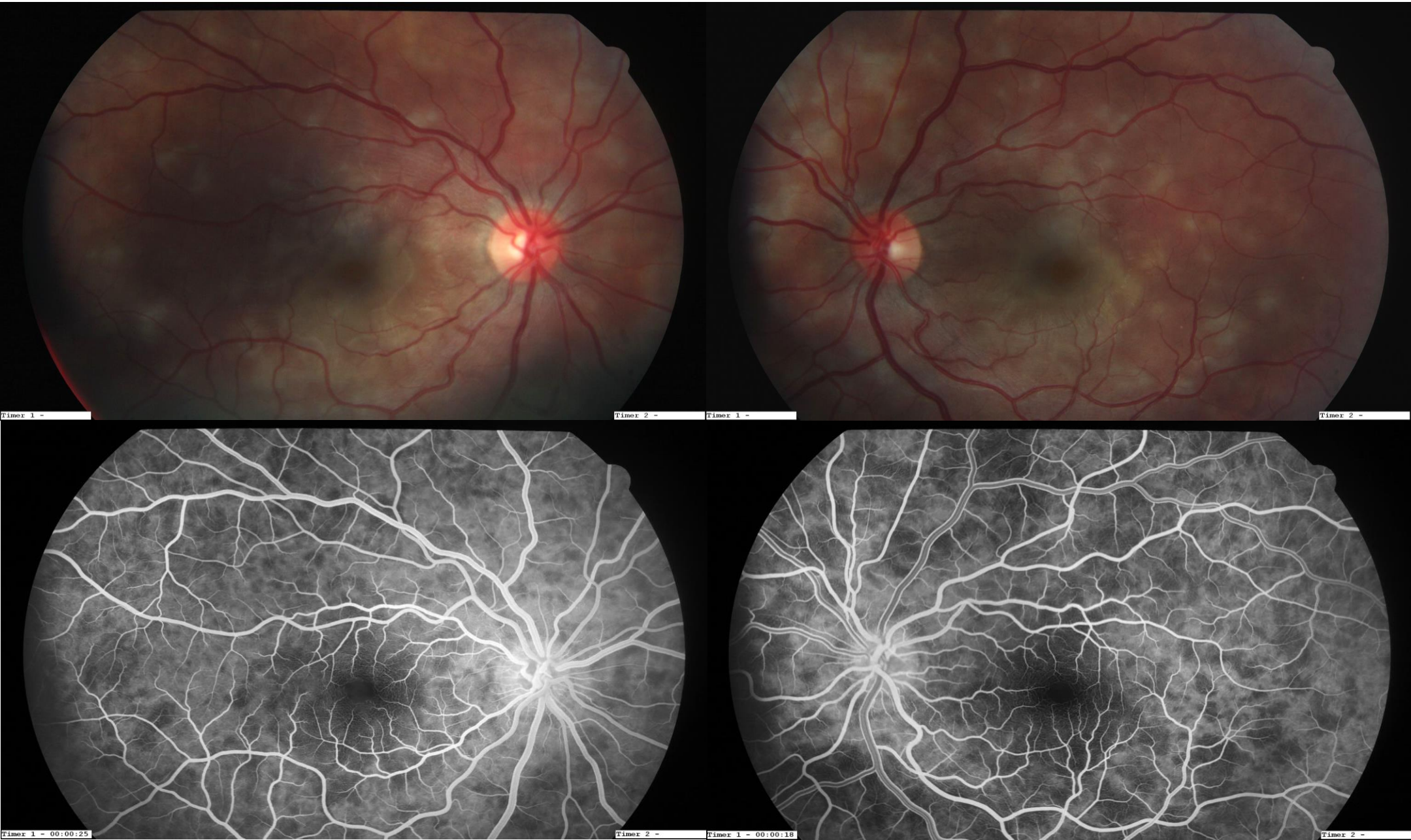


# Objectifs thérapeutiques

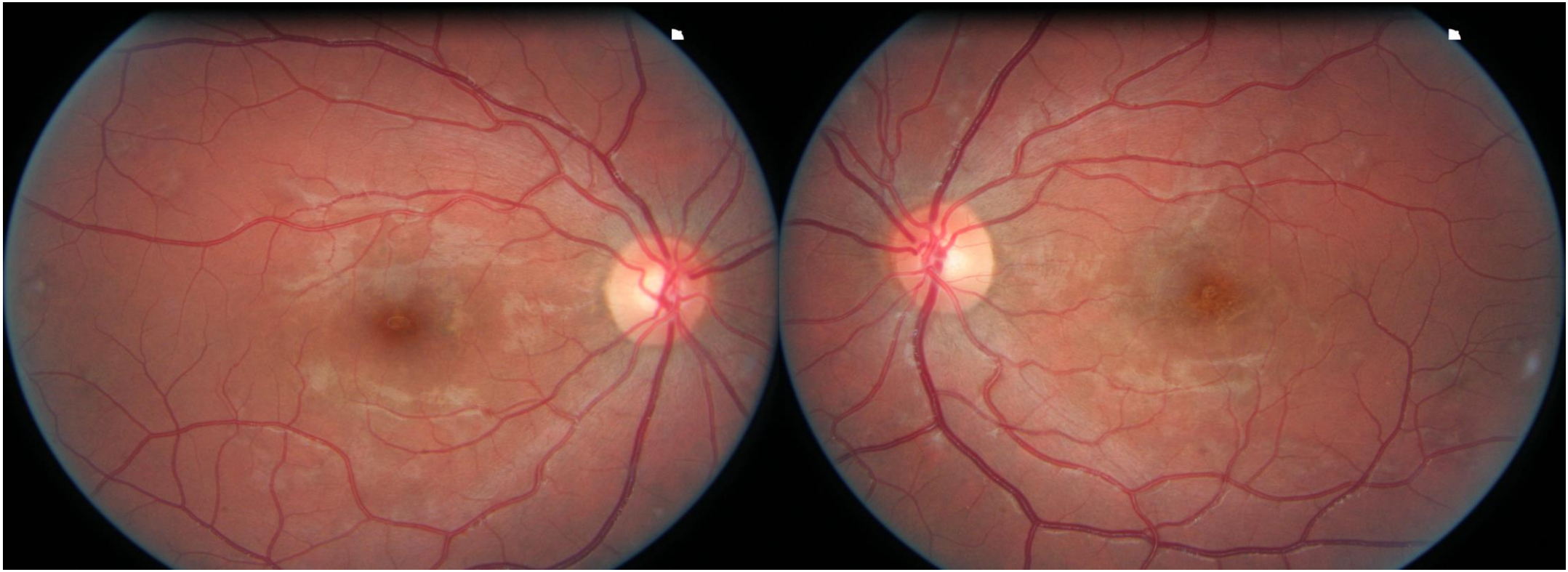



**Quiescence * :**
**Cellules en chambre antérieure = 0**
**Hyalite = 0**
**Lésion choriorétiniednne inflammatoire = 0**

Mlle F., 23 ans, BAV OD le 16 novembre ; BAV OG le 18 novembre – Examen le 21 novembre : VBLM ODG



Fond d’œil à M4



Xerri et al. BMC Ophthalmology (2018) 18:76
https://doi.org/10.1186/s12886-018-0744-z

BMC Ophthalmology

RESEARCH ARTICLE Open Access

# Untreated Acute Posterior Multifocal Placoid Pigment Epitheliopathy (APMPPE): a case series

Olivia Xerri, Sawsen Salah*, Dominique Monnet and Antoine P. Brézin

**Abstract**

**Background:** Acute Posterior Multifocal Placoid Pigment Epitheliopathy (APMPPE) is a rare inflammatory eye disease that affects the Retinal Pigment Epithelium and outer retina. The purpose of this study was to describe its presentations, as well as its prognosis in a series of untreated patients.

**Methods:** Records of patients seen in the department of Ophthalmology at Cochin University Hospital, Paris, between April 2002 and June 2015 were retrospectively studied. Patients were included if they presented with the typical findings of APMPPE characterized by whitish or yellowish bilateral placoid lesions, a typical pattern of early hypofluorescence and late hyperfluorescence on fluorescein angiography. Only untreated patients who had been followed for at least 1 month were included.

**Results:** Out of 22 patients' records with a diagnosis of APMPPE, 10 patients (9 women, 1 man), with a mean age of 24.5 ± 4.2 years, fulfilled the study criteria with a diagnosis of typical untreated APMPPE. Prodromal symptoms were reported in 7/10 patients. Macular lesions were observed in 18/20 eyes. Sub-retinal fluid was seen at presentation in 3 eyes. Initial mean BCVA was 0.56 ± 0.81 LogMAR [− 0.10 to 2.30]. In 9 out of 10 cases, the time interval between manifestations in the first affected eye and the fellow eye was less than 3 days. After 1 month, BCVA had improved to 0.05 ± 0.089 LogMAR [0–0.3], with a decimal BCVA ≥0.8 in 17/20 eyes.

**Conclusions:** In these 10 cases of untreated APMPPE, a favorable outcome was observed.

**Keywords:** Acute posterior multifocal placoid pigment epitheliopathy, Inflammatory disease, Posterior uveitis, Retina, Retinal pigment epithelium

The New England

We conclude that azathioprine is effective in controlling the progression of Behçet's syndrome, especially its most serious manifestation, eye disease. (N Engl J Med 1990; 322:281-5.)

# A CONTROLLED TRIAL OF AZATHIOPRINE IN BEHÇET'S SYNDROME

Hasan Yazici, M.D., Halit Pazarli, M.D., Colin G. Barnes, M.D., Yalçin Tüzün, M.D., Yilmaz Özyazgan, M.D., Alan Silman, M.D., Server Serdaroğlu, M.D., Velieddin Oğuz, M.D., Sebahattin Yurdakul, M.D., George E. Lovatt, M.D., Berrin Yazici, Shenaz Somani, and Asuman Müftüoğlu, M.D.

**Abstract** Cytotoxic agents have long been used in Behçet's syndrome, especially for eye involvement, but their effectiveness has been uncertain. We conducted a two-year randomized, placebo-controlled, double-blind trial of azathioprine (2.5 mg per kilogram of body weight per day) in Turkish men with Behçet's syndrome without eye disease (group 1; n = 25) or with eye disease (group 2; n = 48). Corticosteroid treatment remained available to all the patients.

All six patients withdrawn from the study because of severe eye disease were receiving placebo (P<0.001). Azathioprine was superior to placebo in the prevention of new eye disease in group 1 (1 vs. 8 patients; P<0.01) and in group 2 among the 14 patients who at entry had disease in only one eye (P<0.001). There were fewer episodes of hypopyon uveitis (1 vs. 15; P<0.001) among the group 2 patients who took azathioprine. The patients taking azathioprine also had less frequent oral ulcers, genital ulcers, and arthritis. There were no serious side effects attributable to azathioprine.

We conclude that azathioprine is effective in controlling the progression of Behçet's syndrome, especially its most serious manifestation, eye disease. (N Engl J Med 1990; 322:281-5.)

# Time to Treatment Failure: Multiple Component Endpoint for VISUAL I and VISUAL II

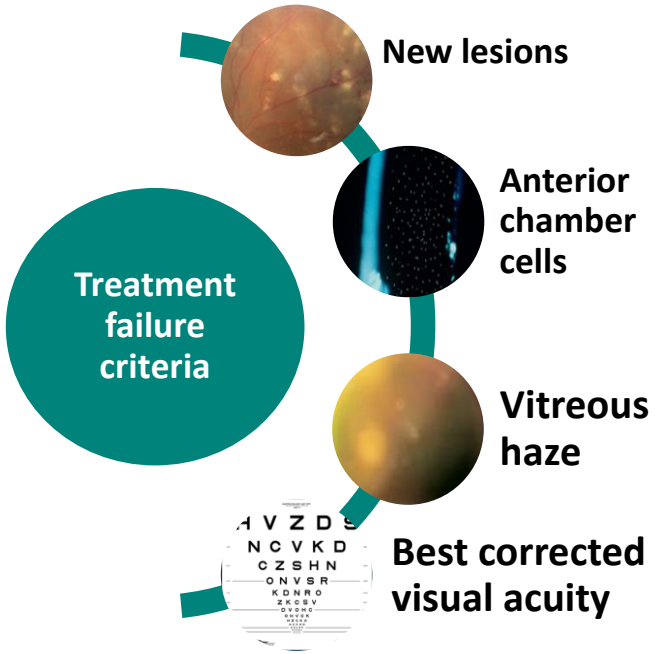
## Time to event analysis[1,2]

Time to treatment failure

Time to treatment failure was defined as the time from randomization to discontinuation due to any of the given criteria

## Multiple component endpoint[1,2]

To be considered a treatment failure, any one of these
four criteria needed to be present in at least one eye




1. Jaffe G, et al. N Engl J Med 2016;375:932–943;
2. Nguyen QD, et al. Lancet 2016;pii: S0140-6736(16)31339–3 [Epub ahead of print]

ORIGINAL ARTICLE

# Adalimumab in Patients with Active Noninfectious Uveitis

Glenn J. Jaffe, M.D., Andrew D. Dick, M.B., B.S., M.D., Antoine P. Brézin, M.D., Ph.D., Quan Dong Nguyen, M.D., Jennifer E. Thorne, M.D., Ph.D., Philippe Kestelyn, M.D., Ph.D., M.P.H., Talin Barisani-Asenbauer, M.D., Ph.D., Pablo Franco, M.D., Arnd Heiligenhaus, M.D., David Scales, M.D., David S. Chu, M.D., Anne Camez, M.D., Nisha V. Kwatra, Ph.D., Alexandra P. Song, M.D., M.P.H., Martina Kron, Ph.D., Samir Tari, M.D., and Eric B. Suhler, M.D., M.P.H.

## ABSTRACT

### BACKGROUND

Patients with noninfectious uveitis are at risk for long-term complications of uncontrolled inflammation, as well as for the adverse effects of long-term glucocorticoid therapy. We conducted a trial to assess the efficacy and safety of adalimumab as a glucocorticoid-sparing agent for the treatment of noninfectious uveitis.

### METHODS

This multinational phase 3 trial involved adults who had active noninfectious intermediate uveitis, posterior uveitis, or panuveitis despite having received prednisone treatment for 2 or more weeks. Investigators and patients were unaware of the study-group assignments. Patients were randomly assigned in a 1:1 ratio to receive adalimumab (a loading dose of 80 mg followed by a dose of 40 mg every 2 weeks) or matched placebo. All patients received a mandatory prednisone burst followed by tapering of prednisone over the course of 15 weeks. The primary efficacy end point was the time to treatment failure occurring at or after week 6. Treatment failure was a multicomponent outcome that was based on assessment of new inflammatory lesions, best corrected visual acuity, anterior chamber cell grade, and vitreous haze grade. Nine ranked secondary efficacy end points were assessed, and adverse events were reported.

### RESULTS

The median time to treatment failure was 24 weeks in the adalimumab group and 13 weeks in the placebo group. Among the 217 patients in the intention-to-treat population, those receiving adalimumab were less likely than those in the placebo group to have treatment failure (hazard ratio, 0.50; 95% confidence interval, 0.36 to 0.70; P<0.001). Outcomes with regard to three secondary end points (change in anterior chamber cell grade, change in vitreous haze grade, and change in best corrected visual acuity) were significantly better in the adalimumab group than in the placebo group. Adverse events and serious adverse events were reported more frequently among patients who received adalimumab (1052.4 vs. 971.7 adverse events and 28.8 vs. 13.6 serious adverse events per 100 person-years).

### CONCLUSIONS

In our trial, adalimumab was found to be associated with a lower risk of uveitic flare or visual impairment and with more adverse events and serious adverse events than was placebo. (Funded by AbbVie; VISUAL I ClinicalTrials.gov number, NCT01138657.)

From Duke University, Durham, NC (G.J.J.); University of Bristol, Bristol Eye Hospital, Bristol, and National Institute for Health Research Biomedical Research Centre at Moorfields Eye Hospital and University College London Institute of Ophthalmology, London — both in the United Kingdom (A.D.D.); Université Paris Descartes, Hôpital Cochin, Paris (A.P.B.); Truhlsen Eye Institute, University of Nebraska Medical Center, Omaha (Q.D.N.); Johns Hopkins Medical Institute, Baltimore (J.E.T.); Ghent University Hospital, Ghent, Belgium (P.K.); Laura Bassi Center of Expertise Ocuvac, Medical University of Vienna, Vienna (T.B.-A.); Organización Médica de Investigación, Buenos Aires (P.F.); the Department of Ophthalmology, St. Franziskus-Hospital Münster, Münster (A.H.), University of Duisburg-Essen, Essen (A.H.), and AbbVie Deutschland, Ludwigshafen (A.C., M.K.) — all in Germany; University of Texas Health Science Center, San Antonio (D.S.); Metropolitan Eye Research and Surgery Institute, Palisades Park, NJ (D.S.C.); AbbVie, North Chicago, IL (N.V.K., A.P.S., S.T.); and Casey Eye Institute, Oregon Health and Science University, and VA Portland Health Care System (E.B.S.) — both in Portland. Address reprint requests to Dr. Jaffe at the Duke Eye Center, Box 3802, Durham, NC 27710, or at glenn.jaffe@duke.edu.

N Engl J Med 2016;375:932-43.
DOI: 10.1056/NEJMoa1509852

# Adalimumab for prevention of uveitic flare in patients with inactive non-infectious uveitis controlled by corticosteroids (VISUAL II): a multicentre, double-masked, randomised, placebo-controlled phase 3 trial

*Quan Dong Nguyen, Pauline T Merrill, Glenn J Jaffe, Andrew D Dick, Shree Kumar Kurup, John Sheppard, Ariel Schlaen, Carlos Pavesio, Luca Cimino, Joachim Van Calster, Anne A Camez, Nisha V Kwatra, Alexandra P Song, Martina Kron, Samir Tari, Antoine P Brézin*

## Summary

**Background** Non-infectious uveitis is a potentially sight-threatening ocular disorder caused by chronic inflammation and its complications. Therapeutic success is limited by systemic adverse effects associated with long-term corticosteroid and immunomodulator use if topical medication is not sufficient to control the inflammation. We aimed to assess the efficacy and safety of adalimumab in patients with inactive, non-infectious uveitis controlled by systemic corticosteroids.

**Methods** We did this multicentre, double-masked, randomised, placebo-controlled phase 3 trial at 62 study sites in 21 countries in the USA, Canada, Europe, Israel, Australia, and Latin America. Patients (aged ≤18 years) with inactive, non-infectious intermediate, posterior, or panuveitic uveitis controlled by 10–35 mg/day of prednisone were randomly assigned (1:1), via an interactive voice and web response system with a block size of four, to receive either subcutaneous adalimumab (loading dose 80 mg; biweekly dose 40 mg) or placebo, with a mandatory prednisone taper from week 2. Randomisation was stratified by baseline immunosuppressant treatment. Sponsor personnel with direct oversight of the conduct and management of the study, investigators, study site personnel, and patients were masked to treatment allocation. The primary efficacy endpoint was time to treatment failure, a multicomponent endpoint encompassing new active inflammatory chorioretinal or inflammatory retinal vascular lesions, anterior chamber cell grade, vitreous haze grade, and visual acuity. Analysis was done in the intention-to-treat population. This trial is registered with ClinicalTrials.gov, number NCT01124838.

**Findings** Between Aug 10, 2010, and May 14, 2015, we randomly assigned 229 patients to receive placebo (n=114) or adalimumab (n=115); 226 patients comprised the intention-to-treat population. Median follow-up time was 155 days (IQR 77–357) in the placebo group and 245 days (119–564) in the adalimumab group. Treatment failure occurred in 61 (55%) of 111 patients in the placebo group compared with 45 (39%) of 115 patients in the adalimumab group. Time to treatment failure was significantly improved in the adalimumab group compared with the placebo group (median not estimated [>18 months] *vs* 8·3 months; hazard ratio 0·57, 95% CI 0·39–0·84; p=0·004). The 40th percentile for time to treatment failure was 4·8 months in the placebo group and 10·2 months in the adalimumab group. No patients in either group had opportunistic infections (excluding oral candidiasis and tuberculosis). No malignancies were reported in the placebo group whereas one (1%) patient in the adalimumab group reported non-serious squamous cell carcinoma. The most common adverse events were arthralgia (12 [11%] patients in the placebo group and 27 [23%] patients in the adalimumab group), nasopharyngitis (16 [17%] and eight [16%] patients, respectively), and headache (17 [15%] patients in each group).

**Interpretation** Adalimumab significantly lowered the risk of uveitic flare or loss of visual acuity upon corticosteroid withdrawal in patients with inactive, non-infectious intermediate, posterior, or panuveitic uveitis controlled by systemic corticosteroids. No new safety signals were observed and the rate of adverse events was similar between groups. These findings suggest that adalimumab is well tolerated and could be an effective treatment option in this patient population. An open-label extension study (NCT01148225) is ongoing to provide long-term safety data for adalimumab in patients with non-infectious uveitis.

**Funding** AbbVie.

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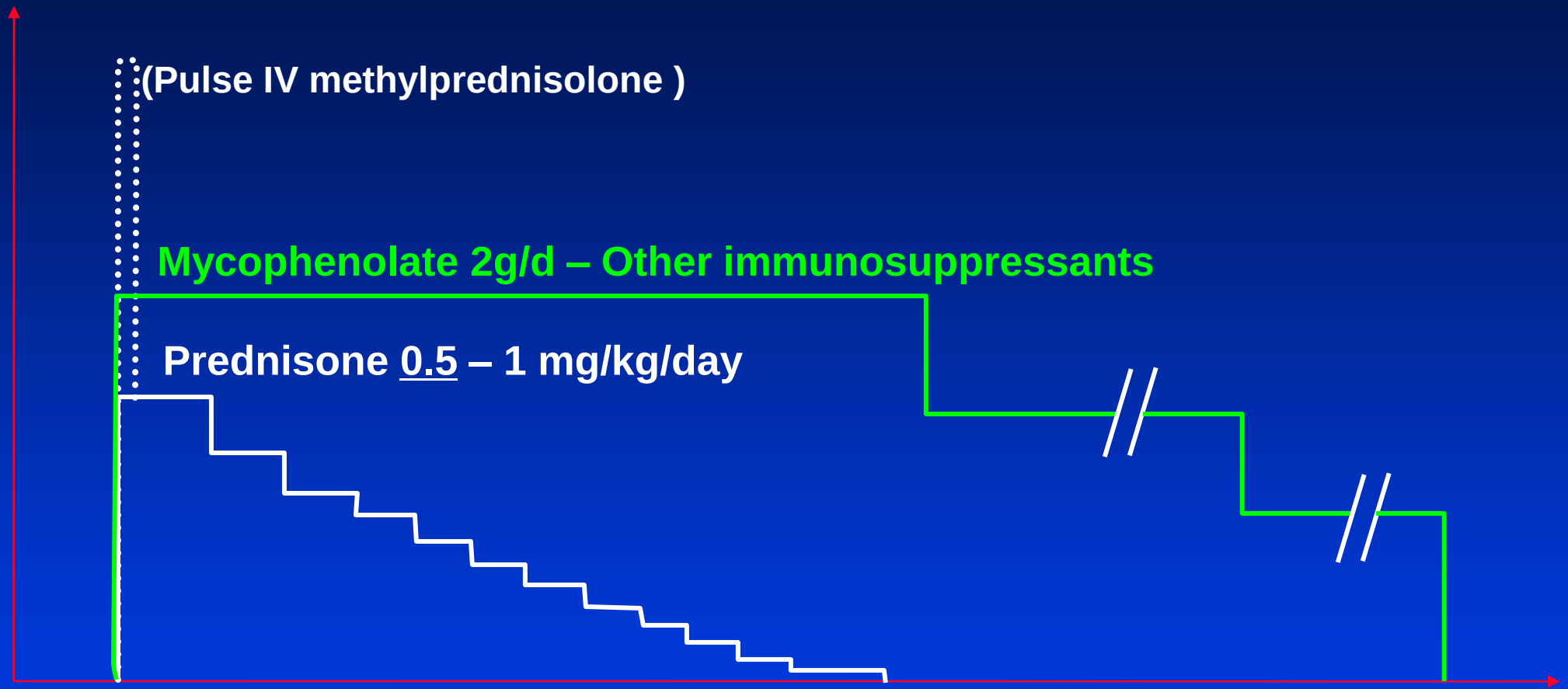
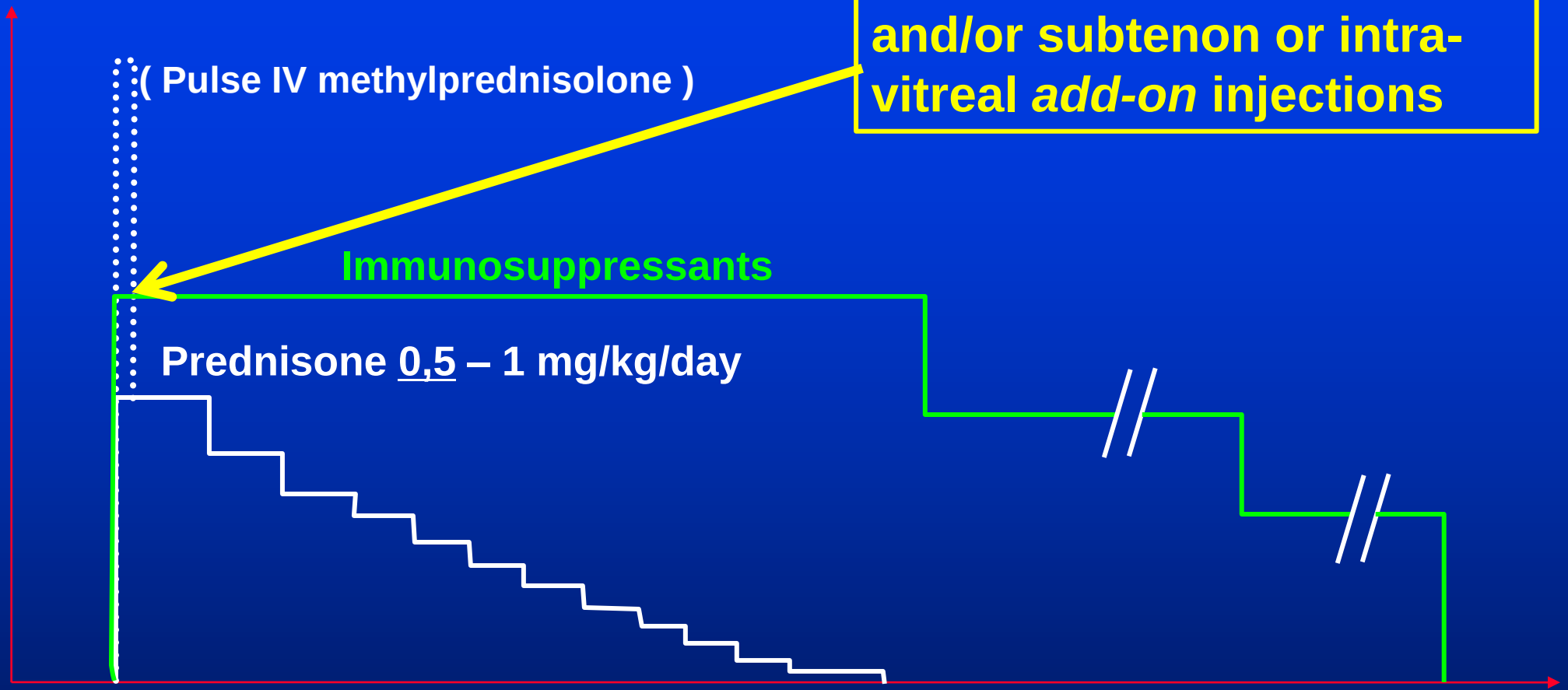
**Ocular Imaging Research and Reading Center (OIRRC), Omaha, NE, USA** (Prof Q D Nguyen MD); **Rush University Medical Center, Chicago, IL, USA** (P T Merrill MD); **Duke University, Durham, NC, USA** (Prof G J Jaffe MD); **University of Bristol, Bristol Eye Hospital, Bristol, UK** (Prof A D Dick MD); **National Institute for Health Research (NIHR) Biomedical Research Centre** (Prof A D Dick), **Moorfields Eye Hospital and University College London, Institute of Ophthalmology, London, UK** (C Pavesio MD); **Wake Forest Baptist Medical Center, Winston-Salem, NC, USA** (Prof S K Kurup MD); **Lions Medical Eye Bank of Eastern Virginia, Eastern Virginia Medical School and Virginia Eye Consultants, Norfolk, VA, USA** (J Sheppard M D); **Austral University, Buenos Aires, Argentina** (A Schlaen MD); **Arcispedale Santa Maria Nuova IRCCS, Reggio Emilia RE, Italy** (L Cimino MD); **University Hospitals Leuven, Leuven, Belgium** (J Van Calster MD); **AbbVie Deutschland, Ludwigshafen, Germany** (A A Camez MD, Prof M Kron PhD); **AbbVie, North Chicago, IL, USA** (N V Kwatra PhD, A P Song M D, S Tari M D); **and Université Paris Descartes, Hôpital Cochin, Paris, France** (Prof A P Brézin MD)




« Standard » treatment strategy

***No evidence-based data to guide therapeutic decisions***


( Pulse IV methylprednisolone )
and/or subtenon or intra-vitreal *add-on* injections
Immunosuppressants
Prednisone 0,5 – 1 mg/kg/day

*Daudin JB, Brézin AP. A white line in the anterior chamber. JAMA Ophthalmol.2013;131:398.*

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# Guidance on Noncorticosteroid Systemic Immunomodulatory Therapy in Noninfectious Uveitis

## *Fundamentals Of Care for UveitiS (FOCUS) Initiative*

*Andrew D. Dick, FMedSci, FRCOphth,[1,2,3,†] James T. Rosenbaum, MD,[4,5,6,†] Hassan A. Al-Dhibi, MD,[7] Rubens Belfort, Jr., MD, PhD,[8] Antoine P. Brézin, MD, PhD,[9] Soon Phaik Chee, FRCOphth, FRCS,[10,11,12,13] Janet L. Davis, MD, MA,[14] Athimalaipet V. Ramanan, FRCP, FRCPCH,[1,15] Koh-Hei Sonoda, MD, PhD,[16] Ester Carreño, MD, PhD,[17] Heloisa Nascimento, MD,[18] Sawsen Salah, MD,[9] Sherveen Salek, MD,[5,19] Jay Siak, FRCOphth, FRCSEd(Ophth),[10,11,12,13] Laura Steeples, FRCOphth, MBChB(Hons),[17,20] for the Fundamentals of Care for Uveitis International Consensus Group®*

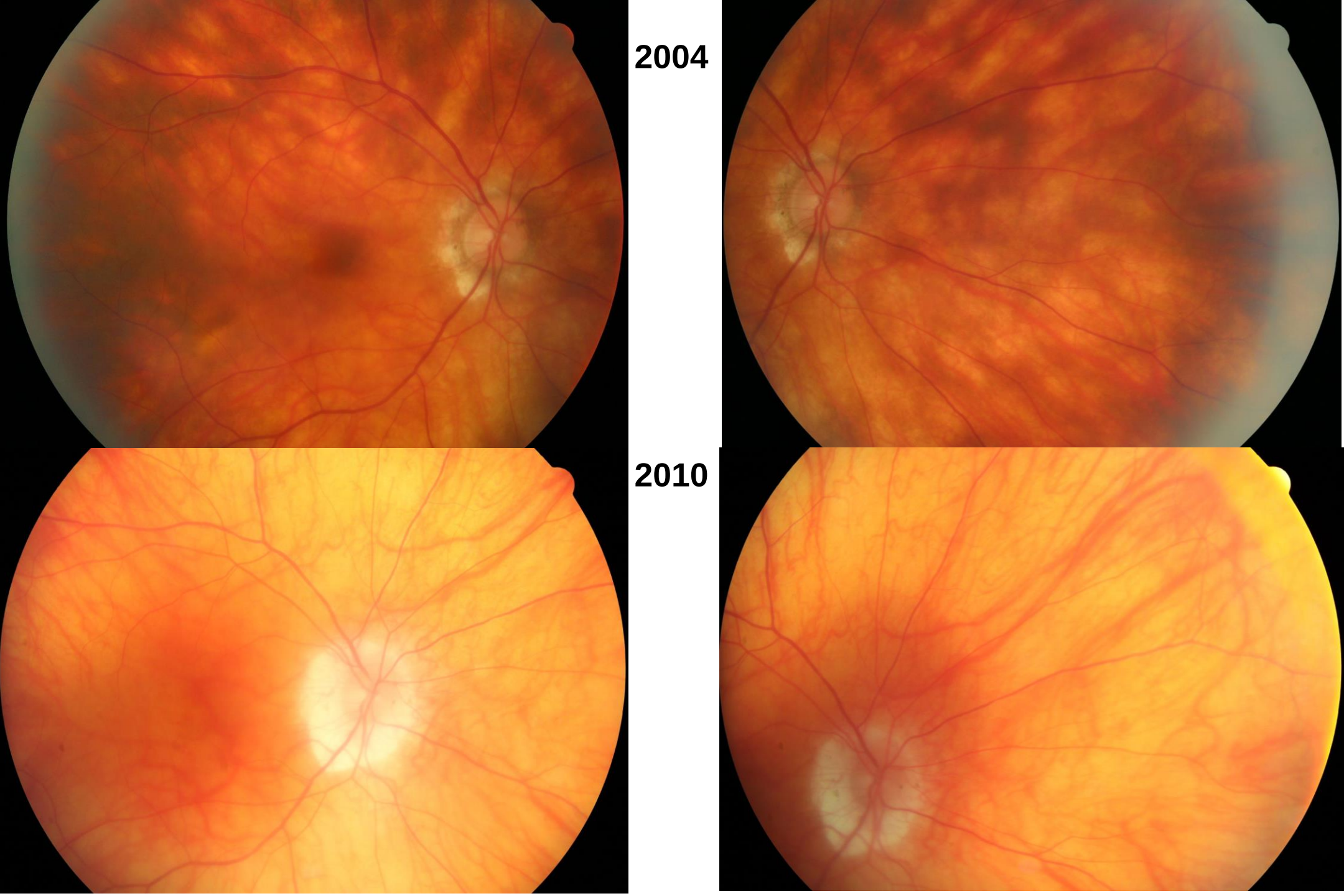
***Topic:*** An international, expert-led consensus initiative to develop systematic, evidence-based recommendations for the treatment of noninfectious uveitis in the era of biologics.

***Clinical Relevance:*** The availability of biologic agents for the treatment of human eye disease has altered practice patterns for the management of noninfectious uveitis. Current guidelines are insufficient to assure optimal use of noncorticosteroid systemic immunomodulatory agents.

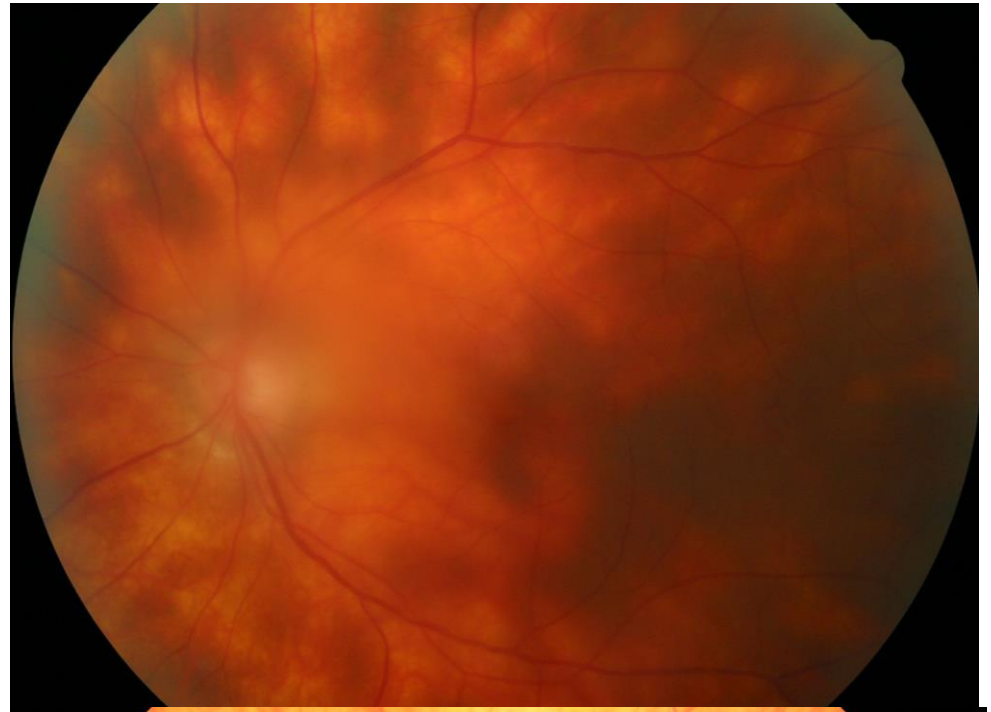
***Methods:*** An international expert steering committee comprising 9 uveitis specialists (including both ophthalmologists and rheumatologists) identified clinical questions and, together with 6 bibliographic fellows trained in uveitis, conducted a Preferred Reporting Items for Systematic Reviews and Meta-Analyses protocol systematic review of the literature (English language studies from January 1996 through June 2016; Medline [OVID], the Central Cochrane library, EMBASE, CINAHL, SCOPUS, BIOSIS, and Web of Science). Publications included randomized controlled trials, prospective and retrospective studies with sufficient follow-up, case series with 15 cases or more, peer-reviewed articles, and hand-searched conference abstracts from key conferences. The proposed statements were circulated among 130 international uveitis experts for review. A total of 44 globally representative group members met in late 2016 to refine these guidelines using a modified Delphi technique and assigned Oxford levels of evidence.

***Results:*** In total, 10 questions were addressed resulting in 21 evidence-based guidance statements covering the following topics: when to start noncorticosteroid immunomodulatory therapy, including both biologic and nonbiologic agents; what data to collect before treatment; when to modify or withdraw treatment; how to select agents based on individual efficacy and safety profiles; and evidence in specific uveitic conditions. Shared decision-making, communication among providers and safety monitoring also were addressed as part of the recommendations. Pharmacoeconomic considerations were not addressed.

***Conclusions:*** Consensus guidelines were developed based on published literature, expert opinion, and practical experience to bridge the gap between clinical needs and medical evidence to support the treatment of patients with noninfectious uveitis with noncorticosteroid immunomodulatory agents. *Ophthalmology 2017;■:1–17* 


2004
2010

2004



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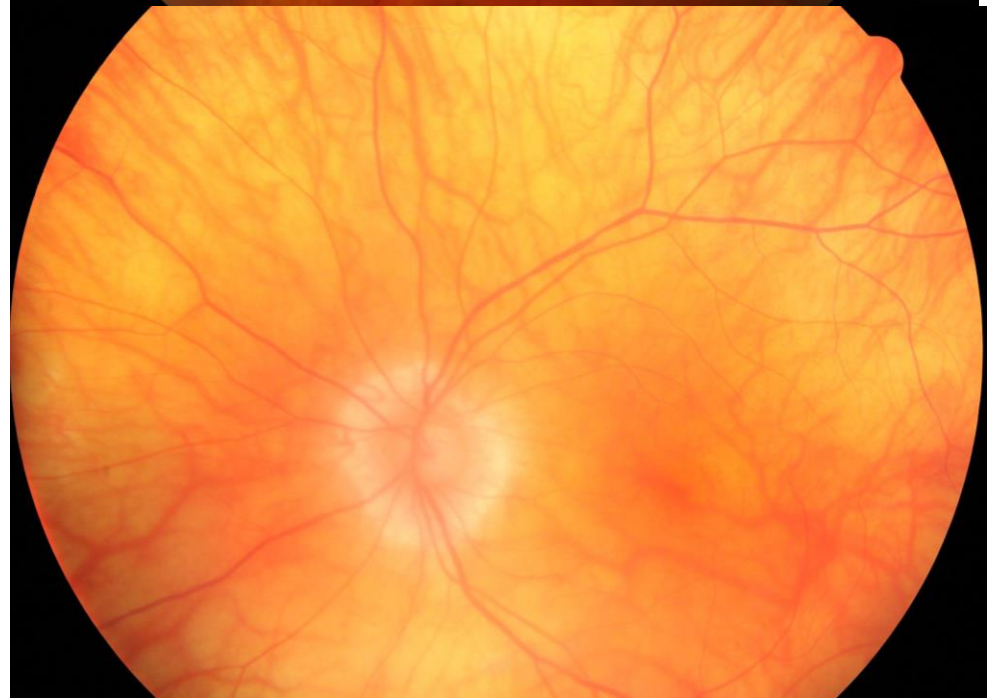
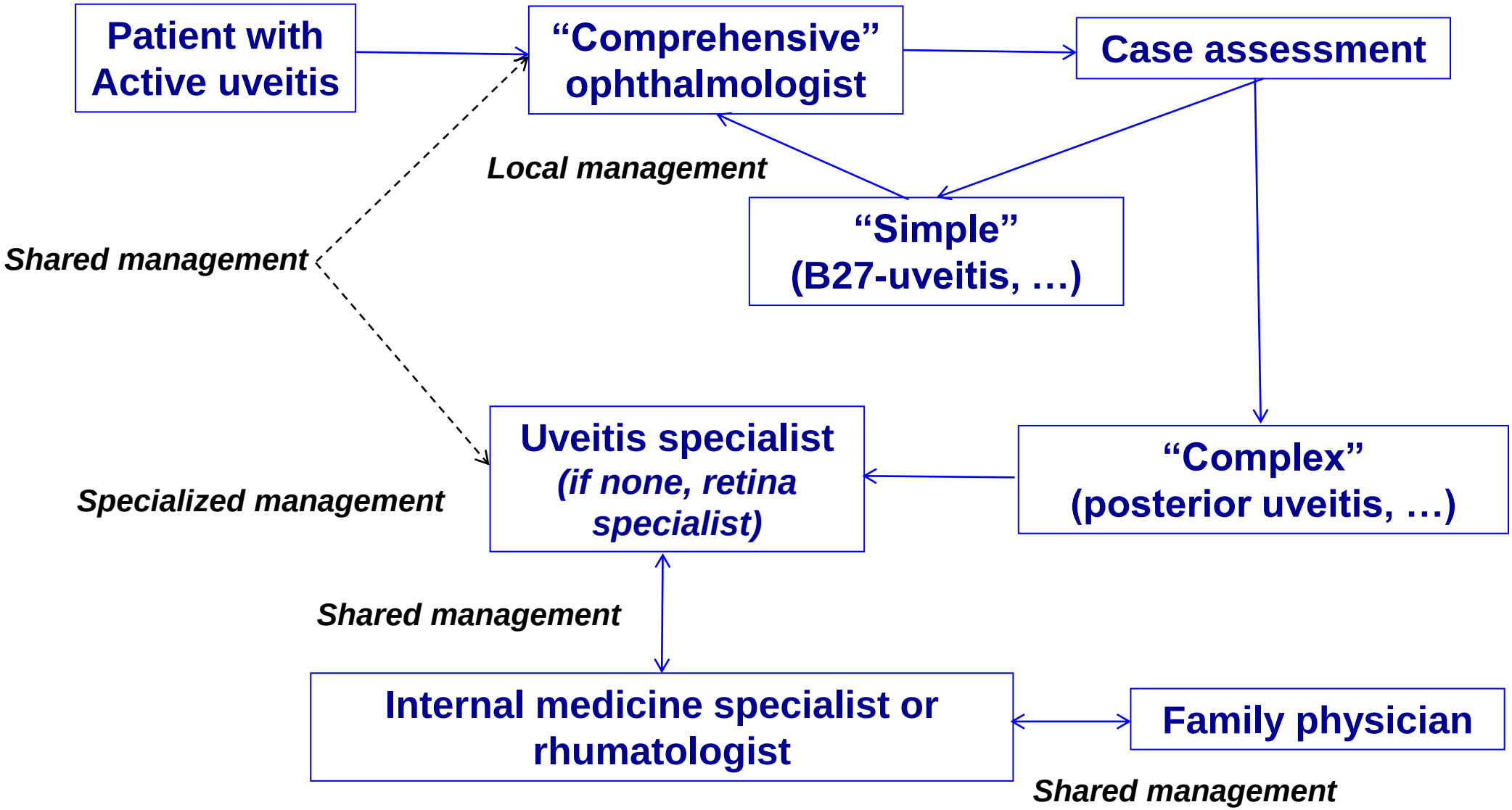


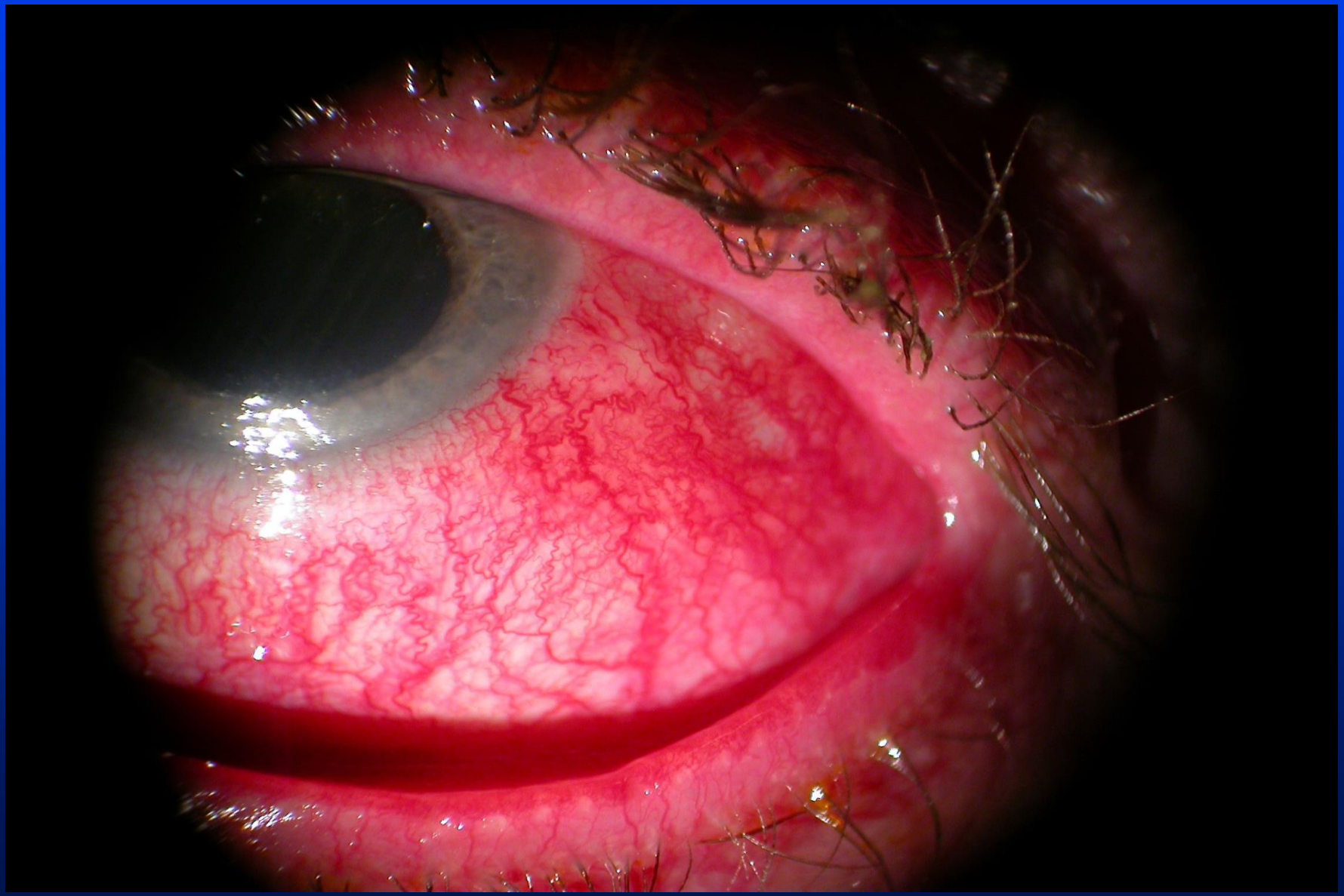
# Patient management pathways



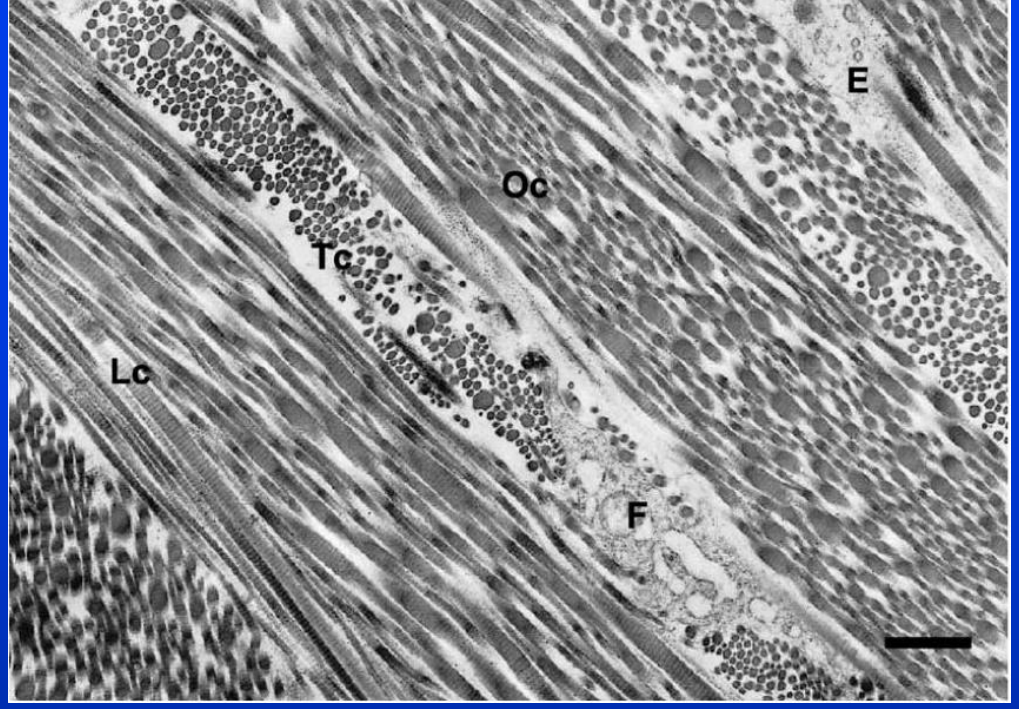
# Collaboration internistes- ophtalmologistes


**L’interniste conduit, l’ophtalmologiste pilote**

# Sclérites



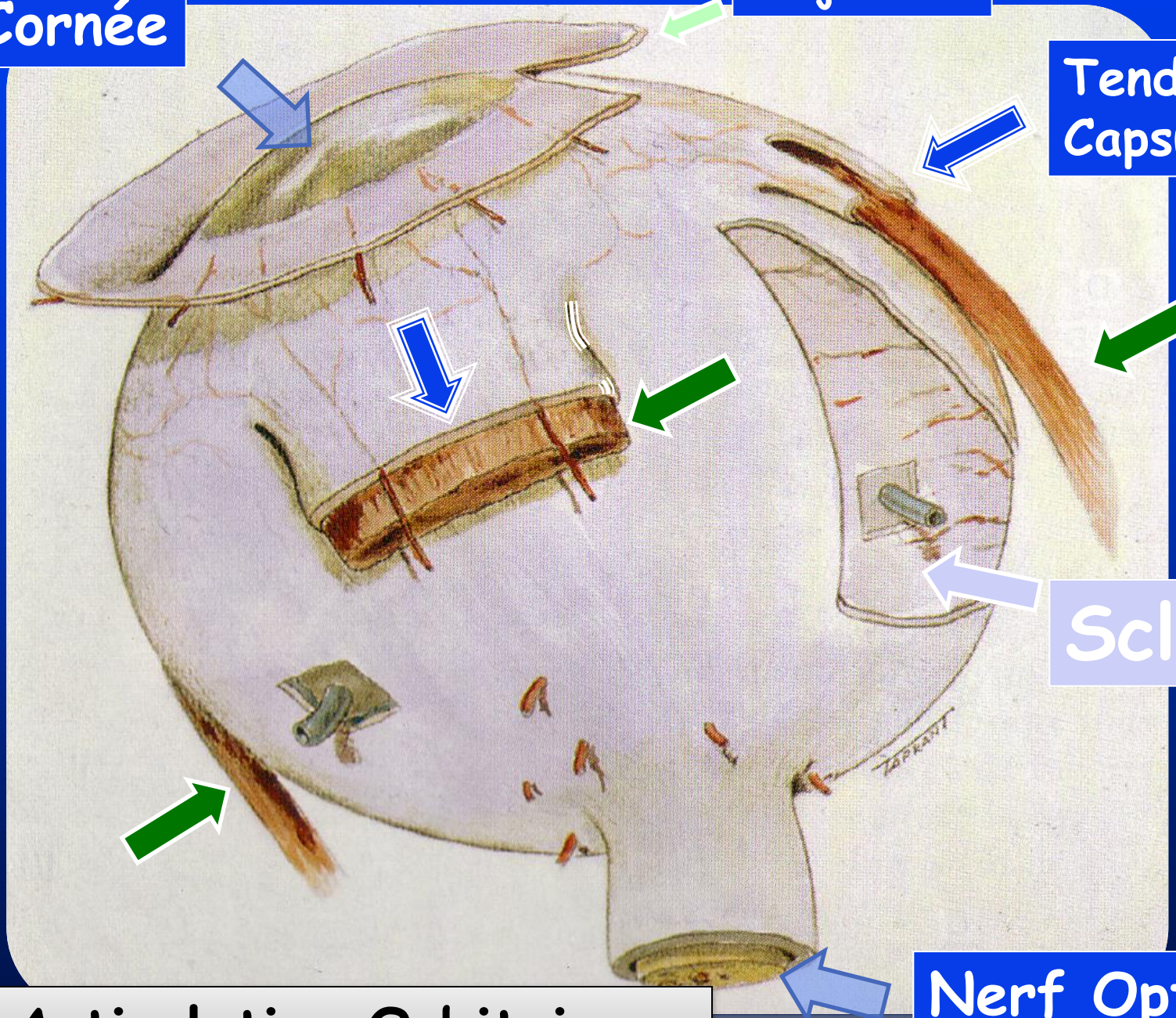
# La Sclère




- Tissu conjonctif
  - 70% de collagène (type I et III)
  - 2% de fibres élastiques
  - Matrice Extra Cellulaire (MEC) : protéoglycans → maintien de la structure fibrillaire des fibres de collagène
  - MEC et collagène synthétisés par des fibrocytes ( = sclérocytes)

- Epaisseur sclérale :

  1 à 1.35 mm en postérieur, 0.3 mm sous muscle droit, 0.8 mm en antérieur




# « Articulation Orbitaire »

# La Sclère

- **Vascularisation pauvre :**

  **Par contiguïté :**

  **- Capillaires épiscléraux**

  **- Capillaires choroïdiens**

  **⇒ L'inflammation sclérale a tendance à persister**

- **Innervation riche :**

  **- Nerfs ciliaires**

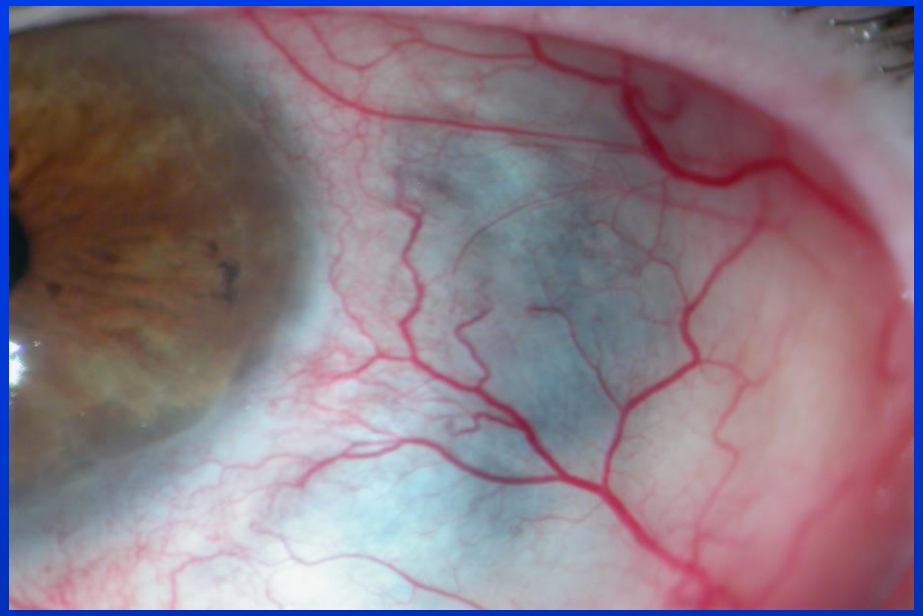
  **⇒ L'inflammation sclérale est douloureuse**

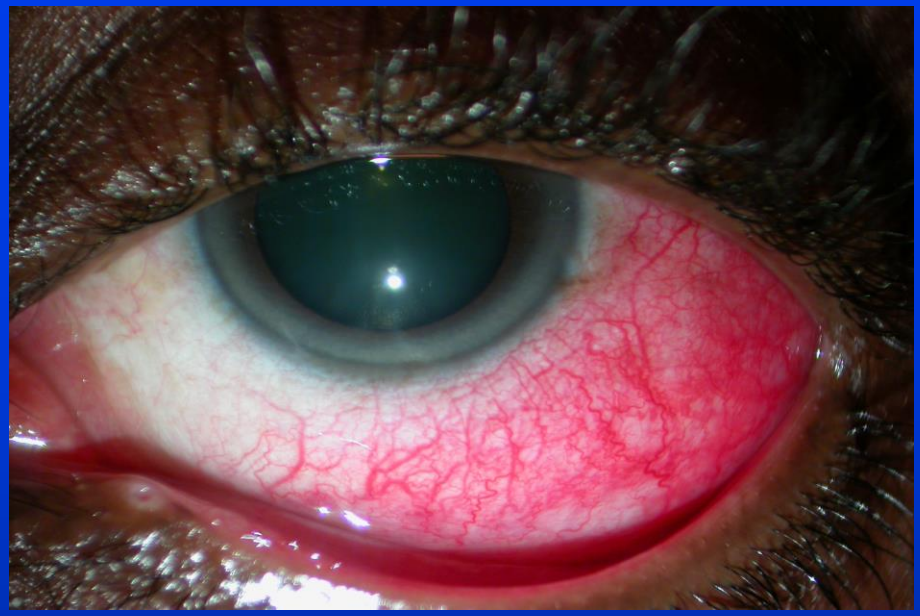
# Sclérites : classification anatomique

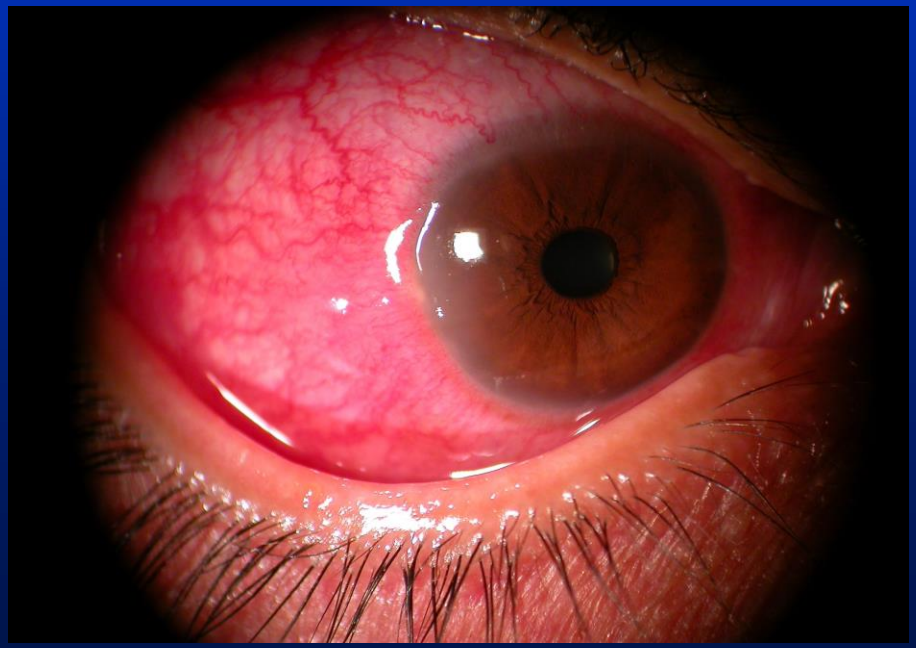
- **Sclérites antérieures : 88 - 94 %**
  - **Diffuse : 42 - 58 %**
  - **Nodulaire : 20 - 39 %**
  - **Nécrosante : 12 - 26 %**
    - **Sans inflammation : scléromalacie perforante**
    - **Avec inflammation : sclérite nécrosante**

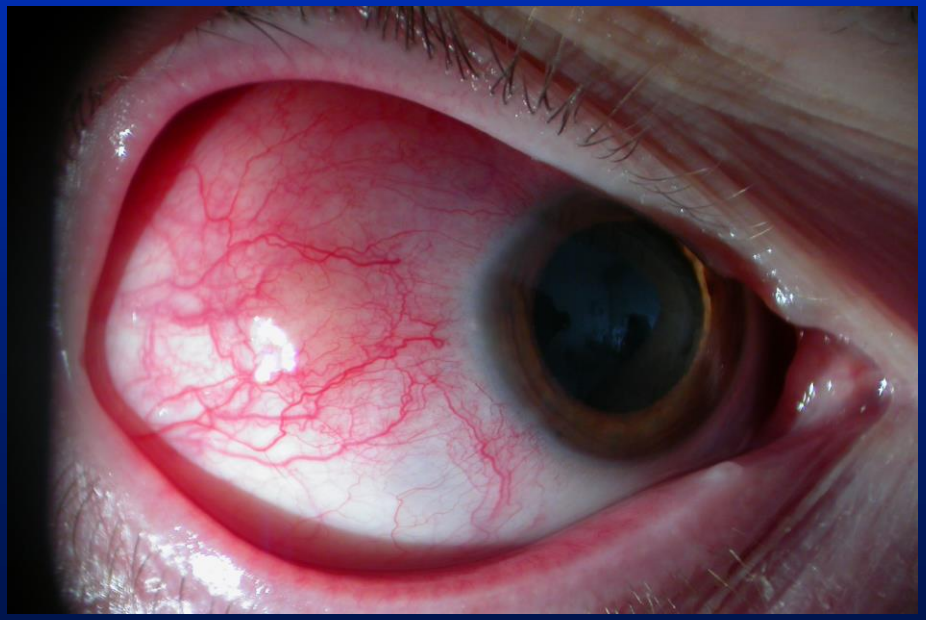
- **Sclérites postérieures : 6 - 12 %**

*–Tuft, Ophthalmology, 1991: 290 patients*
*–Sainz de la Maza, Ophthalmology, 1994 : 172 patients*
*–Jabs, Am J Ophthalmol 2000 : 97 patients*

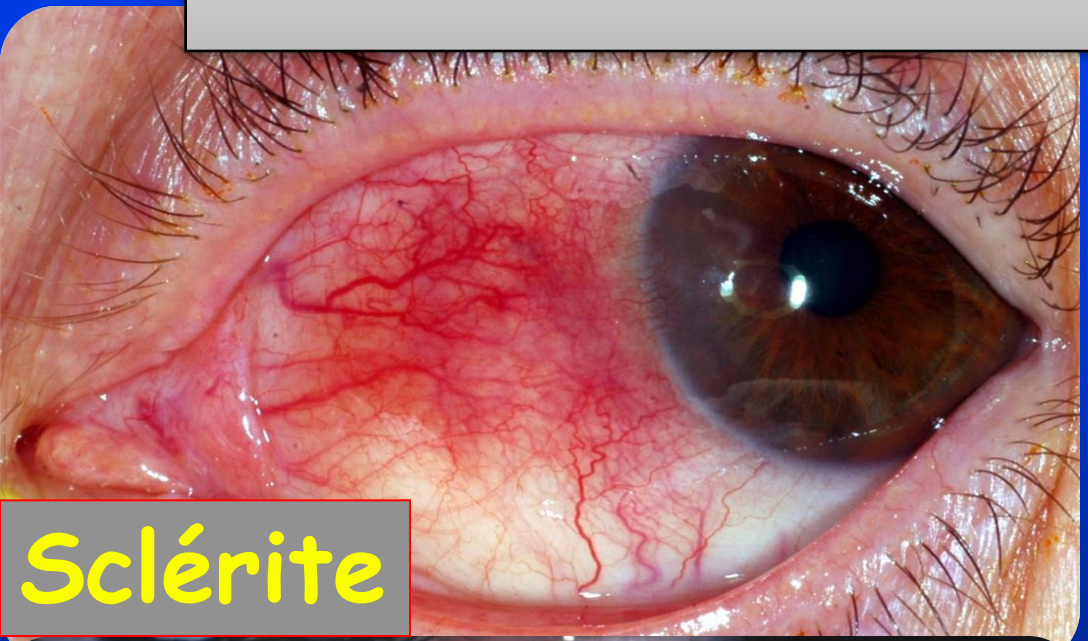








# SCLERITE - EPISCLERITE



Sclérite

Episclérite

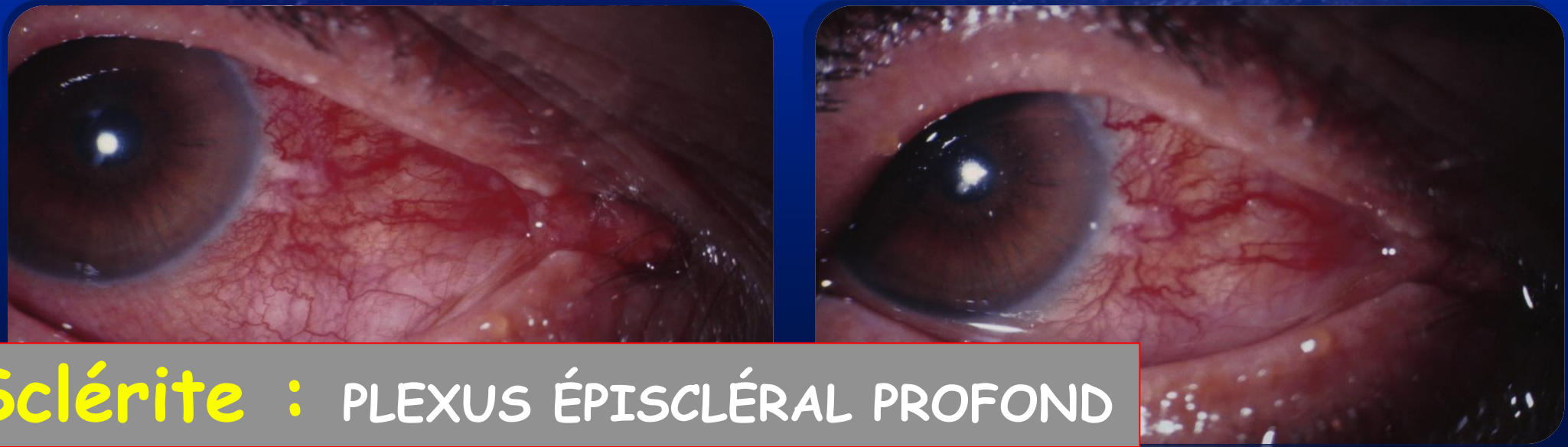
- ŒIL ROUGE « SOMBRE »
- DOULEURS INSOMNIANTES
- DÉBUT PROGRESSIF
- PAS DE RESOLUTION SPONTANEE
- PATHOLOGIE SYSTÉMIQUE 50%

- ŒIL ROUGE « VIF »
- DOULEURS LÉGÈRES
- DÉBUT BRUTAL
- RESOLUTION SPONTANEE
- RAREMENT ASSOCIEE A UNE PATHOLOGIE SYSTEMIQUE

# SCLERITE - EPISCLERITE

**TEST À LA NÉOSYNÉPHRINE®**

**Episclérite : PLEXUS ÉPISCLÉRAL SUPERFICIEL**



**Sclérite : PLEXUS ÉPISCLÉRAL PROFOND**

# Evaluation of Patients with Scleritis for Systemic Disease

*Esen Karamursel Akpek, MD,[1] Jennifer E. Thorne, MD,[1] Faqir A. Qazi, MBBS, FRCS,[1] Diana V. Do, MD,[1] Douglas A. Jabs, MD, MBA[1,2,3]*

***Objective:*** To evaluate the relationship between associated medical conditions and scleritis—particularly, the timing of the diagnosis of these diseases.

***Design:*** Retrospective case series.

***Participants:*** Patients with scleritis presenting to a single center over an 18-year period.

***Methods:*** Medical records were reviewed for the presence of an associated infectious or rheumatic disease and for the timing of the diagnosis of the systemic disease relative to the presentation for evaluation of the scleritis.

***Main Outcome Measures:*** Presence of an associated medical condition and timing of diagnosis relative to that of scleritis.

***Results:*** In a series of 243 patients with scleritis, 44.0% had an associated medical condition: 7.0%, an infection, and 37.0%, a rheumatic disease. The most frequent infection was herpes zoster, and the most frequent rheumatic disease was rheumatoid arthritis, present in 4.5% and 15.2% of patients, respectively. Of the 107 patients with an underlying disease, 77.6% had a previously diagnosed disease, 14.0% had their conditions diagnosed as a result of the initial evaluation, and 8.4% developed a systemic disease during follow-up. Systemic vasculitis was less likely to have been previously diagnosed than other rheumatic diseases (59.1% vs. 83.8%, $P = 0.015$) and more likely to be diagnosed by the initial diagnostic evaluation (27.3% vs. 8.8%, $P = 0.027$). Ten patients (4.1%) had a positive antineutrophil cytoplasmic antibody (ANCA) test result without clinical evidence of a systemic vasculitis. Four of 5 patients with a positive cytoplasmic ANCA test result but no clinical evidence of systemic vasculitis required immunosuppressive drugs for control of the scleritis, whereas 1 of the 5 patients with a positive perinuclear ANCA test result required immunosuppressive drugs. Among patients with no evident systemic disease after the initial diagnostic evaluation, the rate of occurrence of a rheumatic disease was 4% per person-year.

***Conclusions:*** Although associated systemic diseases are frequent among patients with scleritis, the majority are previously diagnosed. Systemic vasculitis is less likely than other rheumatic diseases to have been previously diagnosed. Because vasculitis is a potentially life-threatening disorder, it should be a focus of the diagnostic evaluation. *Ophthalmology 2004;111:501–506 © 2004 by the American Academy of Ophthalmology.*

Table 1. Characteristics of the Study Population

| Characteristic | Result |
|---|---|
| No. of patients | 243 |
| Age (yrs) | |
| Median | 52 |
| Range | 5–93 |
| Gender (percentage of women) | 70.3 |
| Ocular involvement (percentage bilateral) | 49.4 |
| Scleritis type (percentage of patients) | |
| Diffuse anterior | 66.4 |
| Nodular anterior | 16.8 |
| Necrotizing | 7.6 |
| Scleromalacia perforans | 0.8 |
| Posterior | 8.4 |
| Ocular complications (percentage of patients) | |
| Peripheral ulcerative keratitis | 6.2 |
| Interstitial keratitis | 12.0 |
| Uveitis | 29.8 |
| Infectious or rheumatic disease (percentage of patients) | 44.0 |
| Infectious diseases (percentage of patients) | 7.0 |
| Herpes zoster ophthalmicus | 4.5 |
| Herpes simplex keratitis | 1.6 |
| Syphilis | 0.4 |
| Lyme disease | 0.4 |
| Rheumatic disease (percentage of patients)* | 37.0 |
| Rheumatoid arthritis | 15.2 |
| Systemic vasculitis† | 9.1 |
| Systemic lupus erythematosus | 4.1 |
| Relapsing polychondritis | 1.6 |
| Inflammatory bowel disease | 3.3 |
| Spondyloarthropathy‡ | 2.5 |
| Other§ | 1.7 |

Ophthalmology 2004;111:501–506

Table 2. Diagnosis of Infectious and Rheumatic Diseases Relative to Diagnosis of Scleritis

| Systemic Disease | No. of Patients | Present before Scleritis (%) | Diagnosed at Initial Evaluation (%) | Occurred during Follow-up (%) |
|---|---|---|---|---|
| Infectious diseases | 17 | 76.5 | 17.6 | 5.9 |
| Herpes zoster ophthalmicus | 11 | 81.8 | 9.1 | 9.1 |
| Herpes simplex keratitis | 4 | 100 | 0 | 0 |
| Syphilis | 1 | 0 | 100 | 0 |
| Lyme disease | 1 | 0 | 100 | 0 |
| Rheumatic disease | 90 | 78.4 | 11.4 | 10.2 |
| Rheumatoid arthritis | 37 | 88.8 | 5.6 | 5.4 |
| Systemic vasculitis | 22 | 59.1 | 27.3 | 13.6 |
| Systemic lupus erythematosus | 10 | 100 | 0 | 0 |
| Relapsing polychondritis | 4 | 75.0 | 0 | 25.0 |
| Inflammatory bowel disease | 8 | 62.5 | 12.5 | 25.0 |
| Spondyloarthropathy | 6 | 83.3 | 16.7 | 0 |
| Other | 4 | 50.0 | 25.0 | 25.0 |

*Ophthalmology 2004;111:501–506*

# Severity of Episcleritis and Systemic Disease Association

*Esen Karamursel Akpek, MD,[1] Harvey S. Uy, MD,[1] William Christen, ScD,[2] Canan Gurdal, MD,[3] C. Stephen Foster, MD[1]*

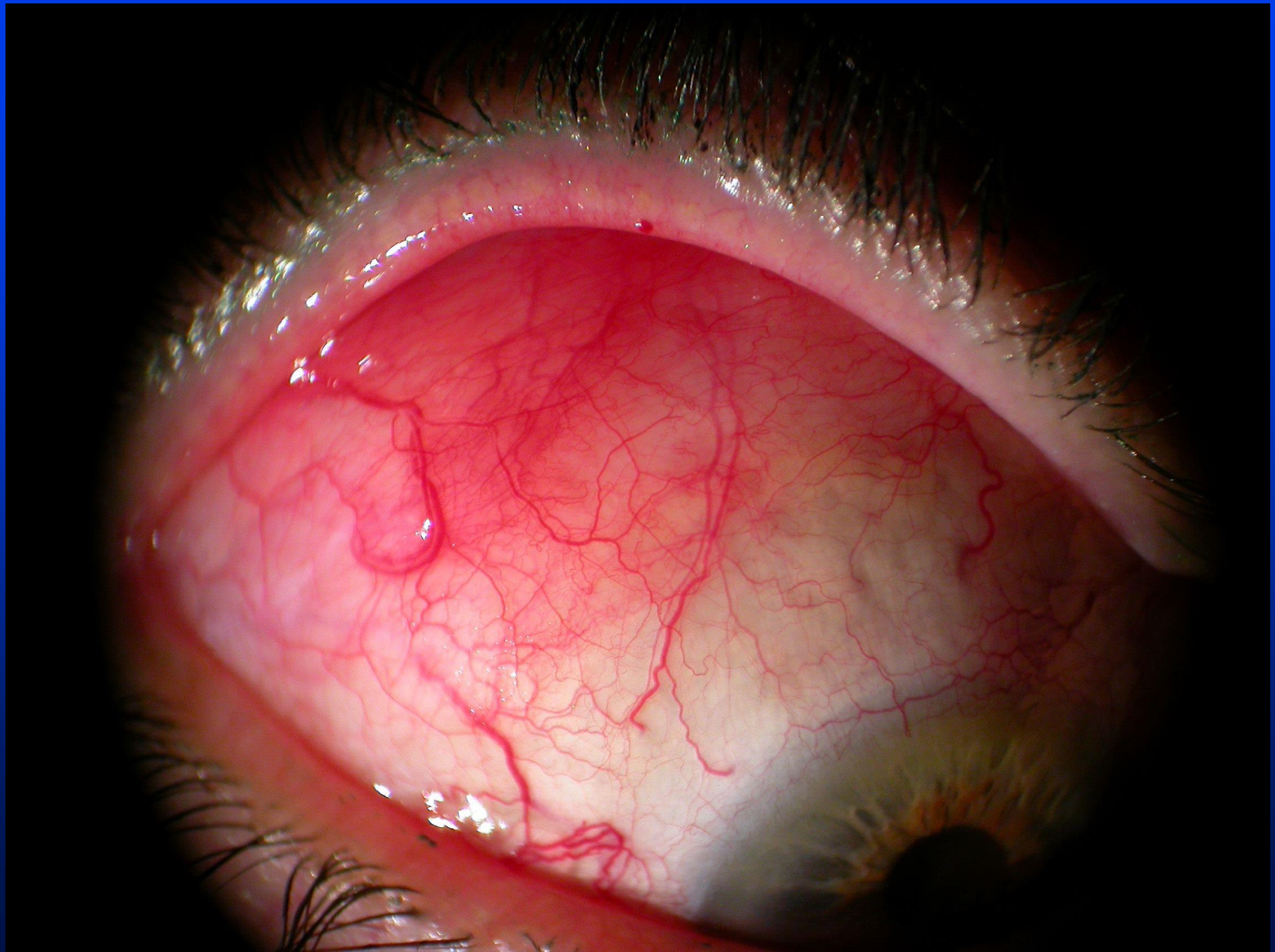
***Objective:*** To analyze patient characteristics and correlate between the site and severity of the inflammation and ocular and/or systemic disease association in a cohort of patients with episcleritis.

***Design:*** Retrospective case series.

***Methods:*** Medical records of 100 patients with episcleritis were reviewed. Data were analyzed using a customized database software.

***Results:*** The age range at presentation was 18 to 76 years (mean, 43; median, 44). Sixty-nine percent of the patients were female. Thirty-two (32%) patients had bilateral involvement. The episcleritis was nodular in 23 eyes (16%). Half of the patients had a concurrent eye disease. Associated systemic disease was found in 36 patients (36%). In two patients, episcleritis preceded a systemic vasculitic disease (Wegener granulomatosis and Cogan syndrome). Ocular complications included uveitis (11.4%), corneal involvement (15%), and glaucoma (7.8%). No significant correlation of the site and severity of inflammation to the presence of associated systemic or ocular diseases was found. The mean follow-up was 16.5 months. Twenty-eight patients experienced recurrence of episcleritis during the follow-up. Half of the patients required treatment with oral nonsteroidal anti-inflammatory drugs.

***Conclusions:*** Episcleritis is usually a benign, self-limited disease, but it should not be trivialized since it may be associated with systemic disease and ocular complications. A careful review of systems should be performed in all patients presenting with episcleritis, and this should be repeated at least annually during the follow-up. A thorough eye examination is obviously essential to detect and treat ocular complications. *Ophthalmology 1999;106:729–731*



# Scleritis

## *A Clinicopathologic Study of 55 Cases*

*Widiarti P. Riono, MD,*[1] *Ahmed A. Hidayat, MD,*[2] *Narsing A. Rao, MD*[1]

***Objective:*** By a clinicopathologic study, to evaluate the histopathologic features associated with various causes of scleritis.

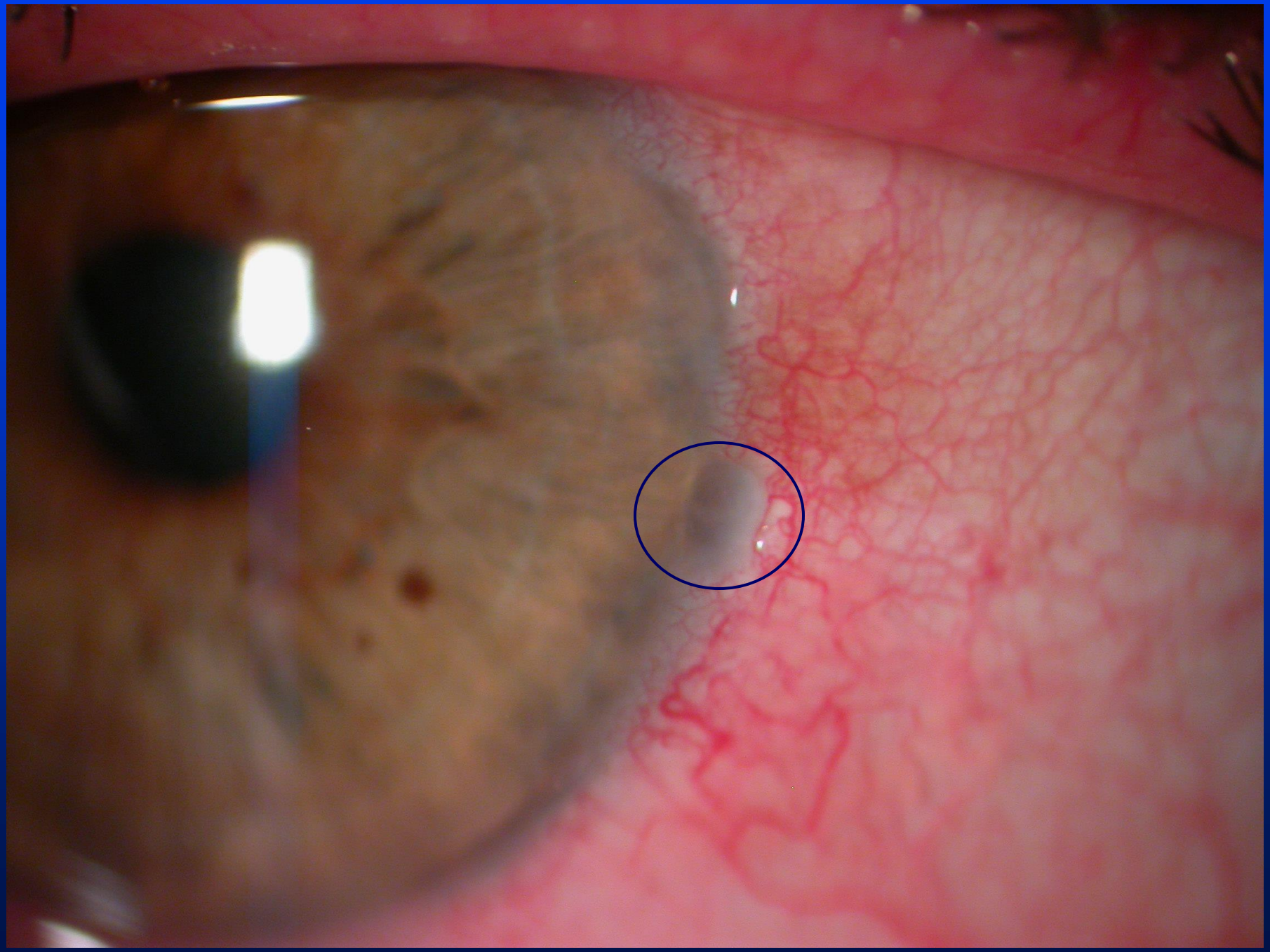
***Design:*** Retrospective observational case series.

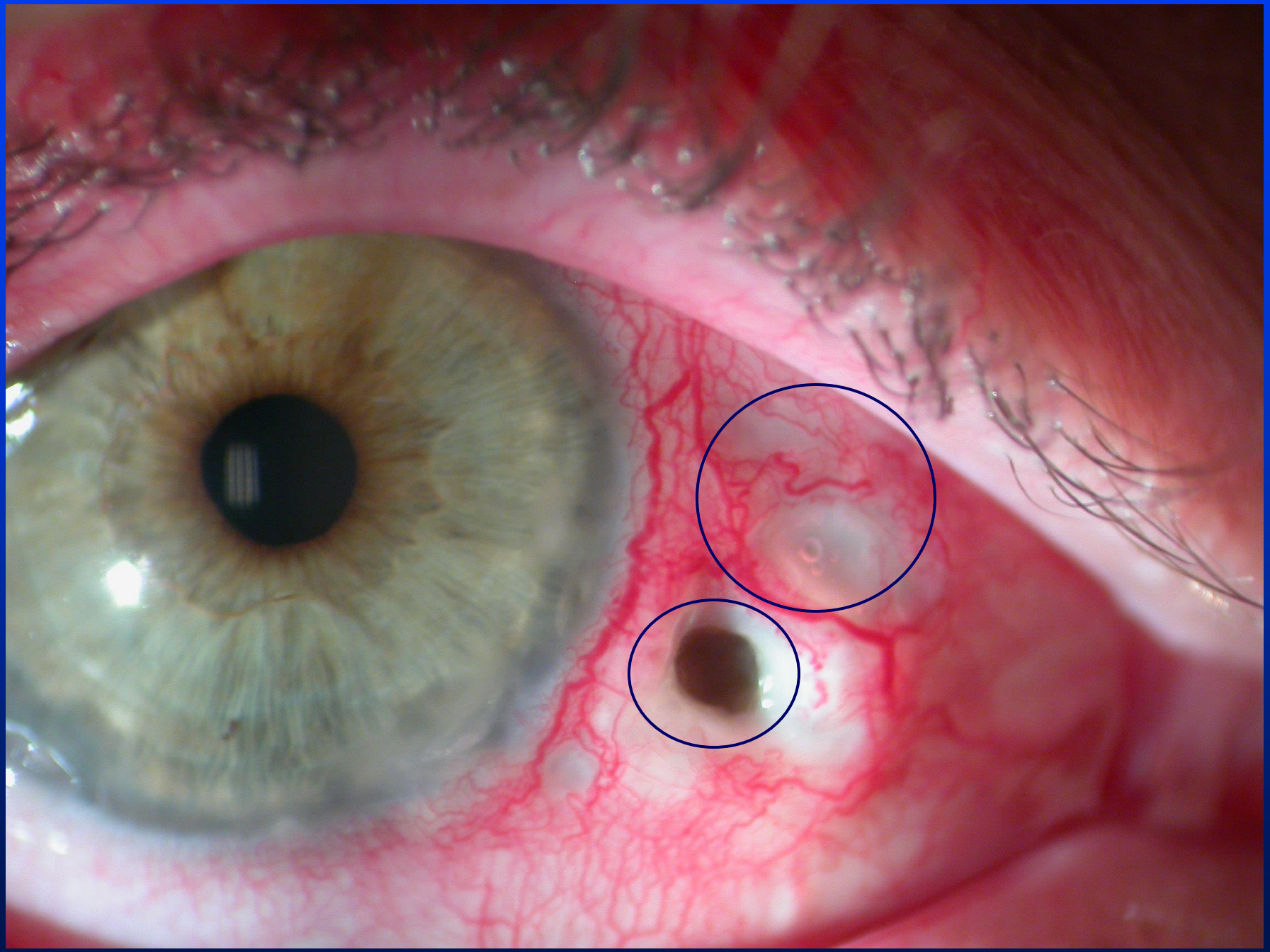
***Participants:*** Enucleated globes or biopsy specimens obtained from 55 cases of clinically diagnosed necrotizing scleritis.

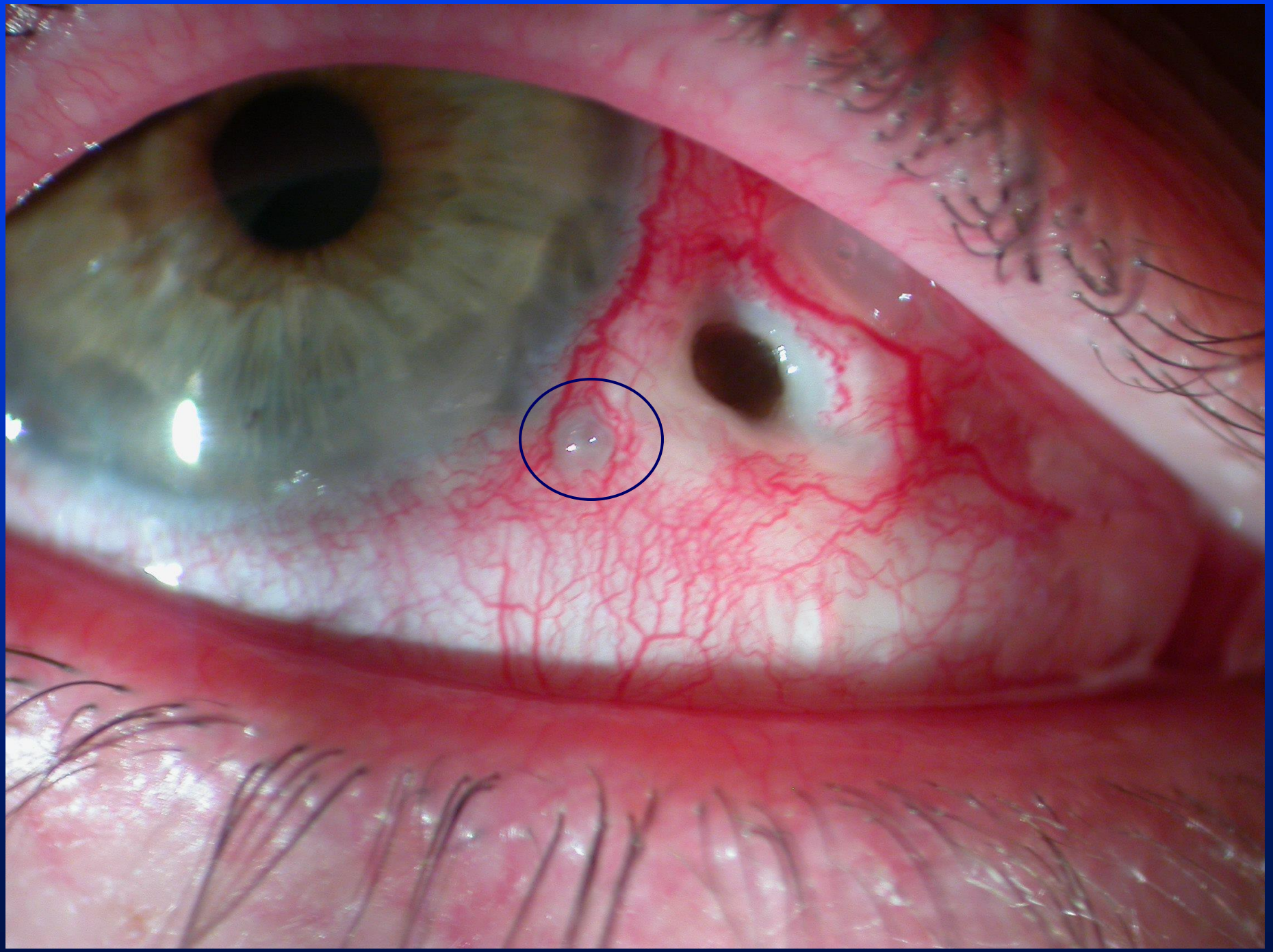
***Methods:*** On the basis of their histologic appearance, these cases were divided into four morphologic groups: (1) zonal necrotizing granulomatous scleral inflammation; (2) nonzonal diffuse scleral inflammation, with or without granulomatous process; (3) necrotizing inflammation with microabscesses, with or without evidence of micro-organisms in the section studied; and (4) sarcoidal granulomatous inflammation. The clinical charts were reviewed for the presence of any associated disease.

***Results:*** There were 14 (25.4%) cases in the first group; 12 had clinical evidence of systemic autoimmune diseases, including 8 cases of rheumatoid arthritis and 1 each of polychondritis, Goodpasture syndrome, Wegener granulomatosis, and collagen vascular disease; of the remaining 2 cases, 1 patient had a history of herpes zoster ophthalmicus, and the other had no history of any systemic autoimmune or infectious disease. None of the 19 (34.5%) patients characteristic of group 2 had any history of systemic autoimmune or infectious disease. Eleven of the 21 (38.2%) patients in group 3 had infections, including Pseudomonas spp., gram-positive cocci, Haemophilus spp., Actinomyces spp., and fungi; in the 10 remaining cases, no micro-organisms could be detected. The one case in group 4 was diagnosed as sarcoidosis.

***Conclusions:*** On the basis of their histologic features, rheumatoid scleritis and related systemic autoimmune-mediated necrotizing scleral inflammations could be differentiated from either idiopathic or infectious scleritis; however, the histologic features of rheumatoid scleritis were similar to those of necrotizing scleritis associated with other systemic autoimmune diseases. *Ophthalmology 1999;106:1328–1333*





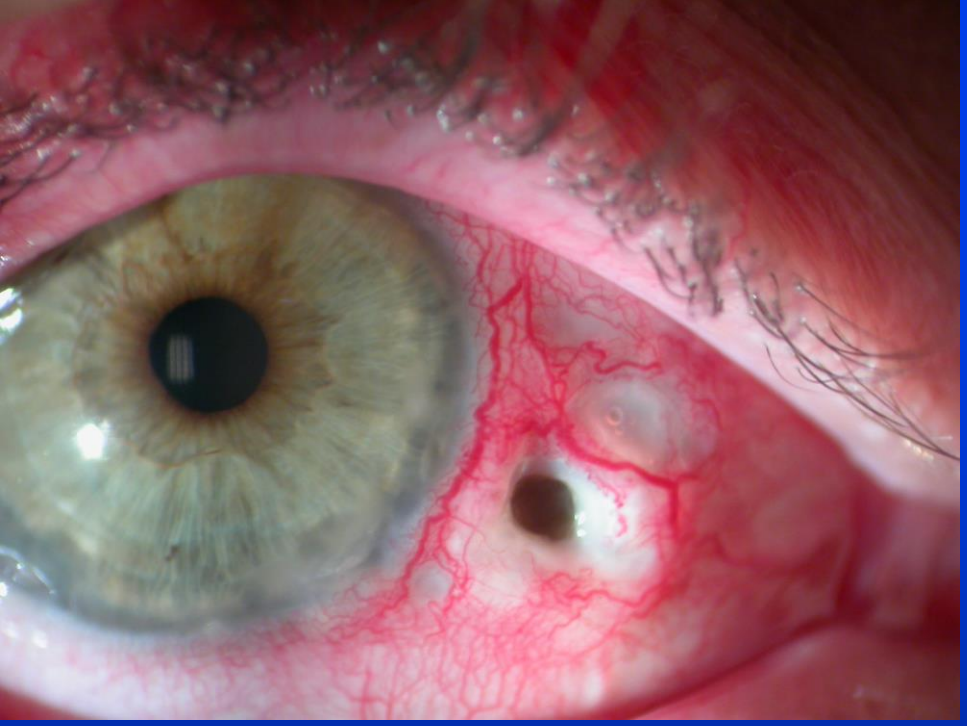


# Conduite à tenir ?

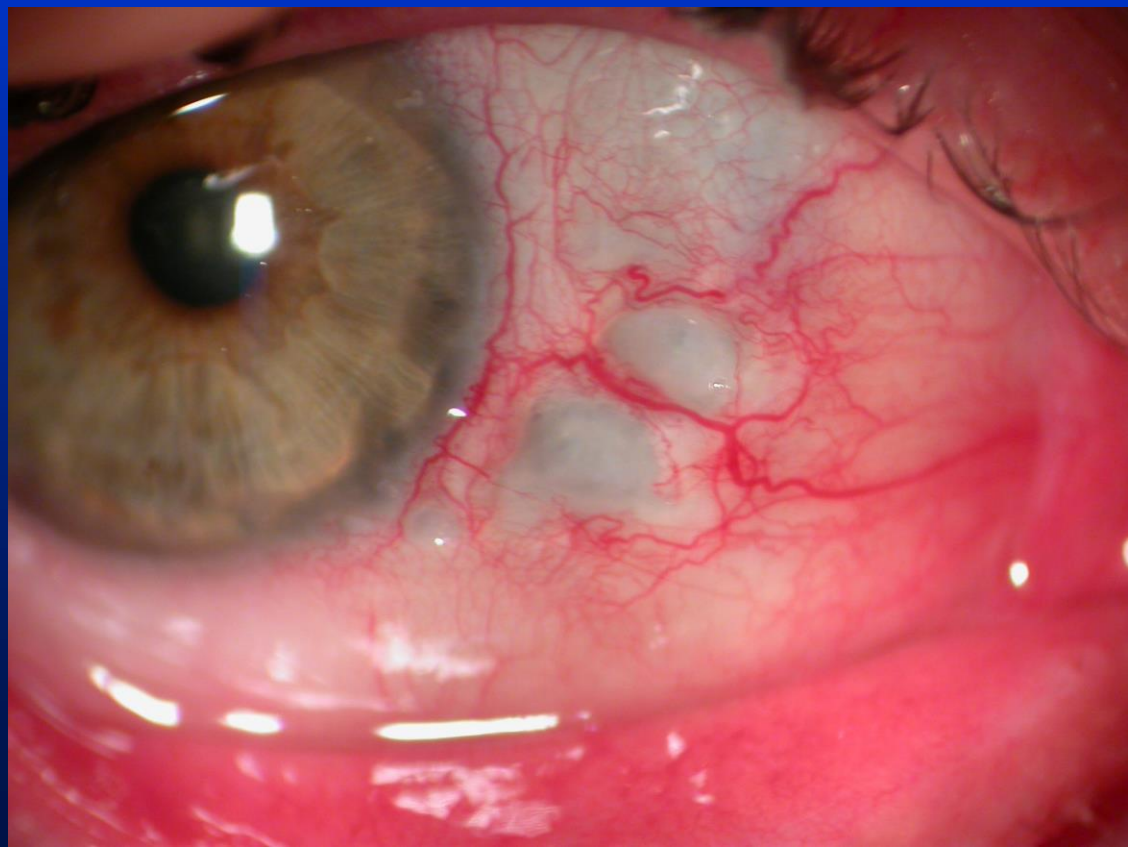
- **Pas de problème diagnostique (Polyarthrite Rhumatoïde connue)**

- **Traitement chirurgical ou/et médical?**

**Bolus Endoxan + Corticoides Bolus 500mg**



10 jours post traitement médical

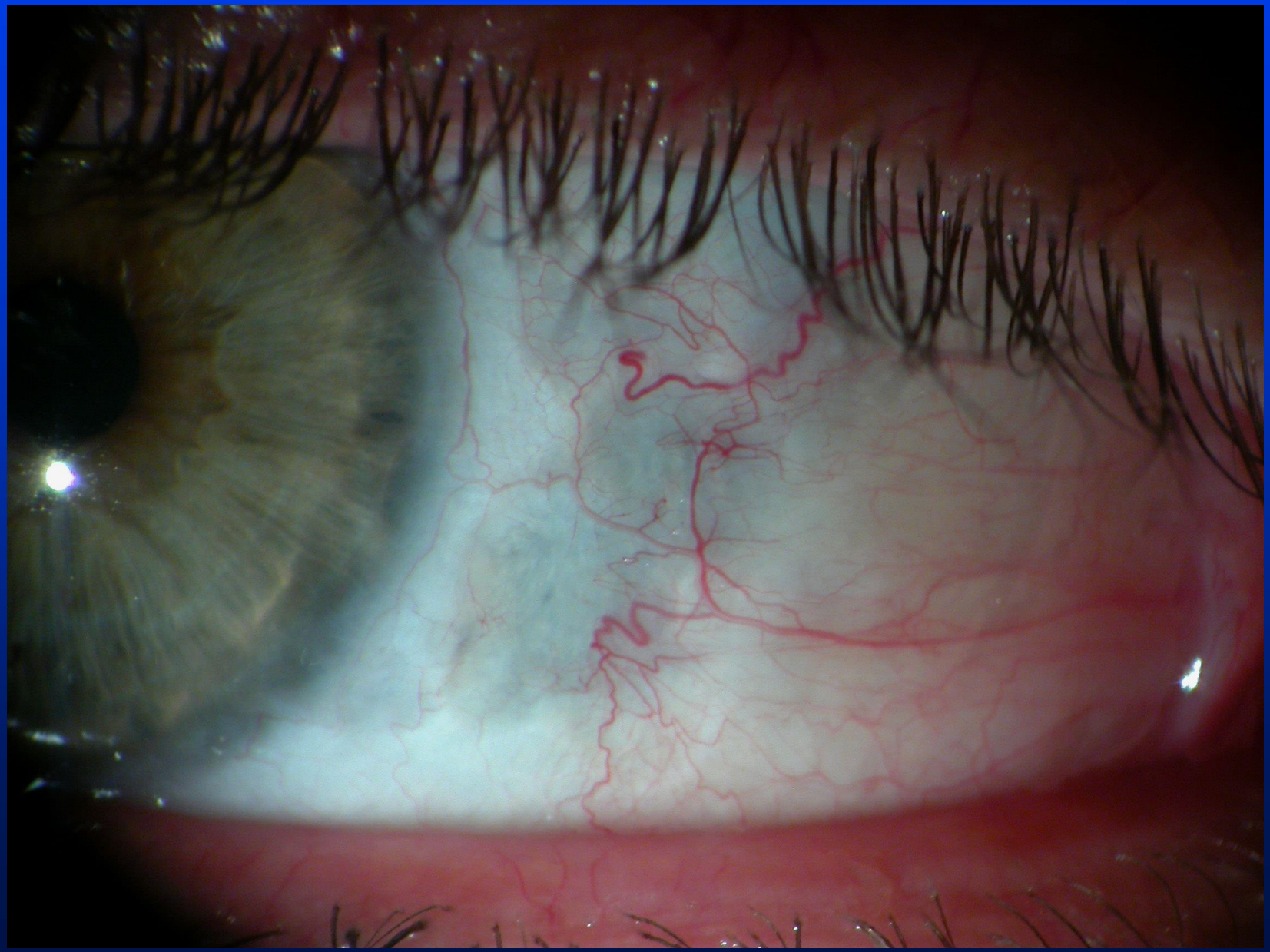


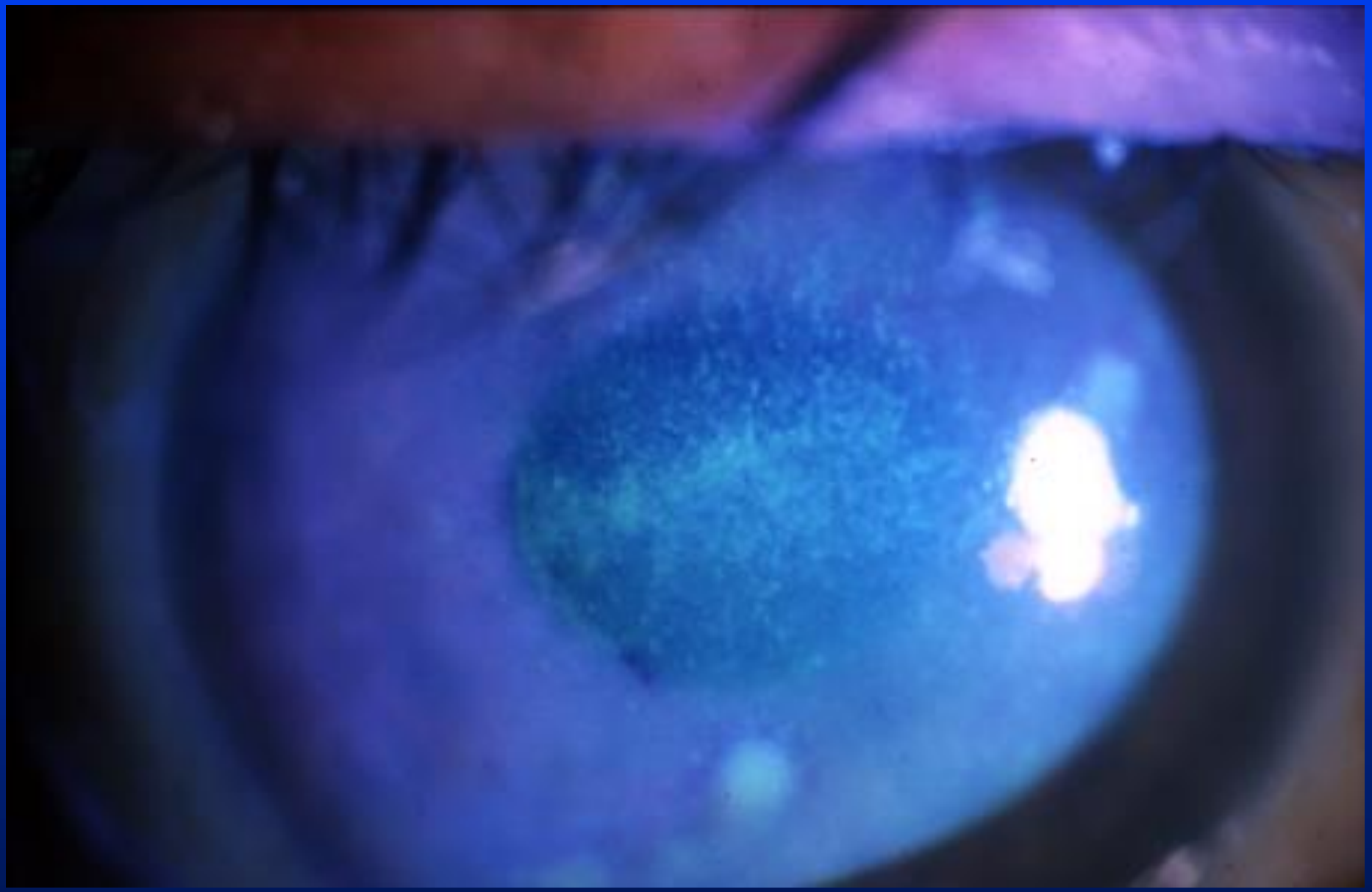
Traitement local inutile, voire dangereux

Retarder la prise en charge chirurgicale

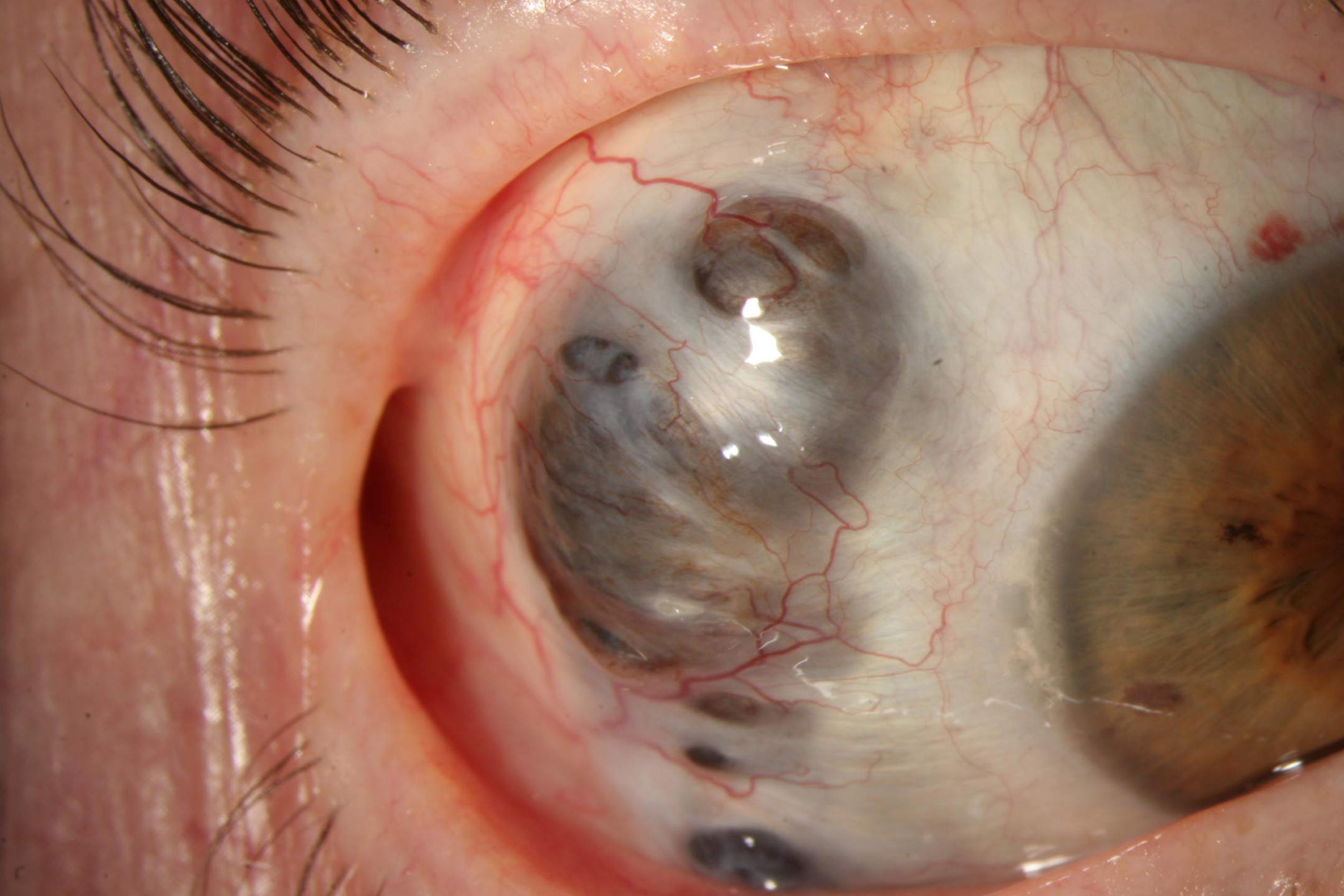
≈ 80% cas de sclérites, une maladie générale est connue

# 2 mois post-traitement





Syndrome sec



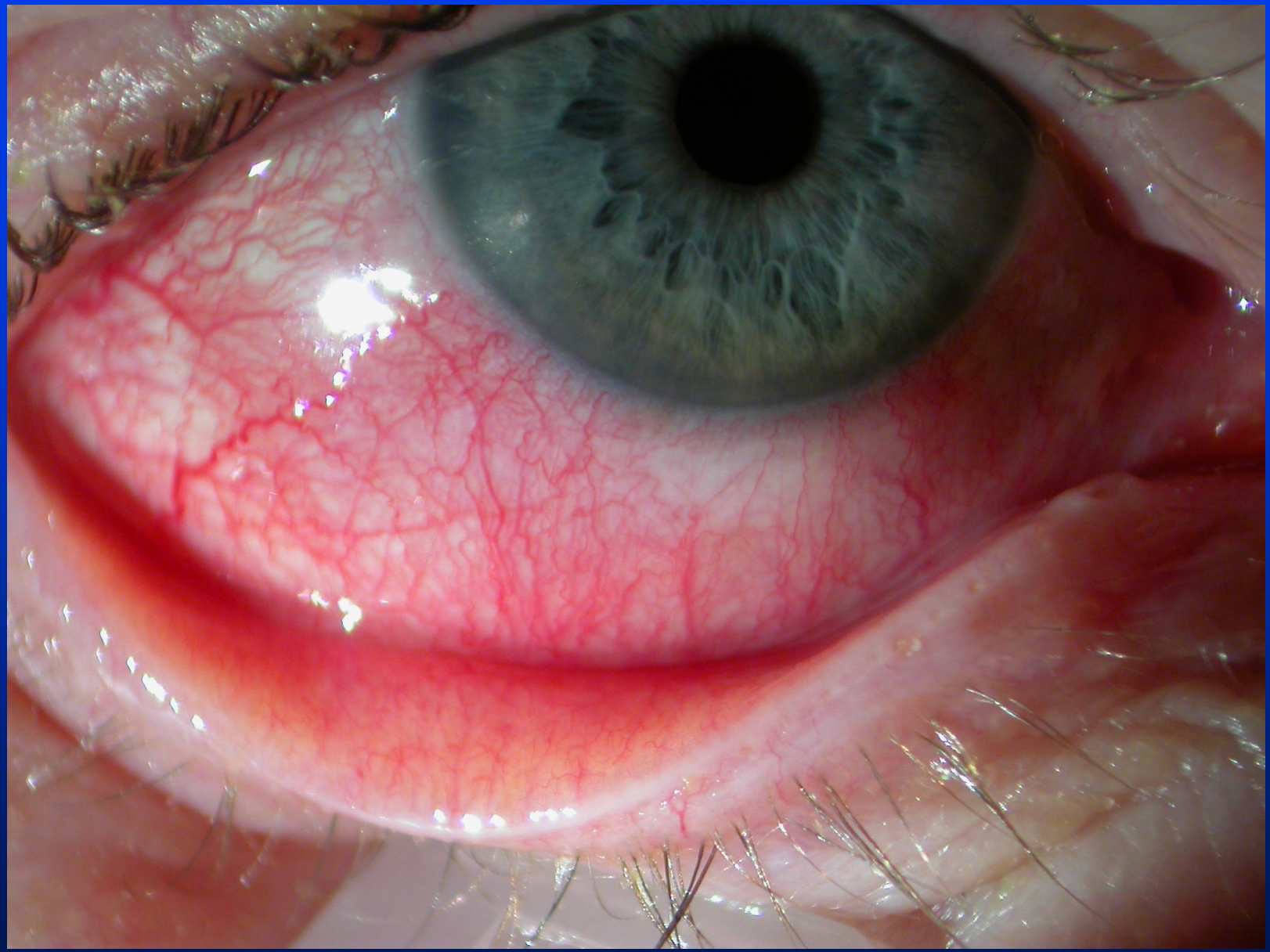
# Evaluation of Patients with Scleritis for Systemic Disease

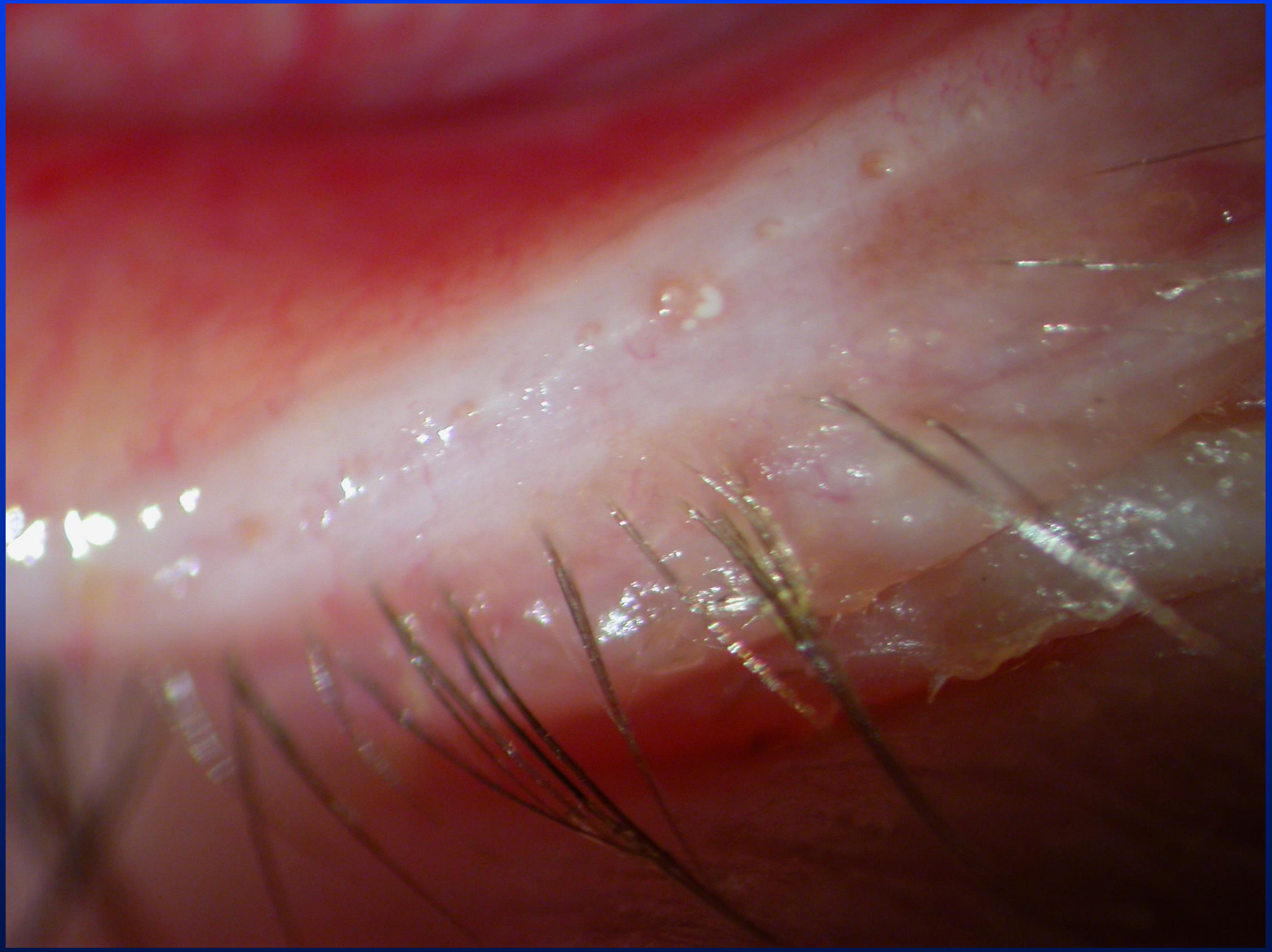
*Esen Karamursel Akpek, MD,[1] Jennifer E. Thorne, MD,[1] Faqir A. Qazi, MBBS, FRCS,[1] Diana V. Do, MD,[1] Douglas A. Jabs, MD, MBA[1,2,3]*

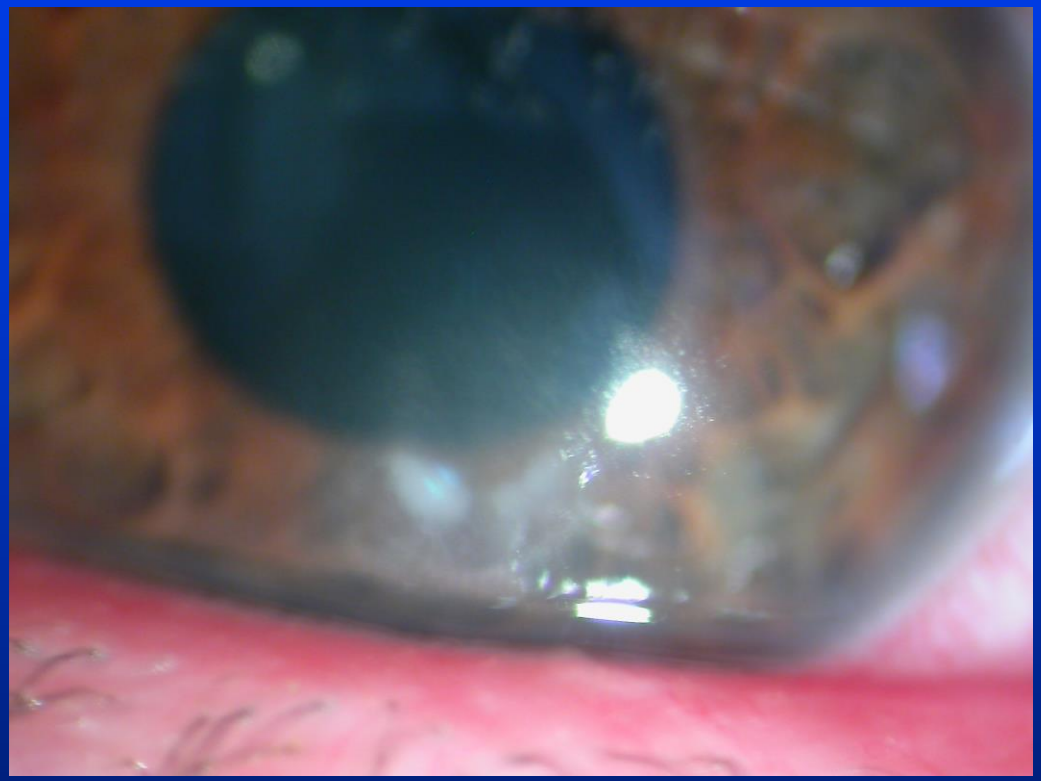
Table 2. Diagnosis of Infectious and Rheumatic Diseases Relative to Diagnosis of Scleritis

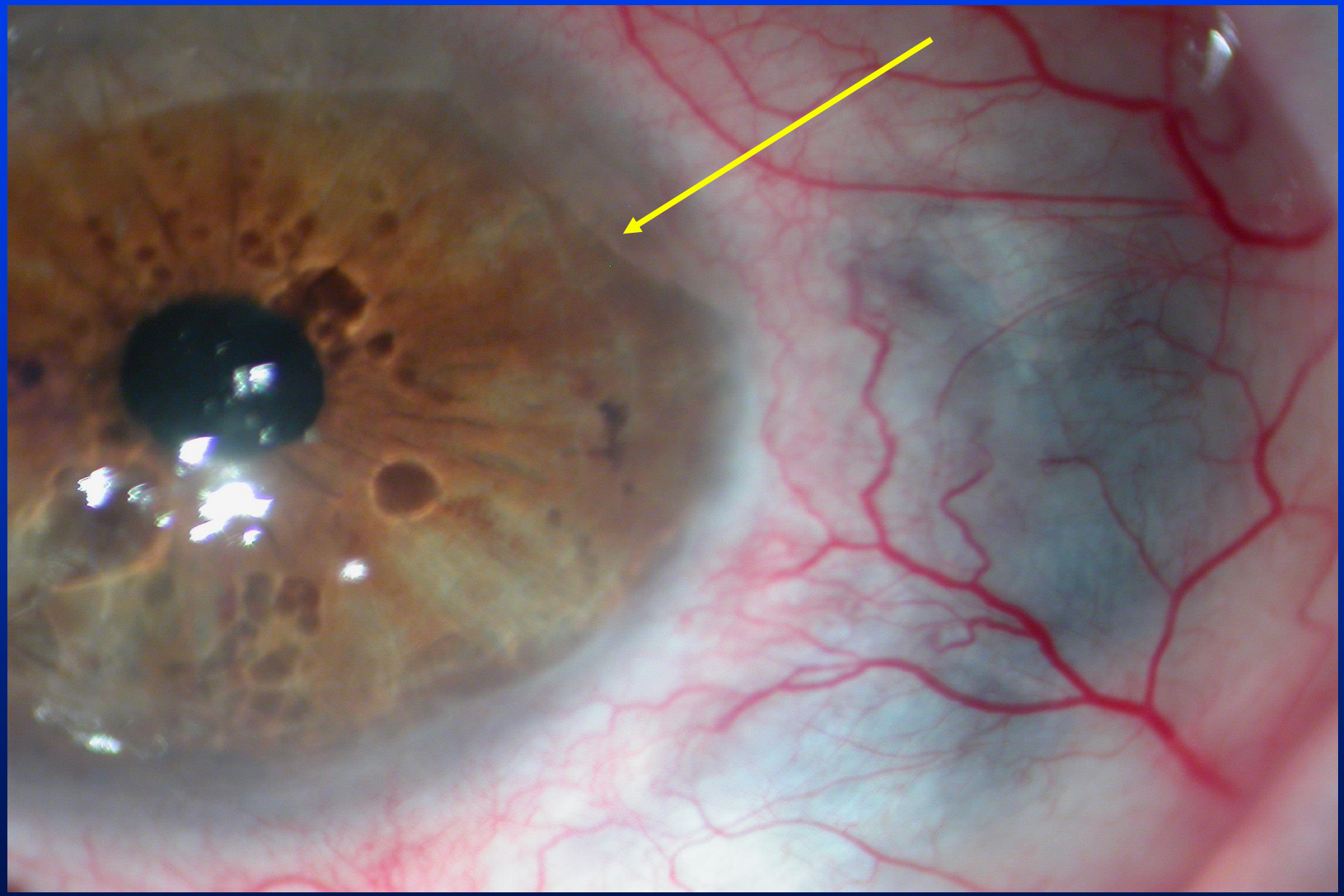
| Systemic Disease | No. of Patients | Present before Scleritis (%) | Diagnosed at Initial Evaluation (%) | Occurred during Follow-up (%) |
|---|---|---|---|---|
| Infectious diseases | 17 | 76.5 | 17.6 | 5.9 |
| Herpes zoster ophthalmicus | 11 | 81.8 | 9.1 | 9.1 |
| Herpes simplex keratitis | 4 | 100 | 0 | 0 |
| Syphilis | 1 | 0 | 100 | 0 |
| Lyme disease | 1 | 0 | 100 | 0 |
| Rheumatic disease | 90 | 78.4 | 11.4 | 10.2 |
| Rheumatoid arthritis | 37 | 88.8 | 5.6 | 5.4 |
| Systemic vasculitis | 22 | 59.1 | 27.3 | 13.6 |
| Systemic lupus erythematosus | 10 | 100 | 0 | 0 |
| Relapsing polychondritis | 4 | 75.0 | 0 | 25.0 |
| Inflammatory bowel disease | 8 | 62.5 | 12.5 | 25.0 |
| Spondyloarthropathy | 6 | 83.3 | 16.7 | 0 |
| Other | 4 | 50.0 | 25.0 | 25.0 |

*Ophthalmology 2004;111:501–506 © 2004 by the American Academy of Ophthalmology.*





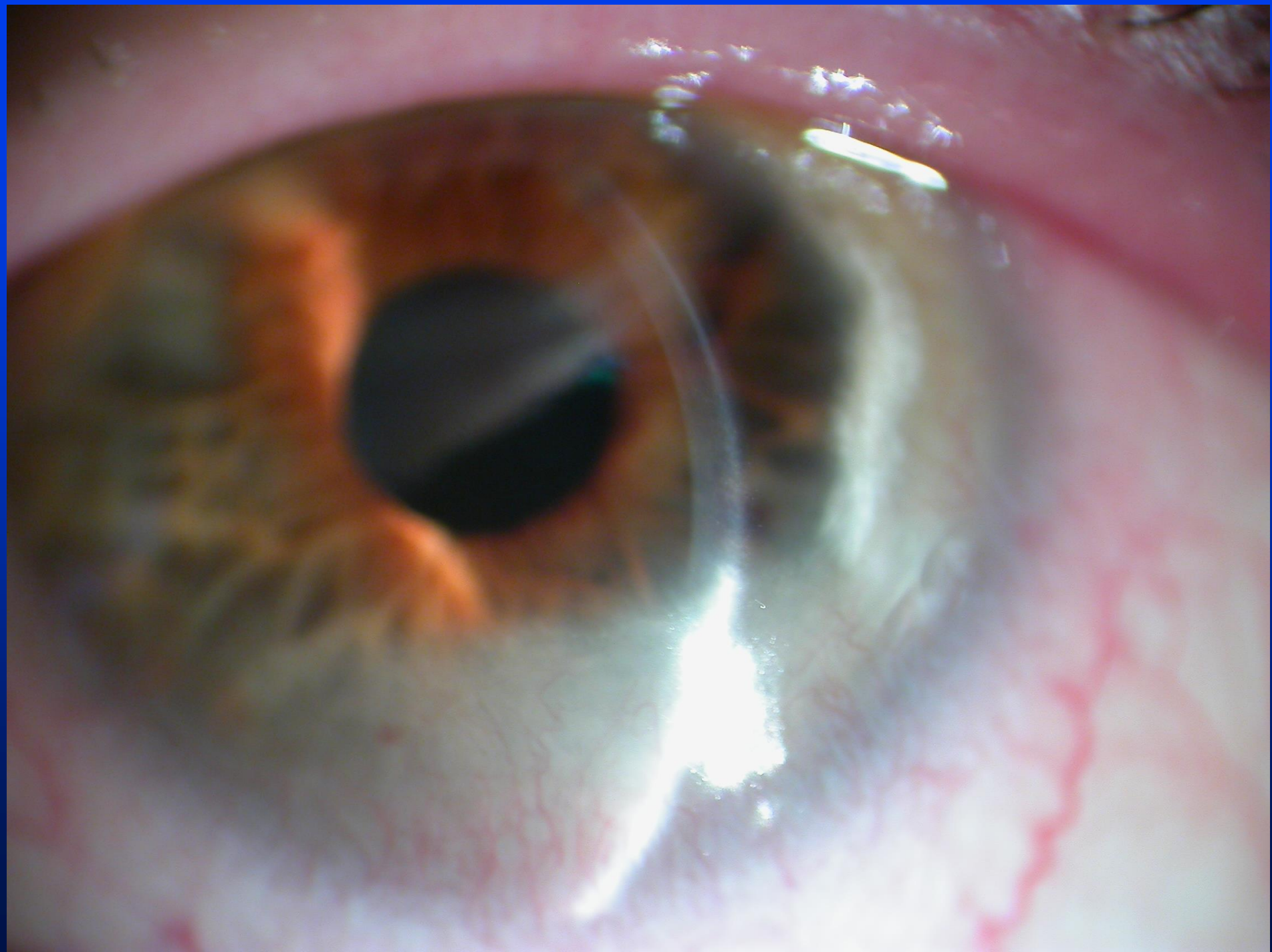


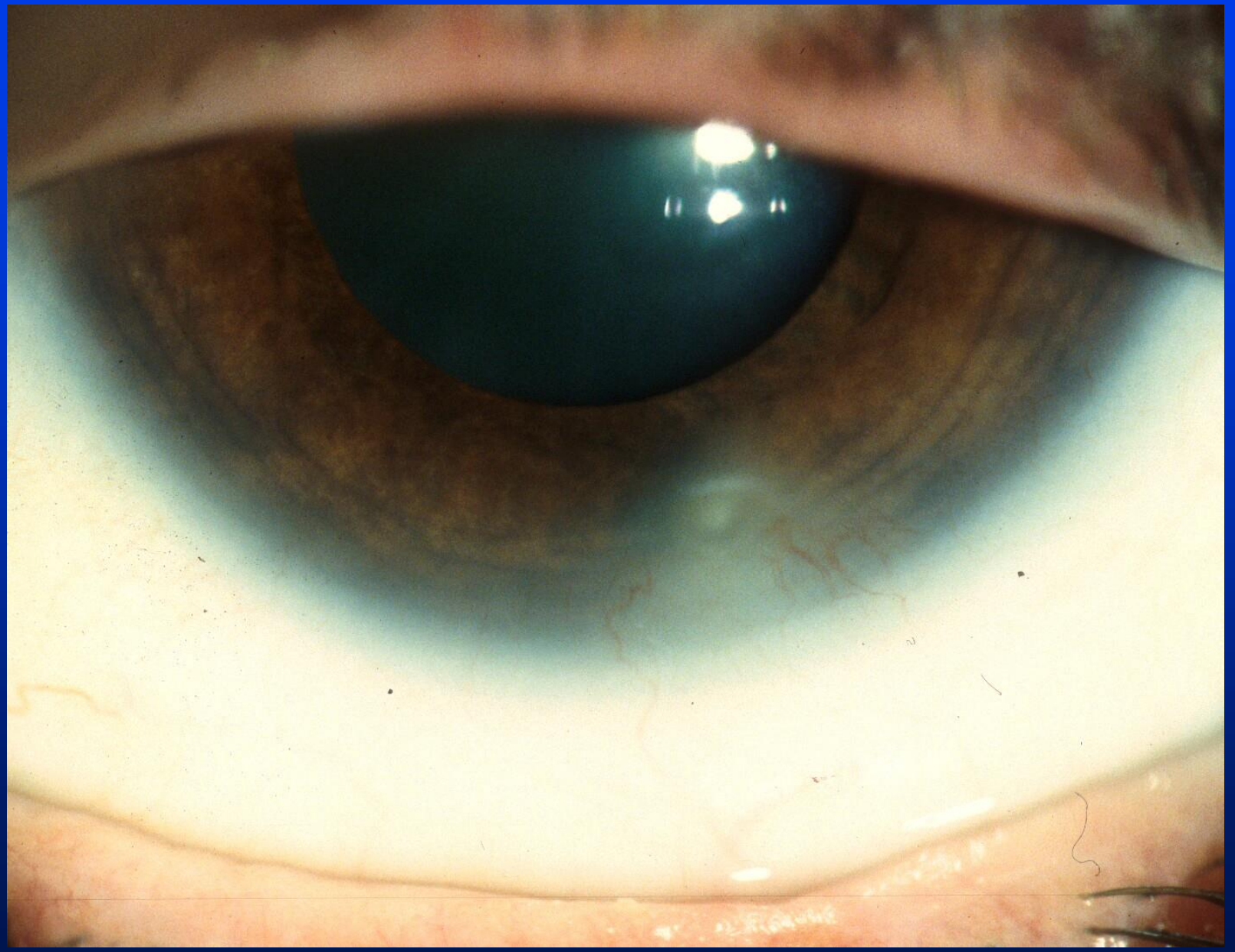


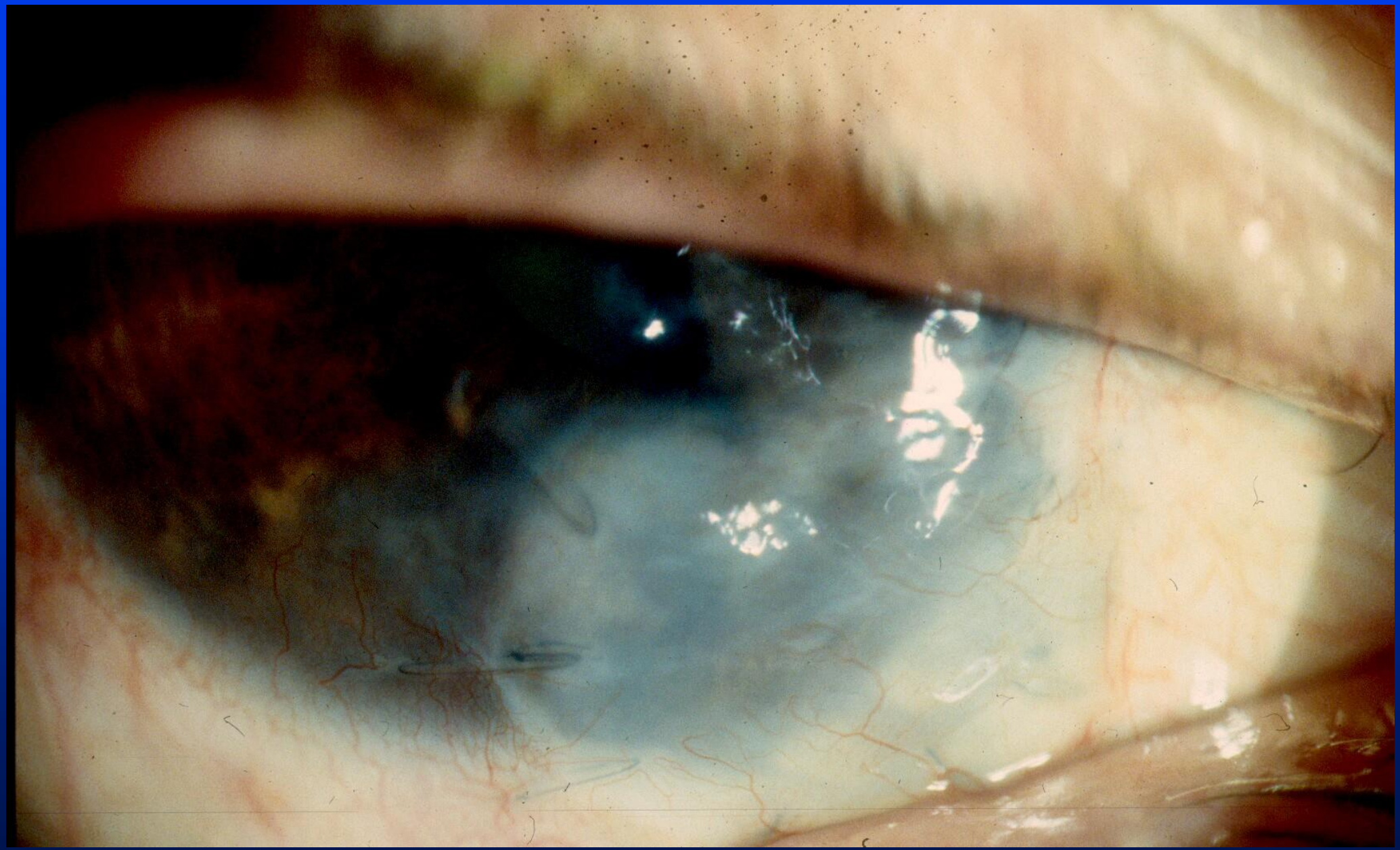
# Kératite Ulcérante Périphérique

- Amincissement cornéen juxta-limbique
- Taille et profondeur variable
- Limbe : complexes immuns contre auto-antigènes ou antigènes microbiens
- risque de perforation cornéenne

pas de corticothérapie locale







# Œil et Wegener

- **Atteinte dans 29 à 58 % des cas**

  *Fauci AS et al. Wegener's granulomatosis : prospective clinical and therapeutic experience with 85 patients for 21 years. Ann Intern Med 1983 ;98 :76-85.*

  *Bullen C, Liesegang T, McDonald T, DeRemee R. Ocular complications of Wegener's granulomatosis. Ophthalmology 1983 ;90 :279-290.*

- **2 mécanismes :**

  **- formation d'un granulome**

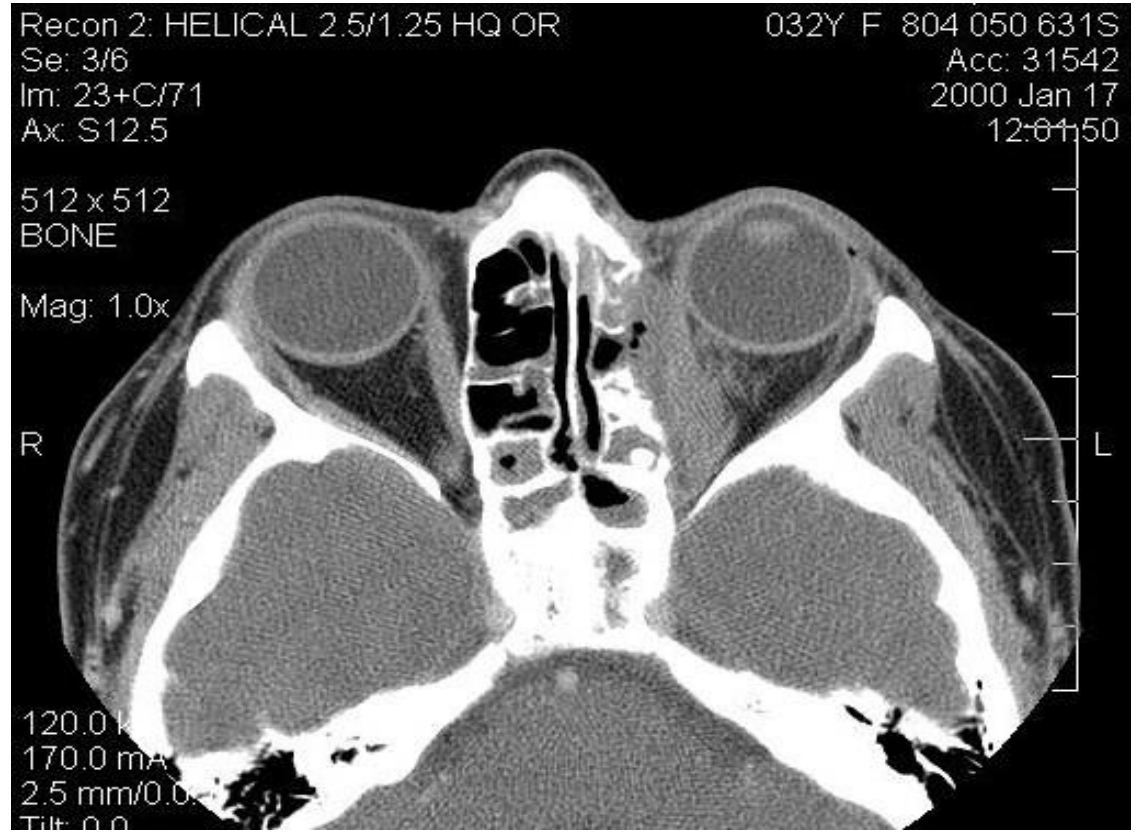
  **- liées à la présence de vascularites**

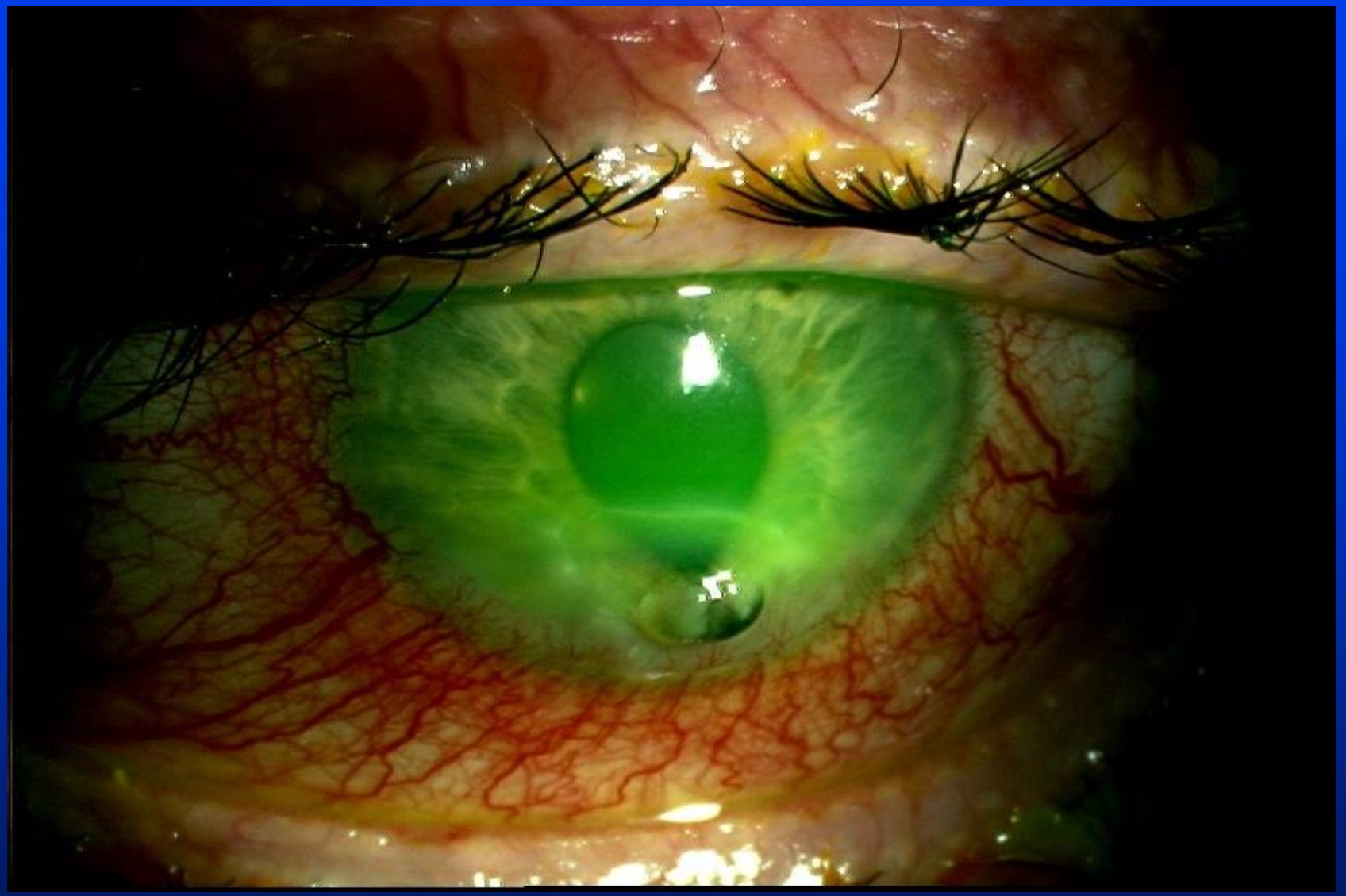
- **Associées à des manifestations extra-ophtalmologiques ou isolées**

- **Manifestations initiales de la maladie ou survenant sur MW déjà connue**

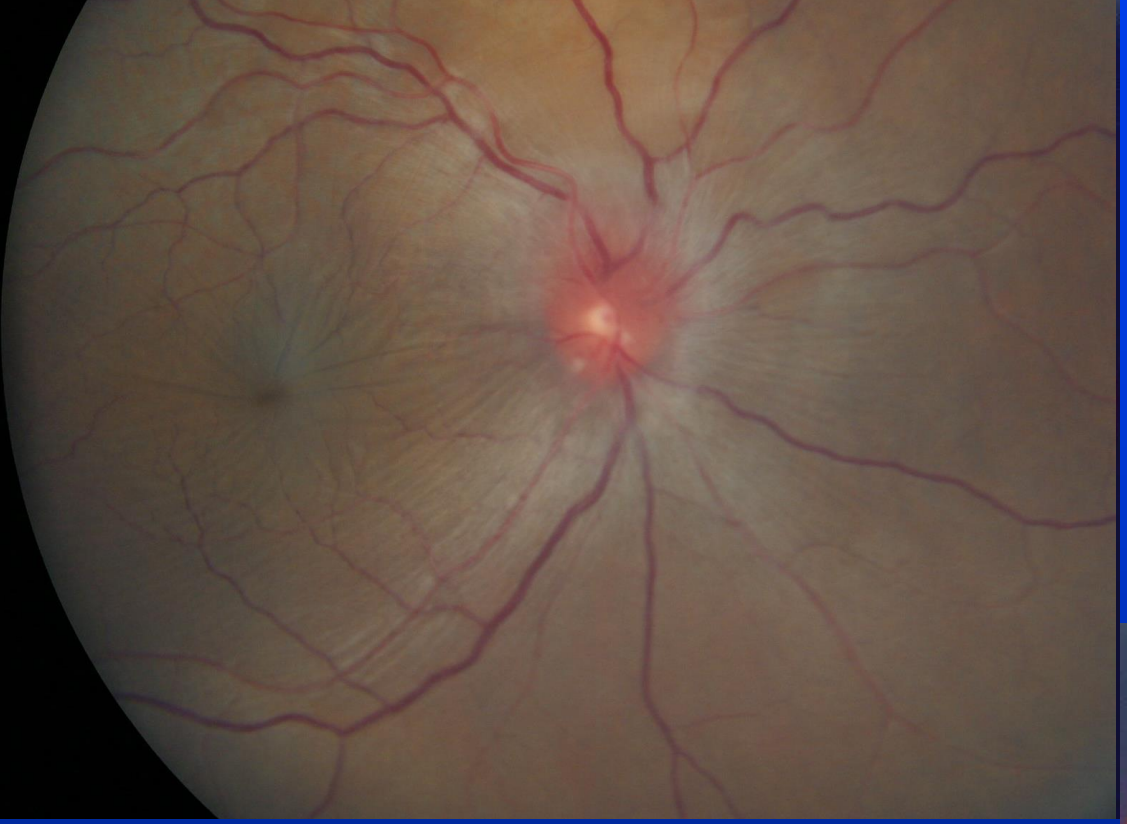
# Granulomatose avec polyangéite et exophtalmie

- Granulome orbitaire (glande lacrymale, intra-orbitaire, intra-sinusien)
- Non réductible
- IRM orbitaire
- Complications :
  - compression du nerf optique
  - kératite d’exposition
  - perforation cornéenne

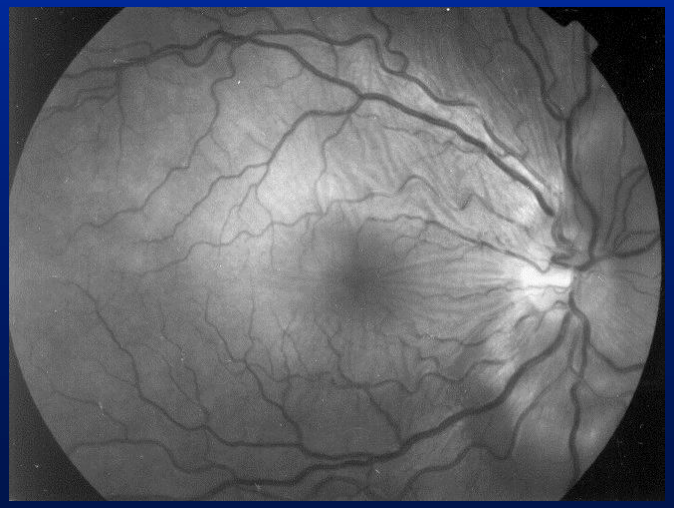


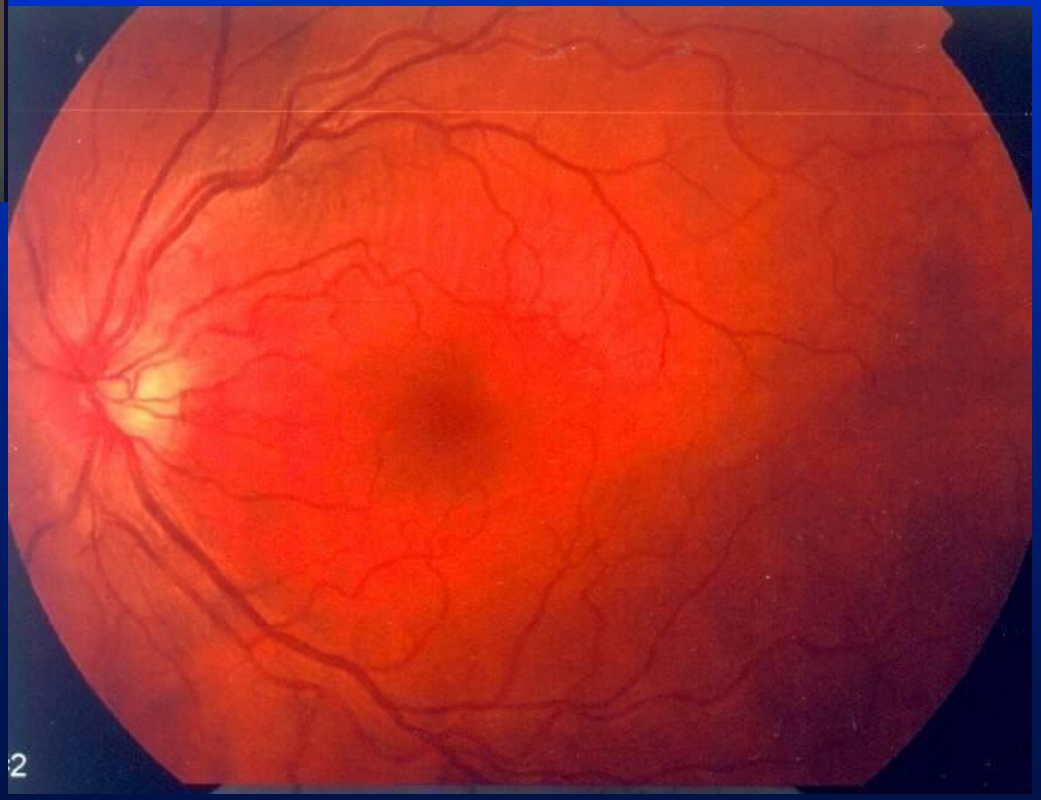


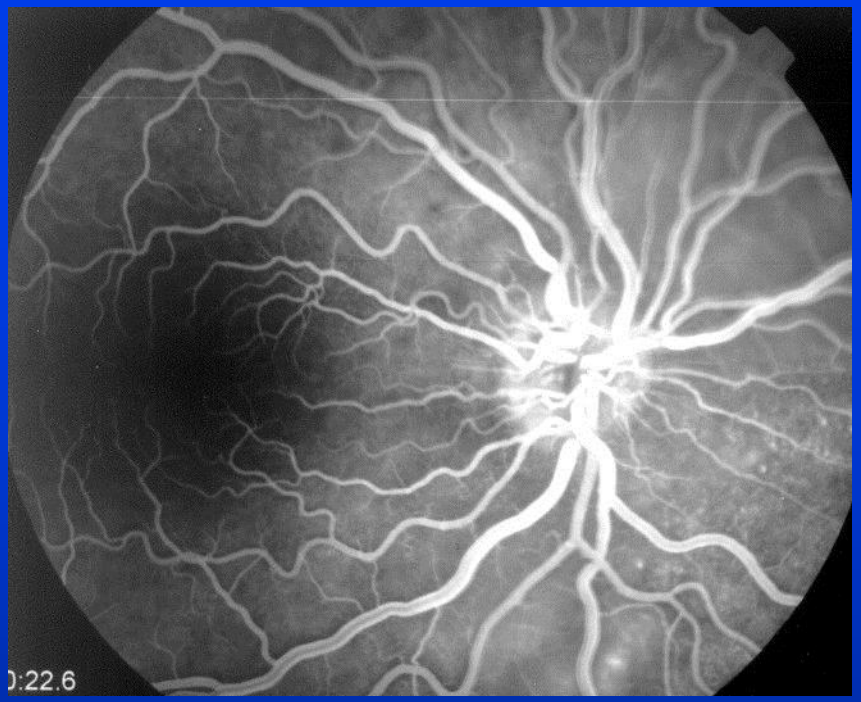
**Kératite ulcérante périphérique : diagnostic différentiel**
**Perforation cornéenne / kératite d'exposition**



- H 37 ans
- BAV + douleurs rétro-orbitaires OD



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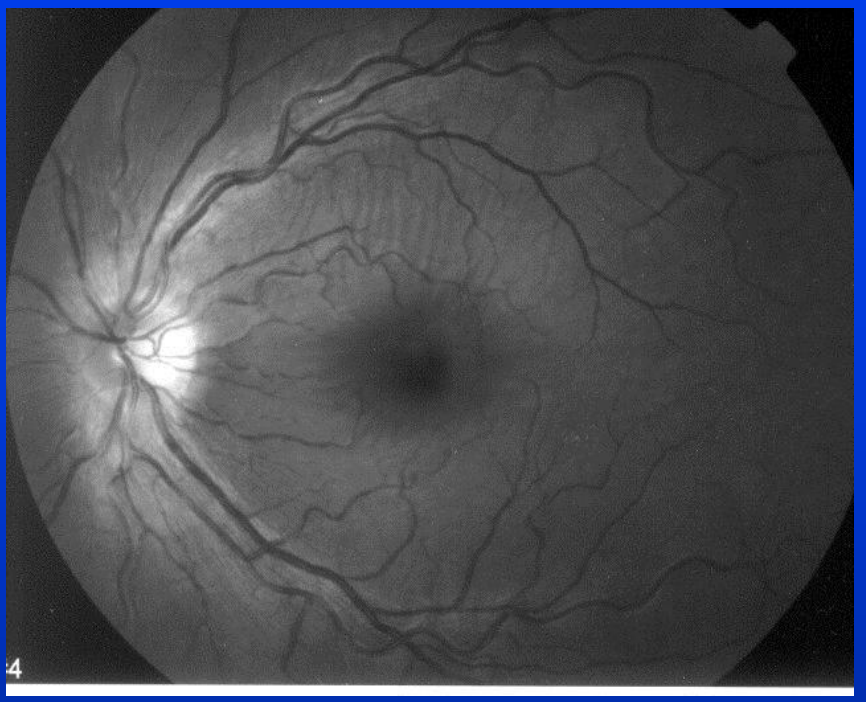
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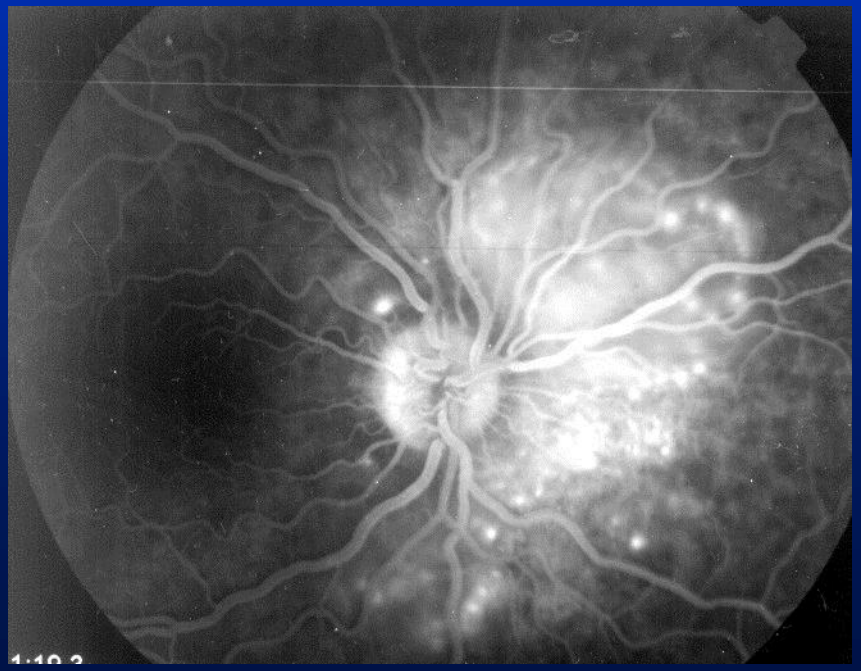

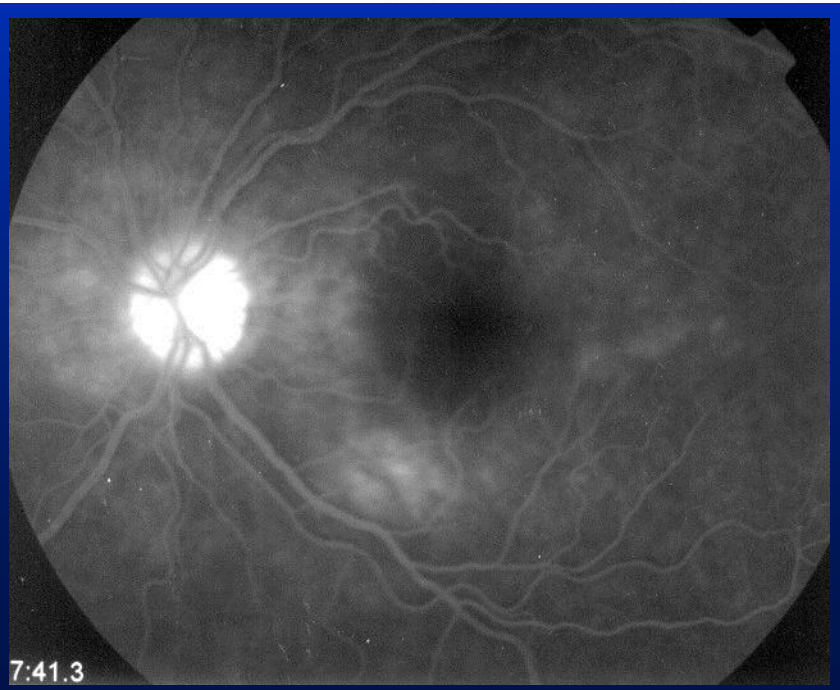
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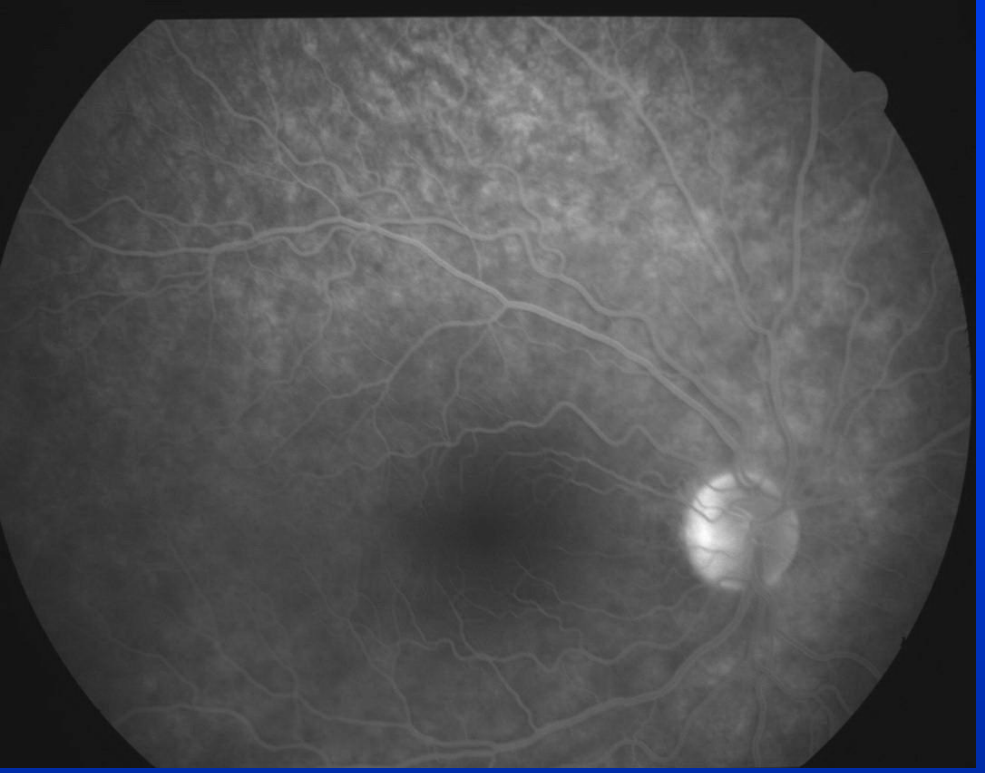
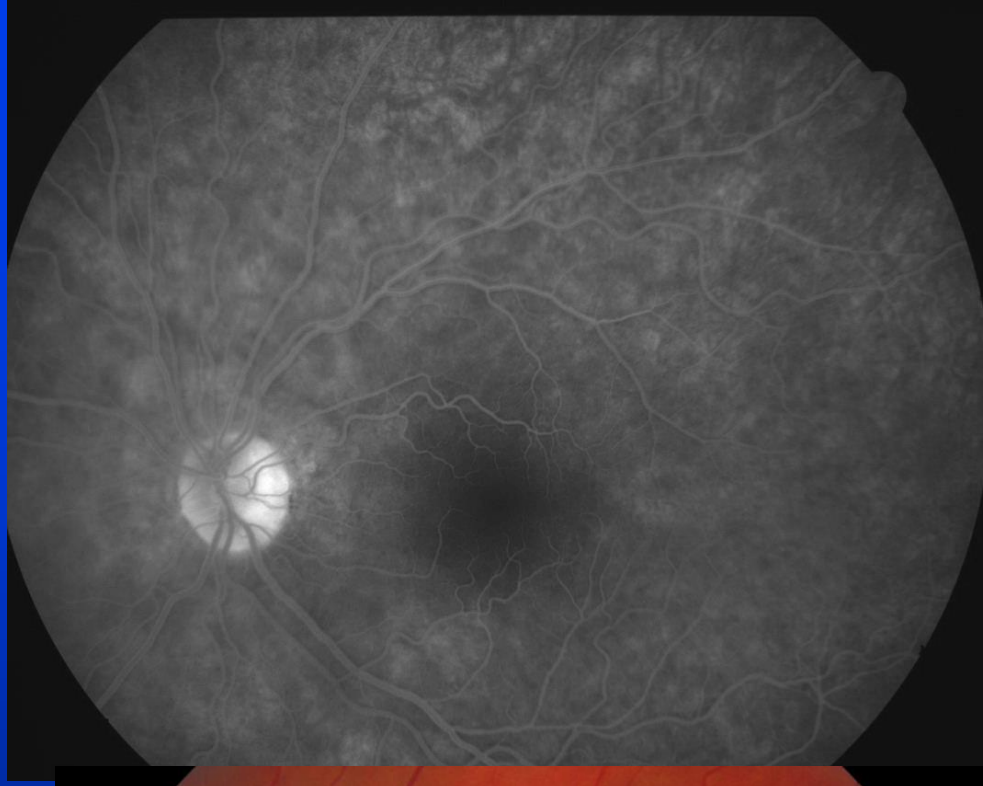
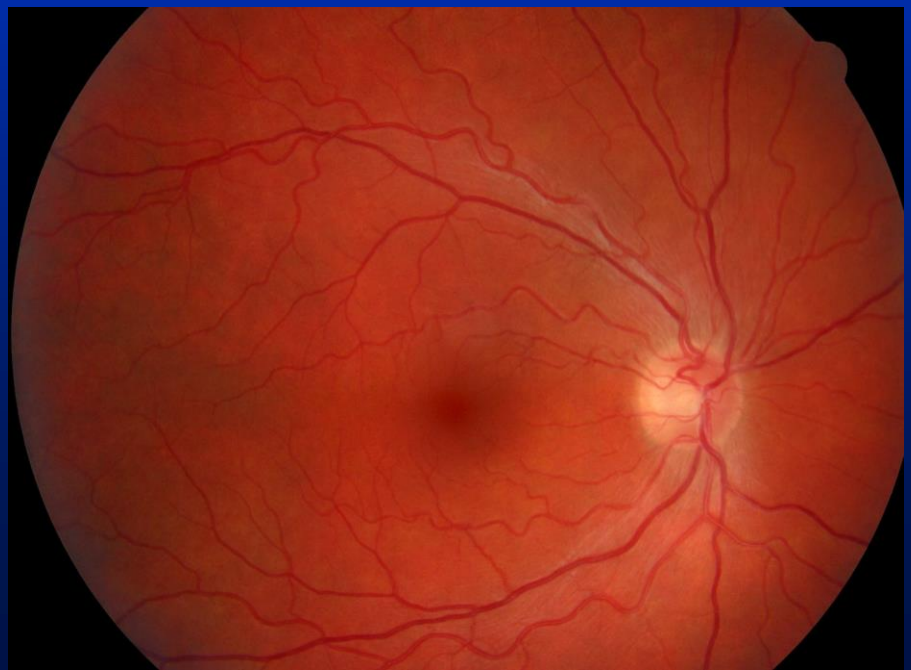
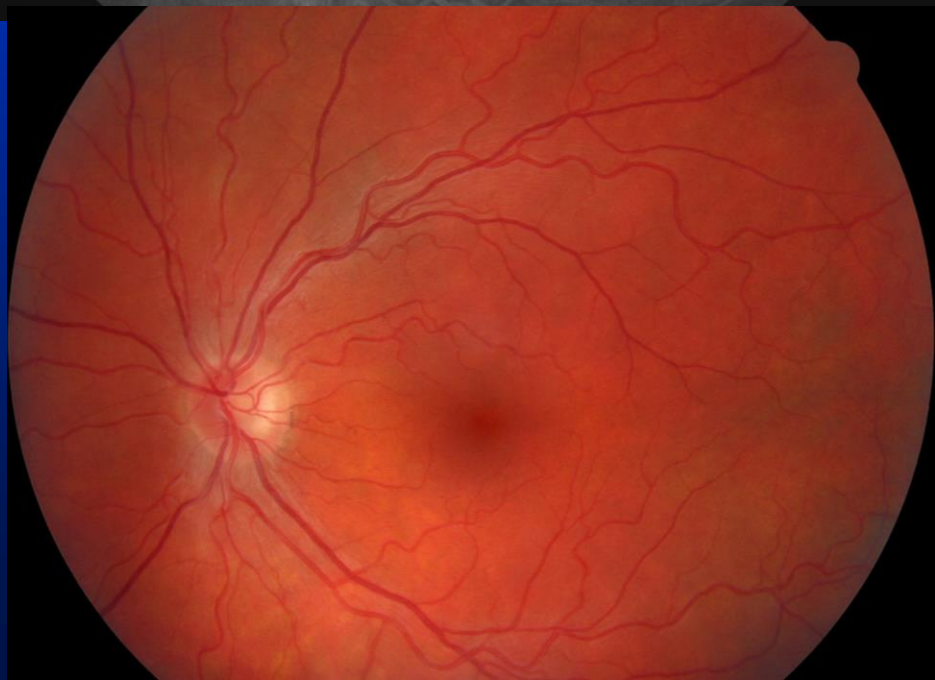








# Sclérites Postérieures

- **Définition :**
  - **Inflammation de la sclère en arrière de l'équateur**
  - **Augmentation de l'épaisseur sclérale >2mm**

- **Diagnostic différentiel +++**

# Sclérites postérieures

**Signes fonctionnels :**

- **Douleur : 55 %**
- **BAV : 31%**
- **Rougeur : Sclérite antérieure**
  - **Concomitante : 36 %**
  - **Dans les antécédents ou dans les suites : 60 %**
- **Autres : diplopie, ptosis, œdème palpébral**

# Sclérites postérieures

| Manifestations | *Mc Cluskey* | *Benson* |
|---|---|---|
| Unilatéralité | 65 % | 84 % |
| Sclérite antérieure | 36 % | |
| DSR | 34 % | 35 % |
| Masse sous rétinienne | 13 % | 12 % |
| Plis rétiniens | | 14 % |
| Plis choroidiens | | 15 % |
| HTO | 12 % | |
| Décollement choroidien | 4 % | 16 % |
| Papillitte | 21 % | 1 % |
| Uvéite | 2 % | 25 % |
| Aucun | 17 % | |

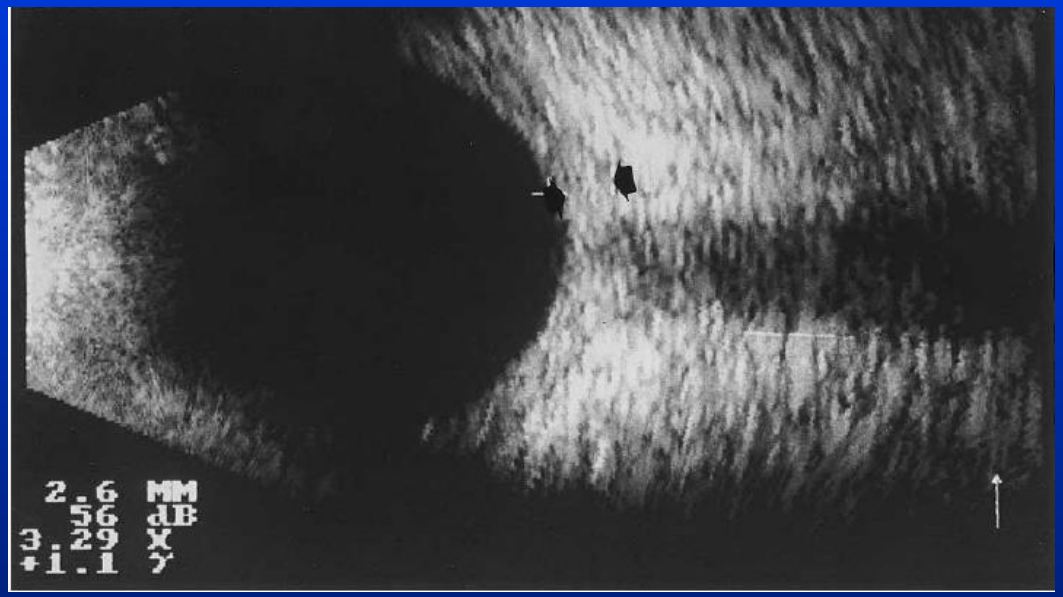
1. Souvent unilaterales
2. Signe le plus frequent: DSR
3. Pseudo-masse sous rétinienne
4. Plis choroïdiens
5. Inflammation assez rare

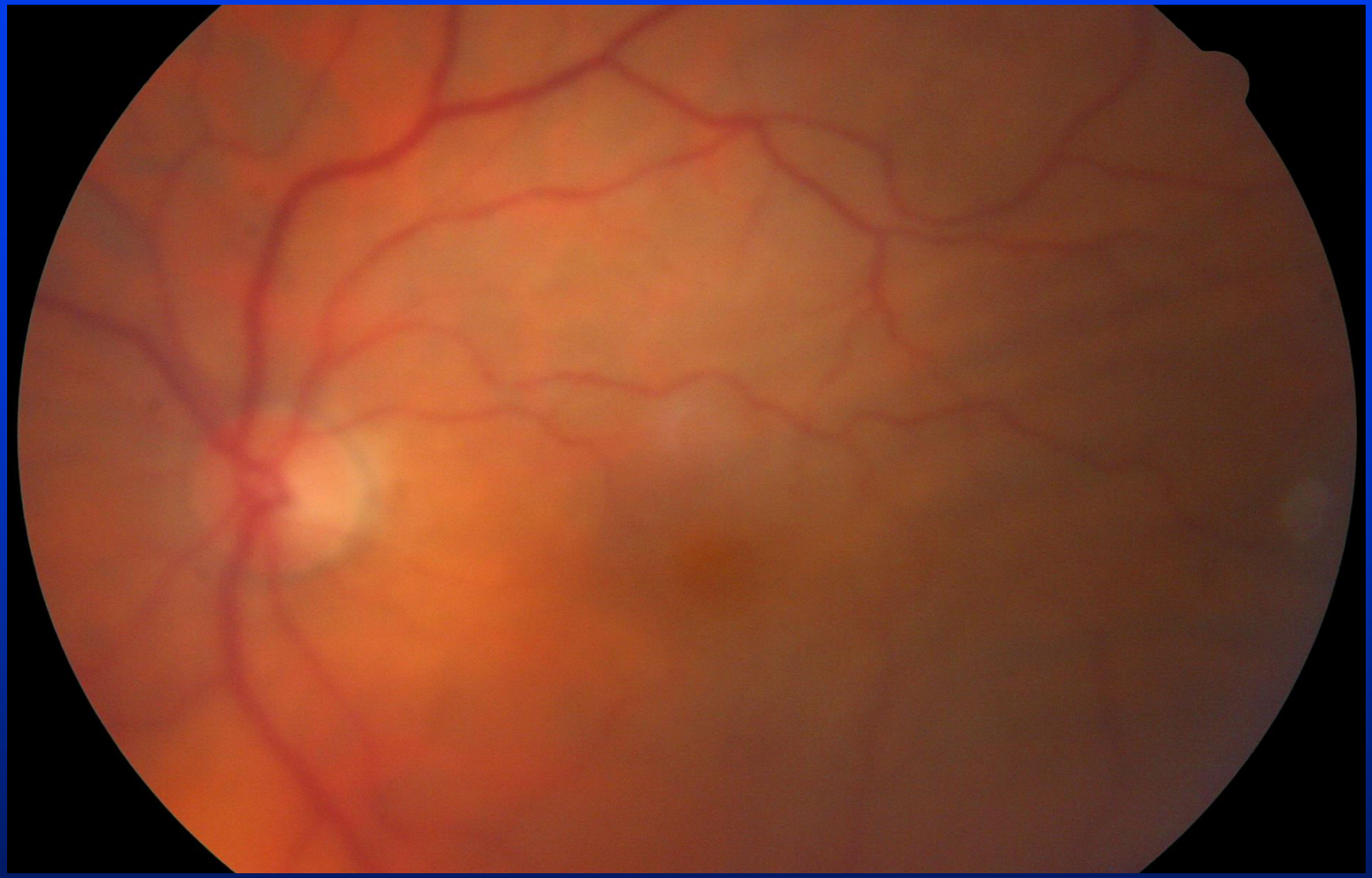
# Sclérites postérieures : examens complémentaires

- Angiographie à la fluorescéine : DSR peu d'intérêt (multiples points de fuite, idem selon l'étiologie), montre les plis choroidiens

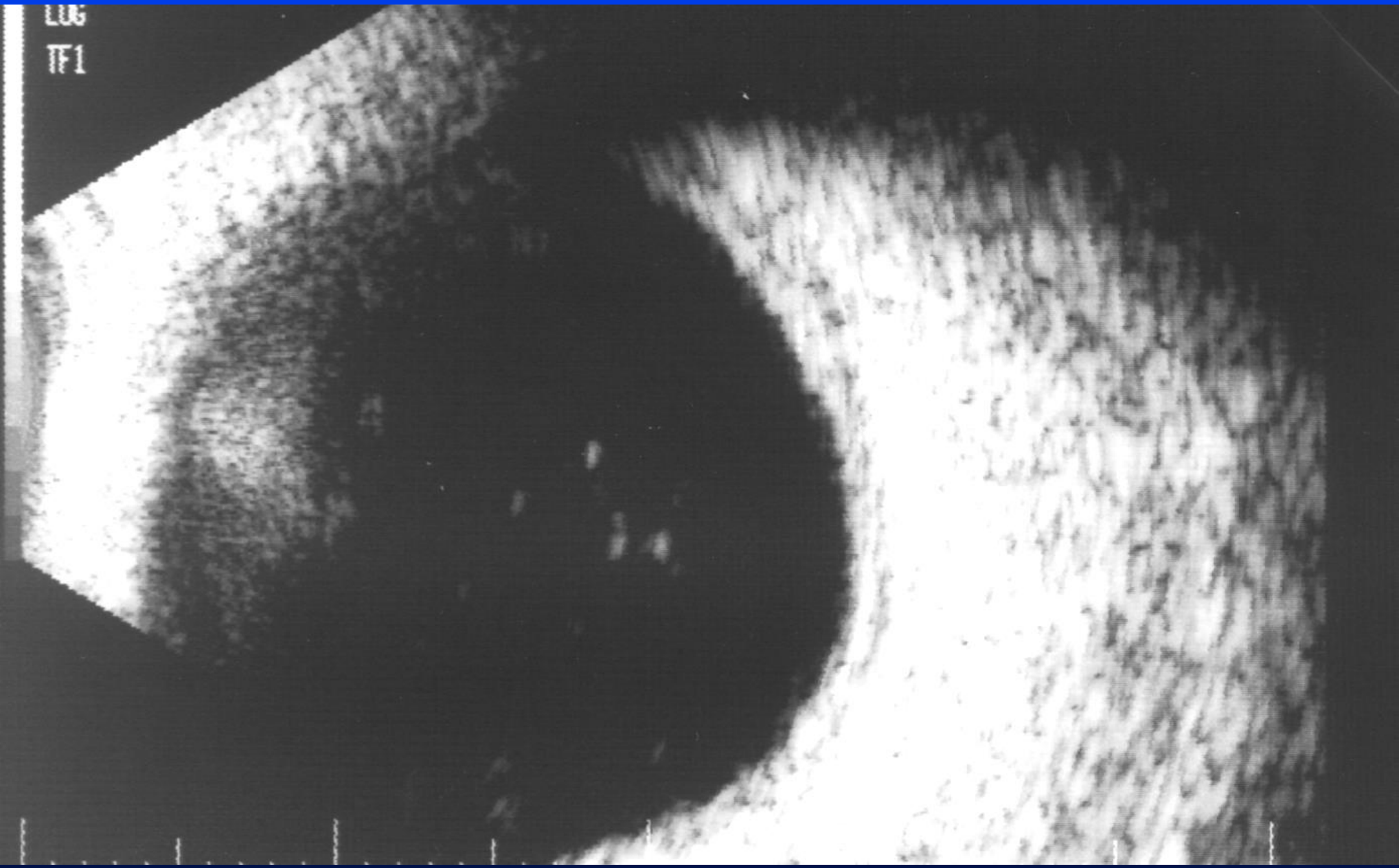
- Echographie B : épaississement scléral nodulaire ou diffus > 2 mm avec œdème rétrobulbaire et périoptique réalisant le signe du T

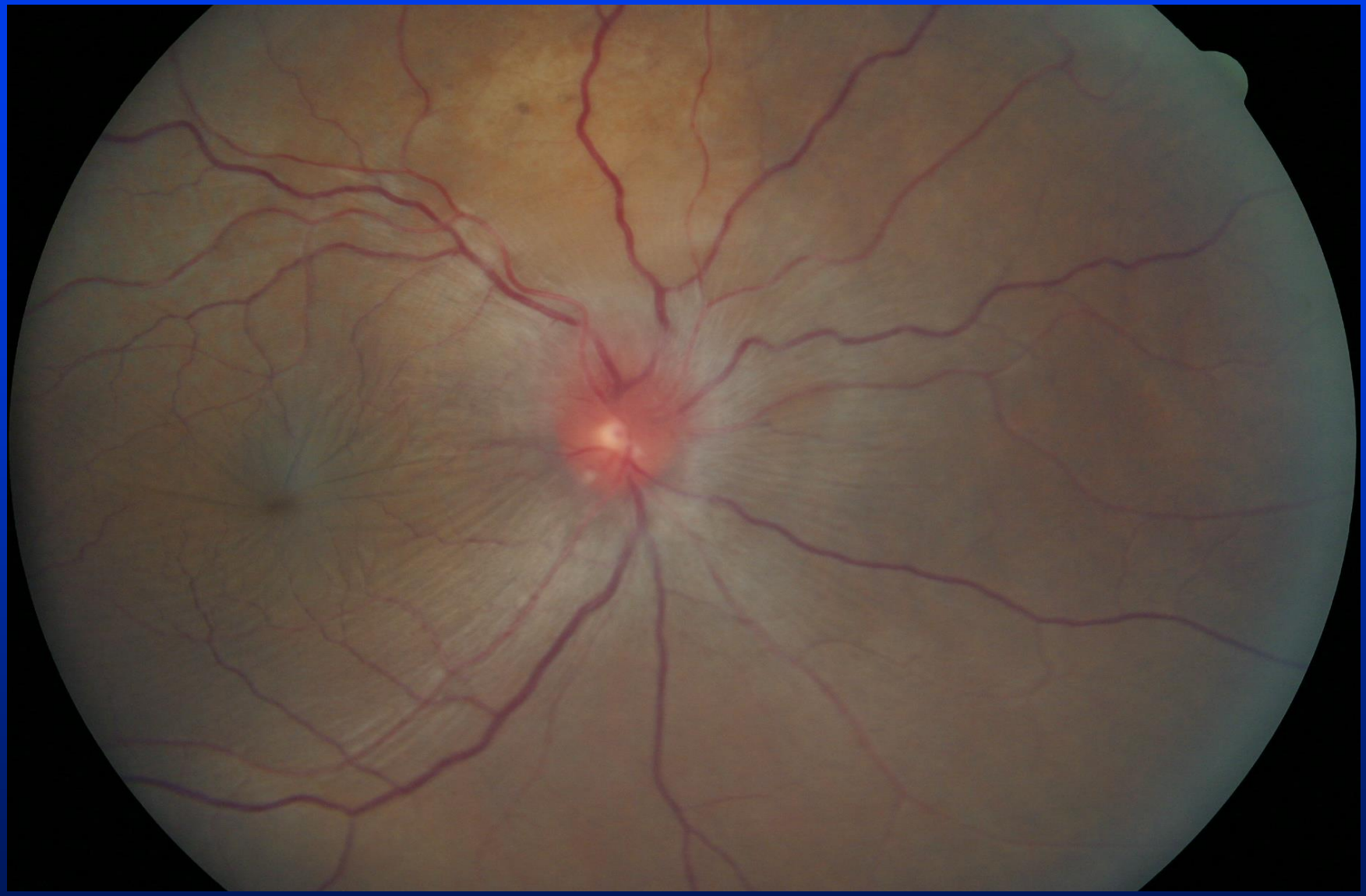
- TDM et surtout IRM : Hyperintensité en T1 avec rehaussement par le gadolinium, hypointensité en T2





**Sclérites Postérieures – Plis Choroïdiens**


LOG
TF1



**Diagnostic différentiel : masse choroïdienne**

# Sclérites : principes thérapeutiques

- AINS
- Corticoïdes per os
- Immunosuppresseurs

# Tumor Necrosis Factor α Blockade with Infliximab for Refractory Uveitis and Scleritis

*Conor C. Murphy, MMedSc, MRCOphth,[1] William H. Ayliffe, PhD, FRCOphth,[2] Anthony Booth, MRCP,[3] David Makanjuola, MRCP,[3] Peter A. Andrews, MA, FRCP,[3] David Jayne, FRCP[3]*

***Objective:*** To assess the efficacy and safety of the anti–tumor necrosis factor α agent infliximab in treatment-resistant uveitis and scleritis.

***Design:*** Retrospective, noncomparative interventional case series.

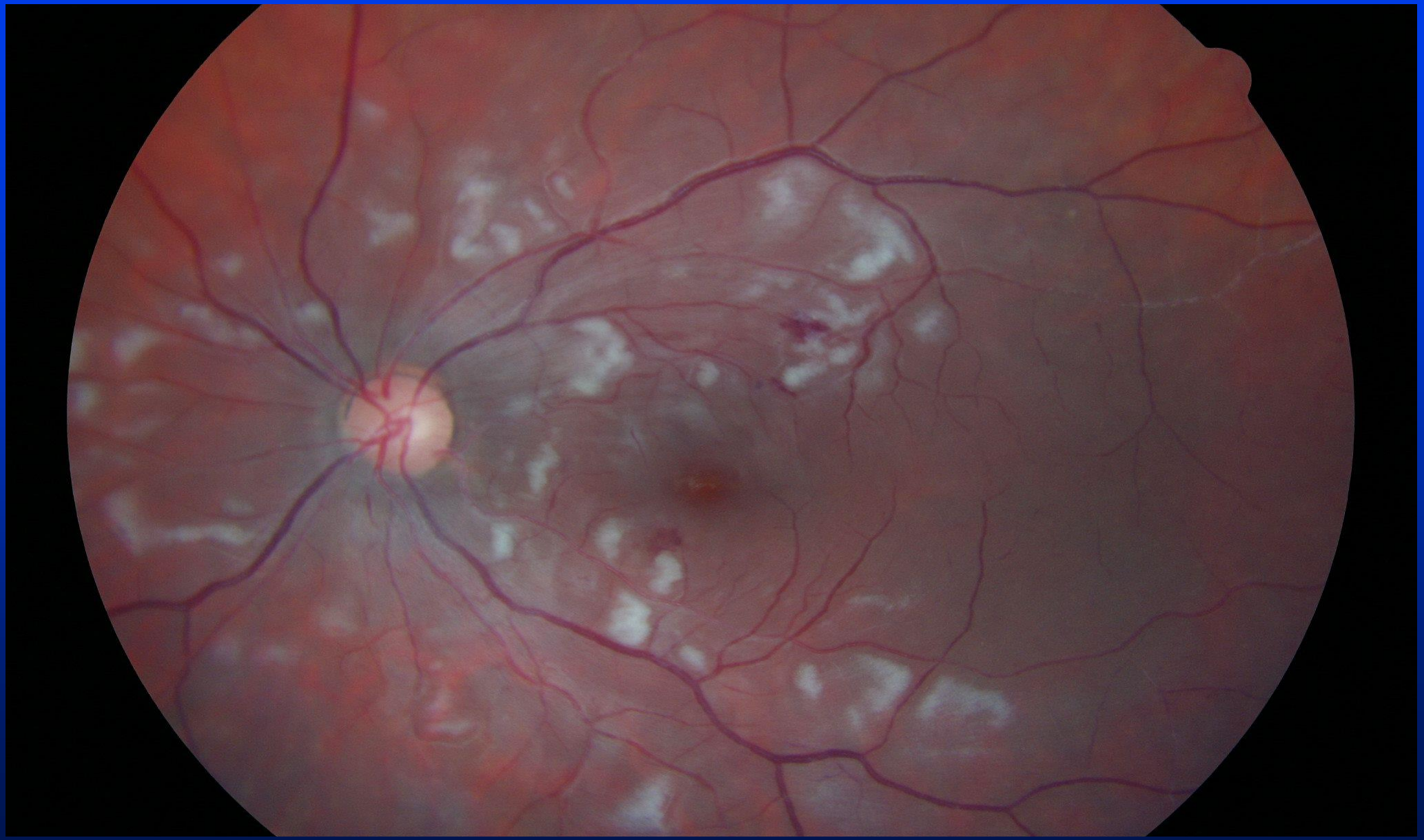
***Participants:*** Seven patients with noninfectious ocular inflammatory disease that was refractory to alternative immunosuppression. These included one patient with idiopathic retinal vasculitis and panuveitis, one patient with intermediate uveitis, one patient with chronic juvenile anterior uveitis, three patients with scleritis, and one patient with scleritis and peripheral ulcerative keratitis. Four patients had an underlying systemic disease that was in remission in three cases.

***Intervention:*** Infusions of infliximab, 200 mg, were given at 4-week to 8-week intervals, depending on the clinical response.

***Main Outcome Measures:*** Clinical response, including symptoms, visual acuity, degree of scleral vascular engorgement, corneal thinning, anterior chamber activity, and posterior segment inflammation, reduction in concomitant immunosuppression, and adverse effects.

***Results:*** The mean patient age was 47 years (range, 24–78), and four patients were female. The mean number of infliximab infusions was seven (range, 2–19), and the mean follow-up period was 12 months (range, 4–22 months). Six patients experienced a clinical improvement, with five achieving remission and significant reduction in immunosuppression. One patient showed an initial response but developed a delayed hypersensitivity response that precluded further treatment. No other adverse effects occurred.

***Conclusions:*** Infliximab seems to be an effective and safe treatment for noninfectious uveitis and scleritis and may be indicated as rescue therapy for relapses of ocular inflammation or as maintenance therapy when conventional immunosuppression has failed. Further investigation of infliximab for treatment-resistant scleritis and uveitis is warranted. *Ophthalmology 2004;111:352–356 © 2004 by the American Academy of Ophthalmology.*



Rétinopathie lupique

# Merci