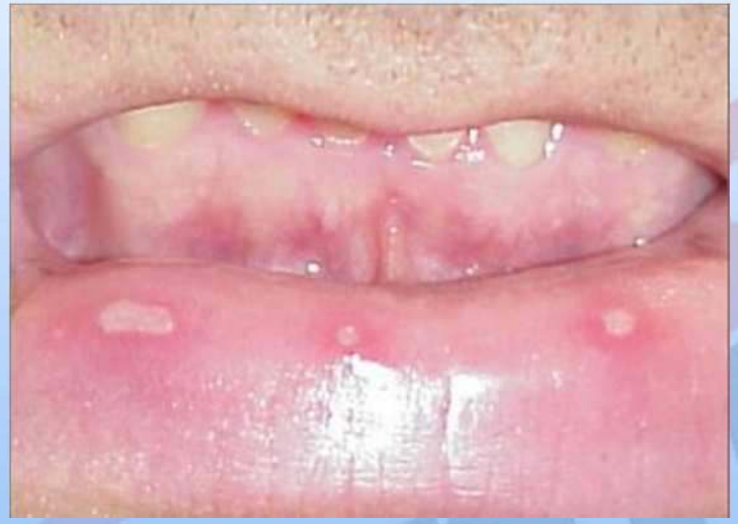
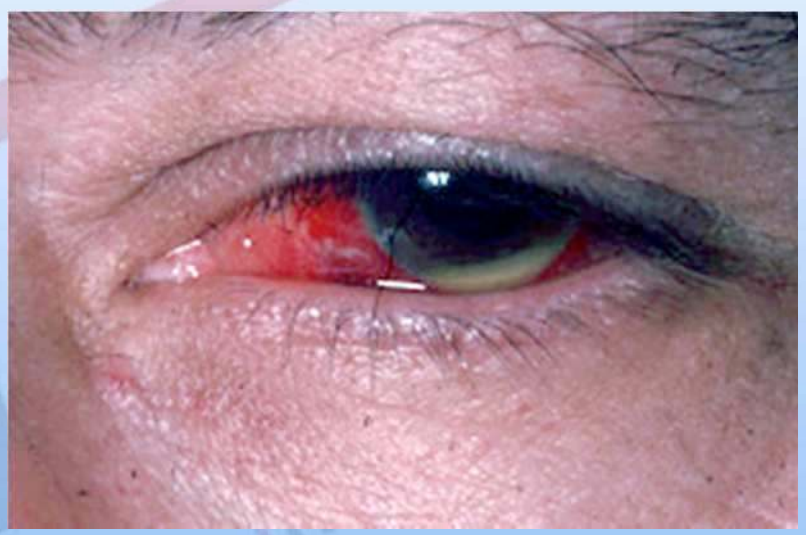
Œil et maladie de Behçet

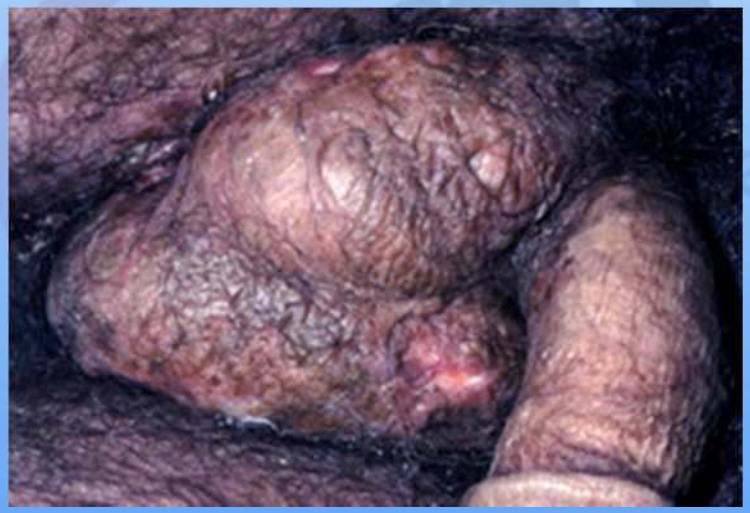
J. Gueudry
Hôpital Charles Nicolle, Rouen

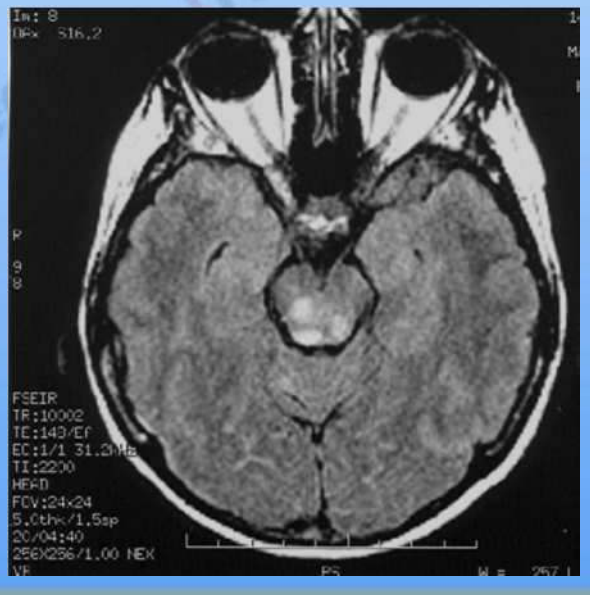
Club Médecine Interne et Œil
FMC du 4 octobre 201

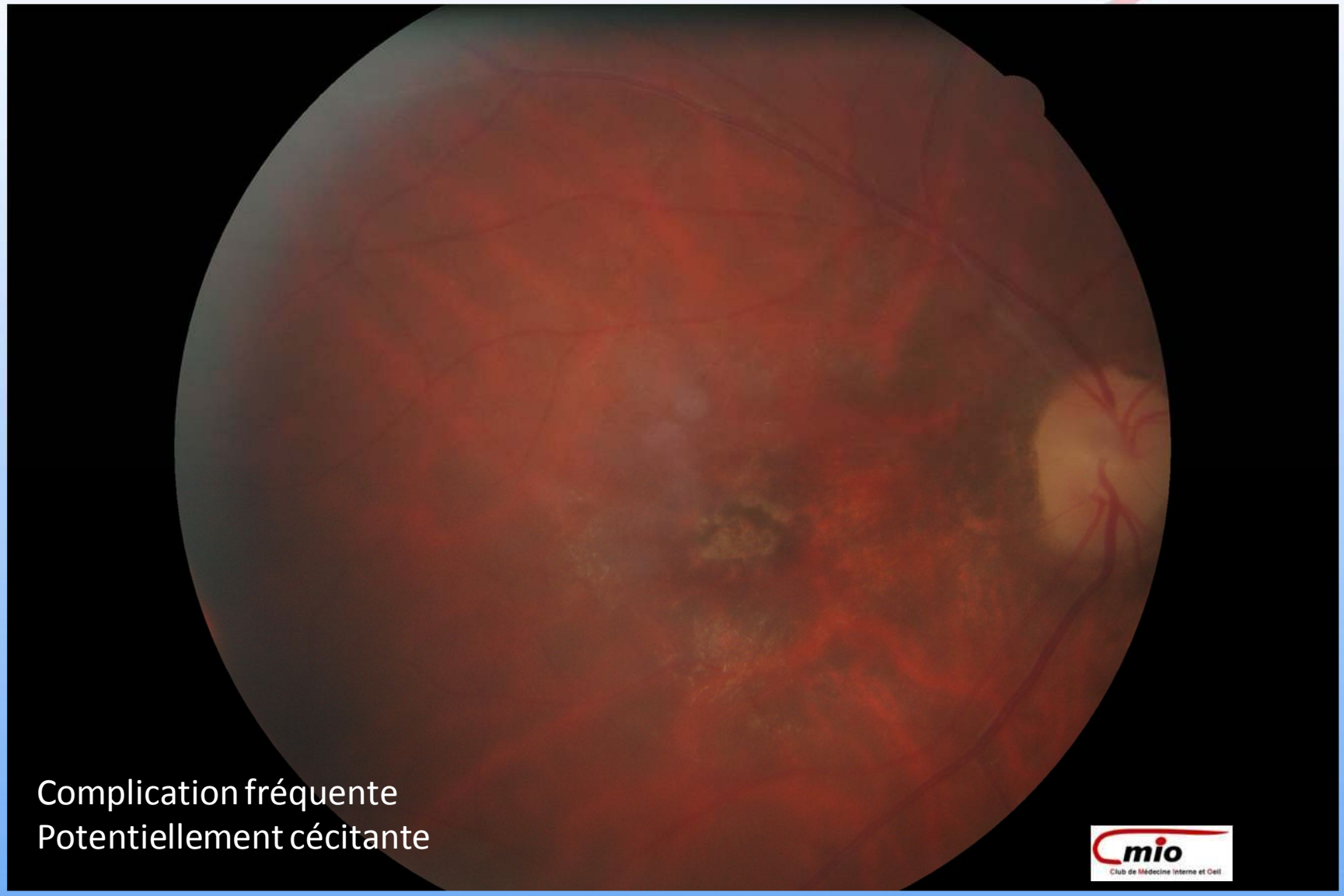
Maladie de Behçet










Complication fréquente
Potentiellement cécitante
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Œil et Behçet (60-70%)

- Révélatrice 20 à 30 % des cas
- >90% bilatéralisation à 2 ans
- Cécité (10-15%)

Critères diagnostiques

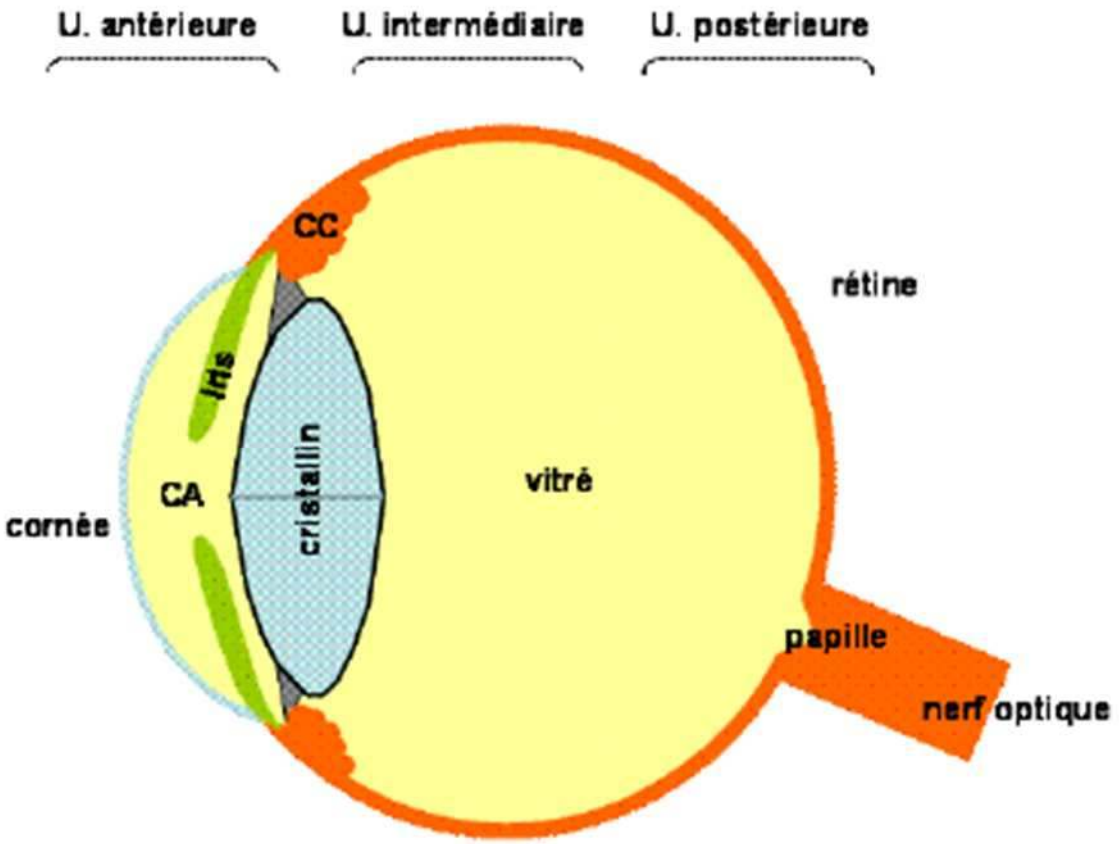
INTERNATIONAL STUDY GROUP FOR BEHÇET'S DISEASE. Criteria for diagnosis of Behçet's disease. Lancet, 1990, *335* : 1078-1080

- Ulcérations orales récurrentes: récidivant plus de 3 fois en 12 mois

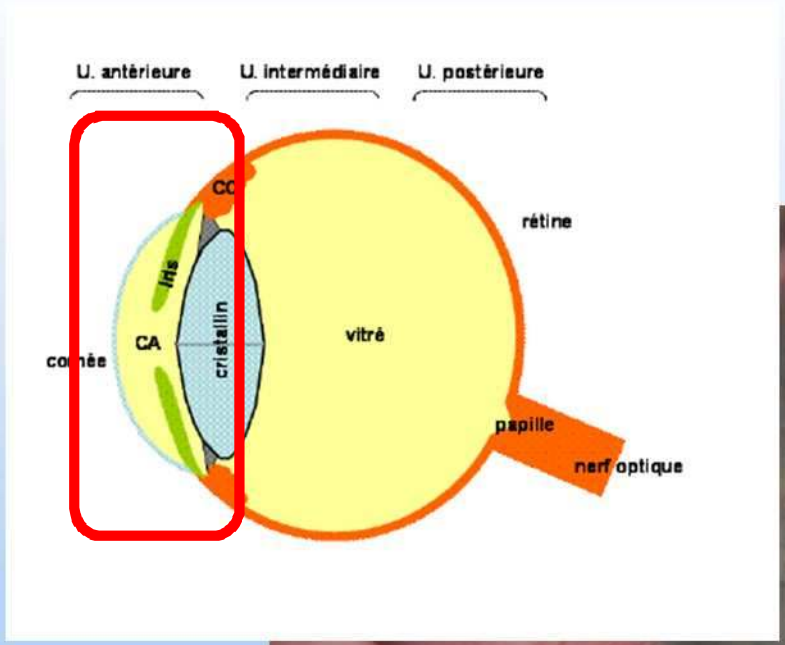
- + 2 des manifestations suivantes:
  - ulcérations génitales récurrentes
  - lésions cutanées
  - test pathergique positif
  - Uvéite

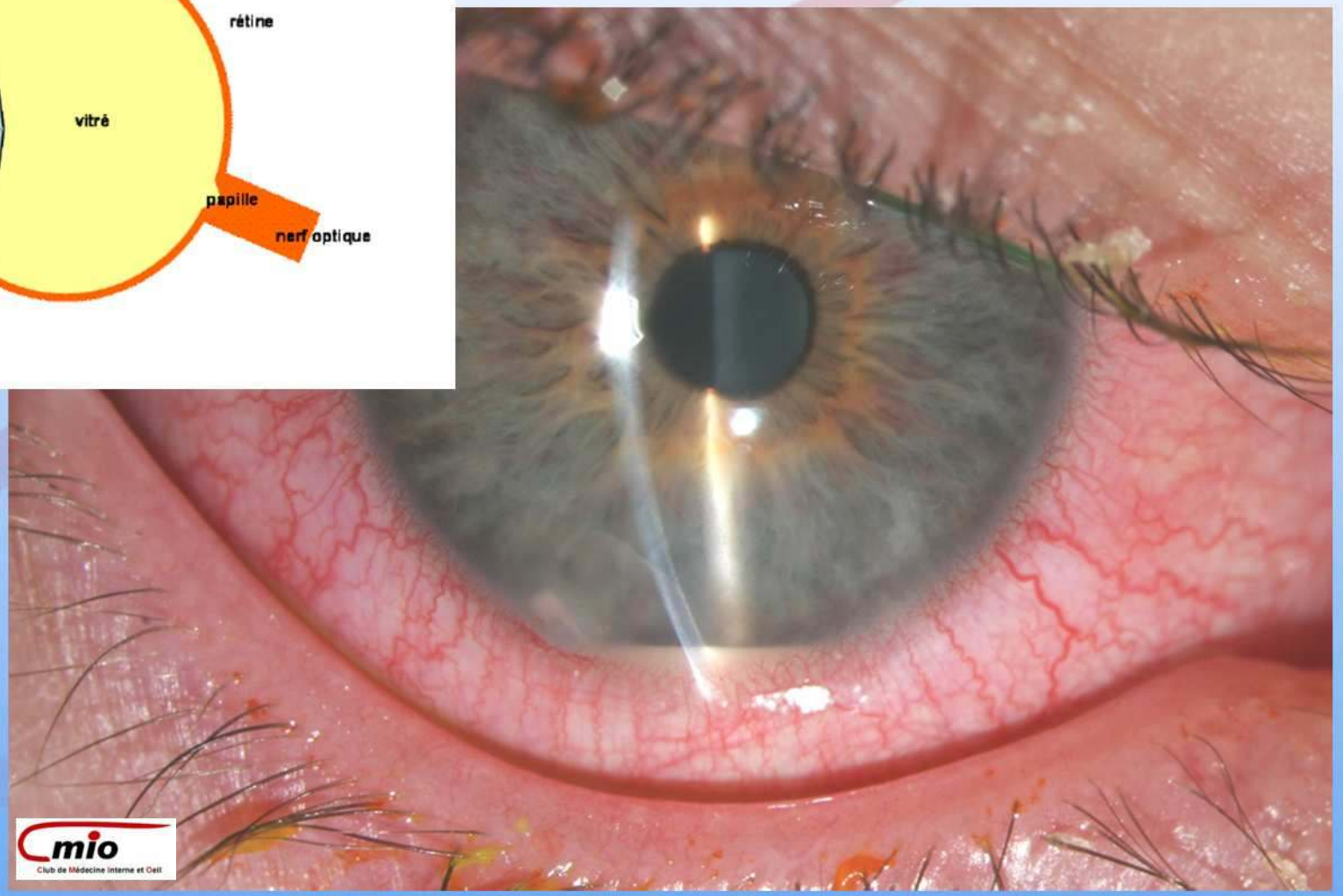
- Critères applicables uniquement en l'absence d'autres explications cliniques

Uvéite….



Standardization of uveitis study nomenclature working group (SUN). ***Am J Ophthalmol 2005;140:509-16***


U. antérieure
U. intermédiaire
U. postérieure
CC
iris
CA
cristallin
cornée
vitré
rétine
papille
nerf optique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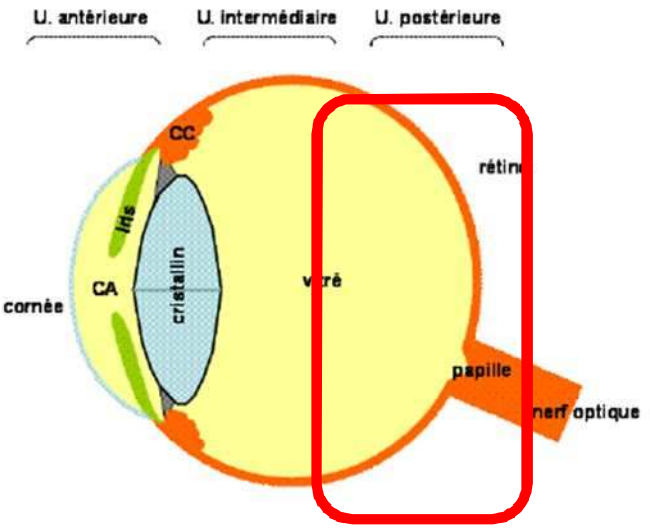
U. antérieure
U. intermédiaire
U. postérieure
CC
iris
CA
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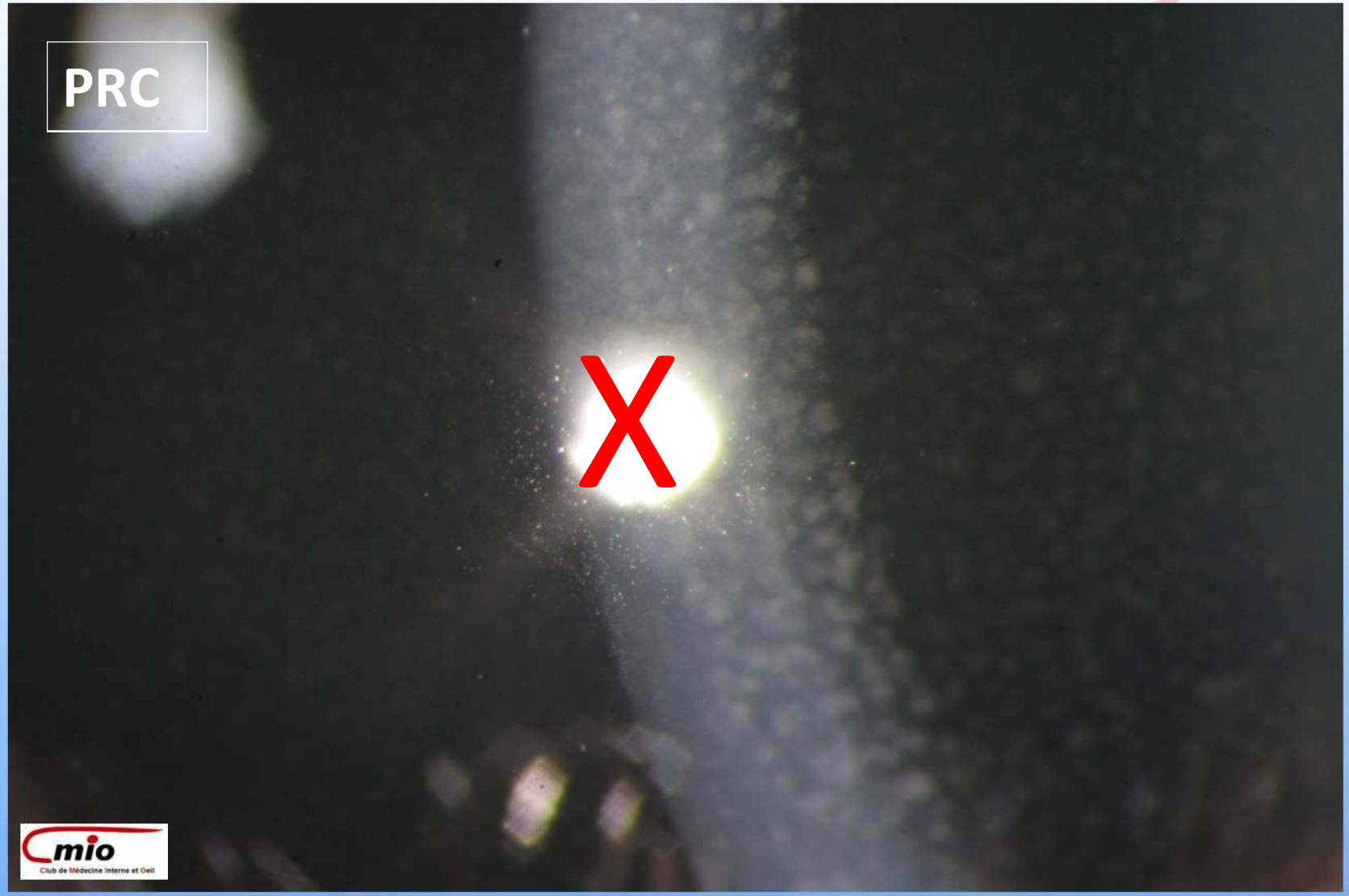
nerf optique


PRC
X
mio
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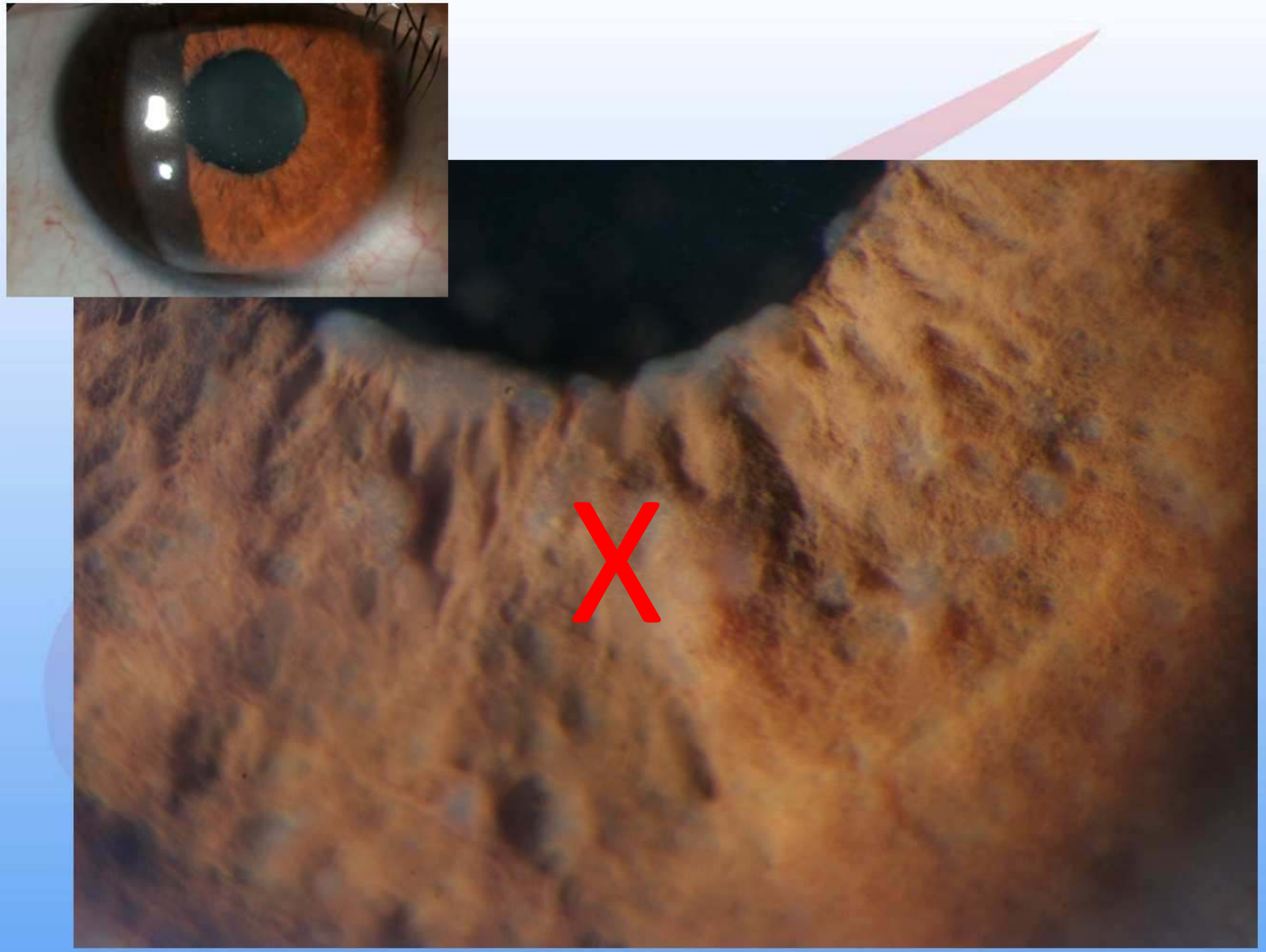
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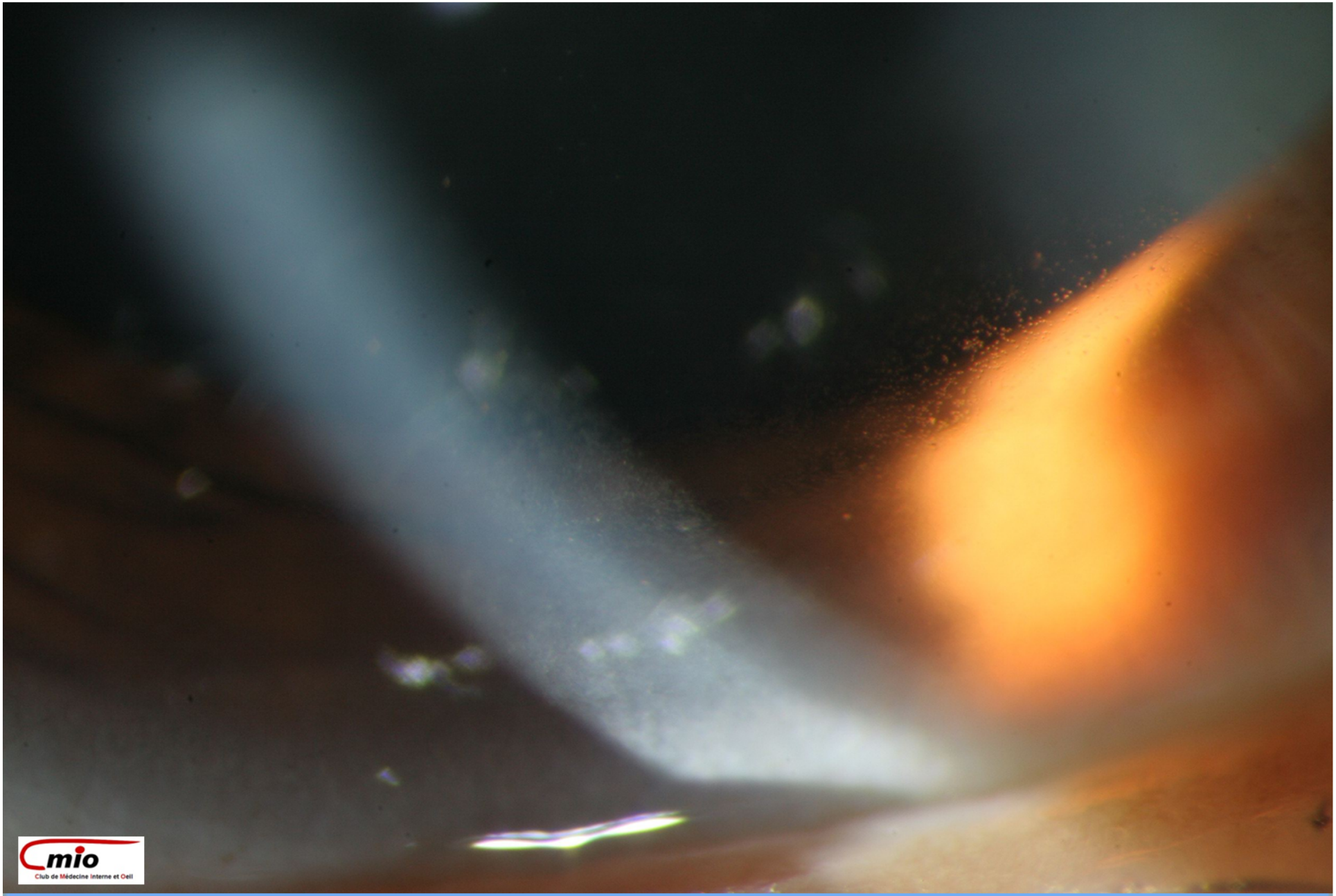
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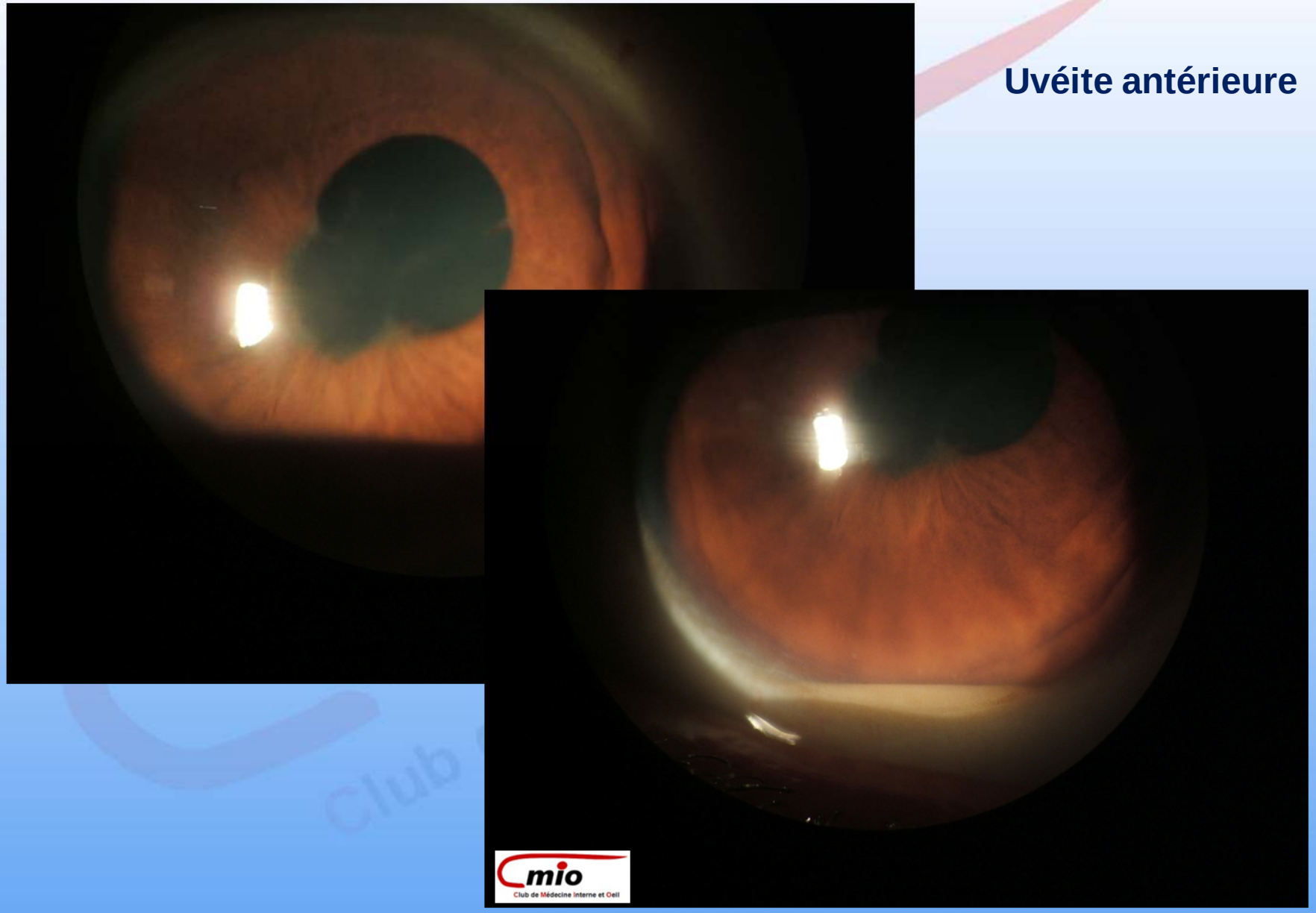
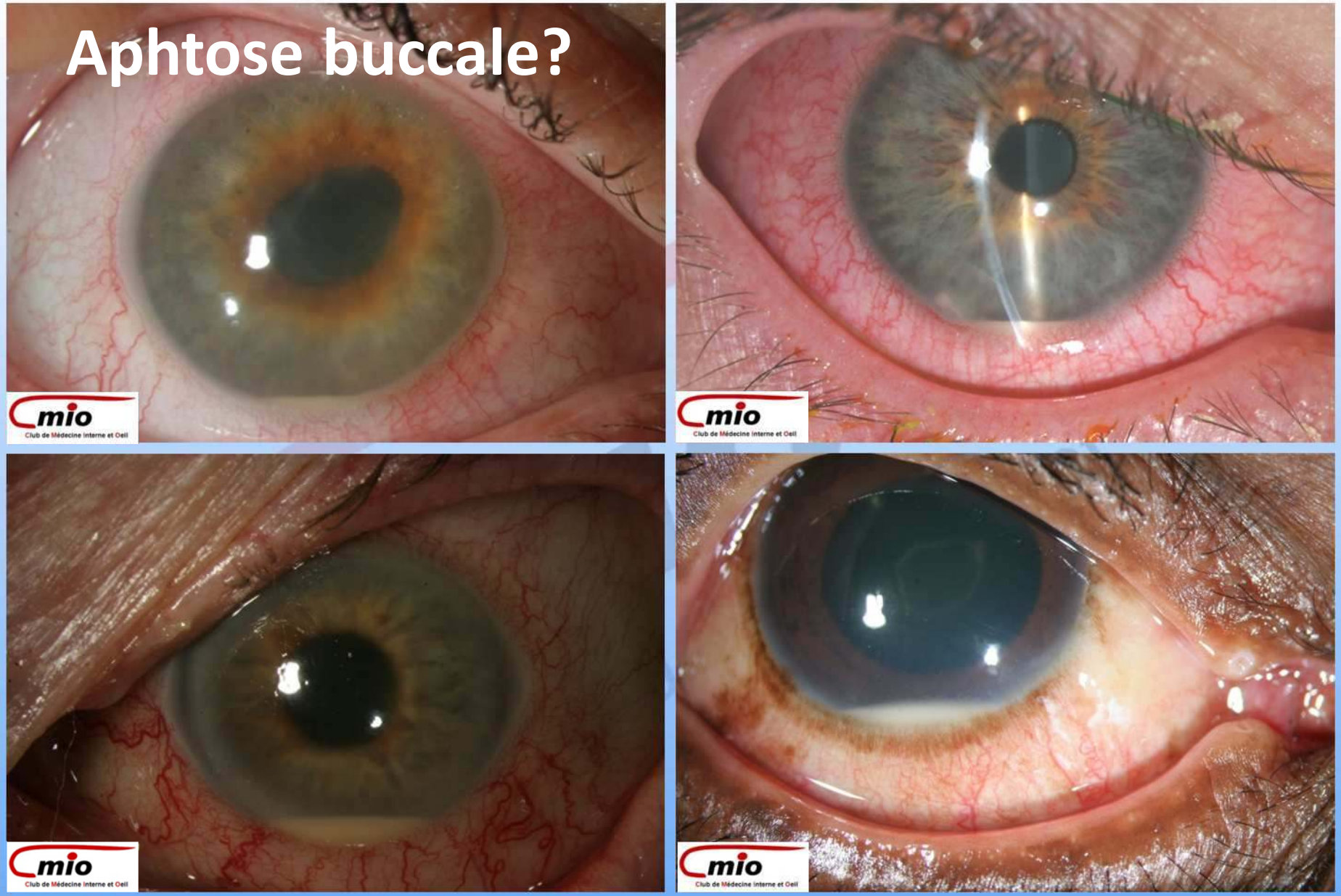
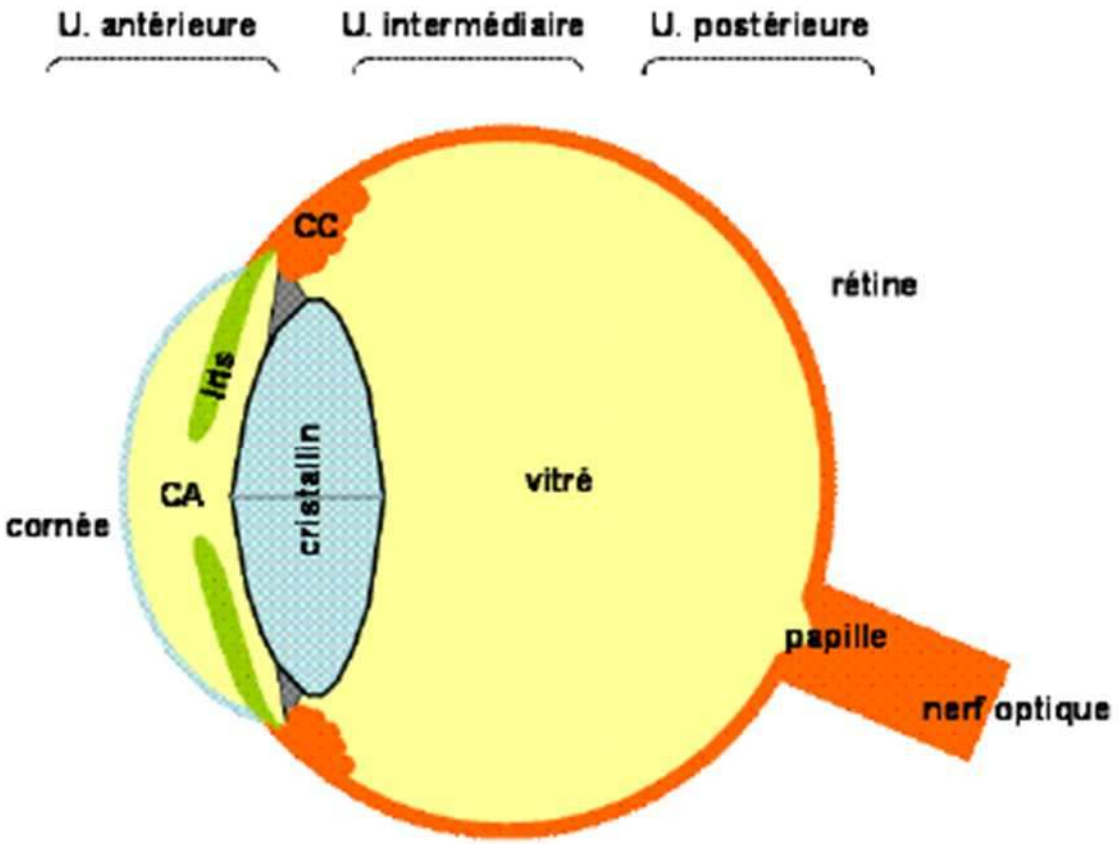
Uvéite antérieure



Aphtose buccale?



Uvéite postérieure



Standardization of uveitis study nomenclature working group (SUN). ***Am J Ophthalmol 2005;140:509-16***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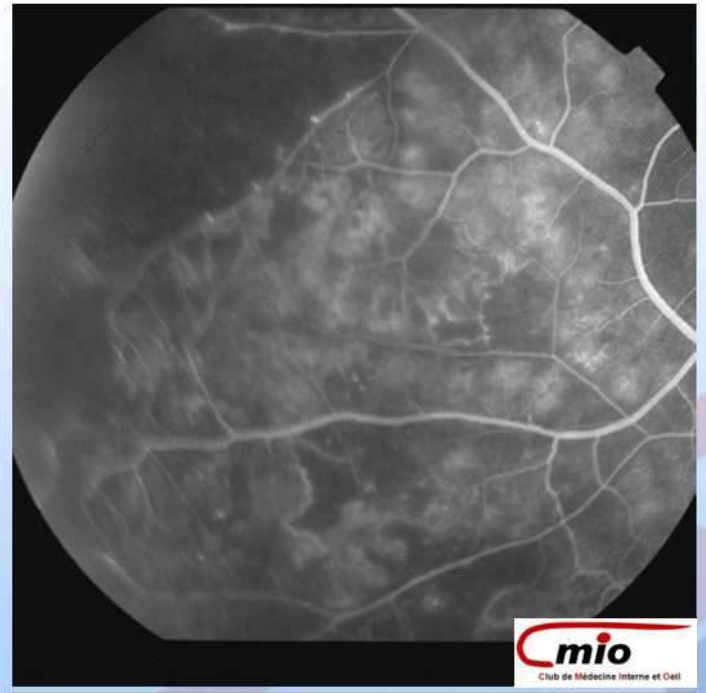
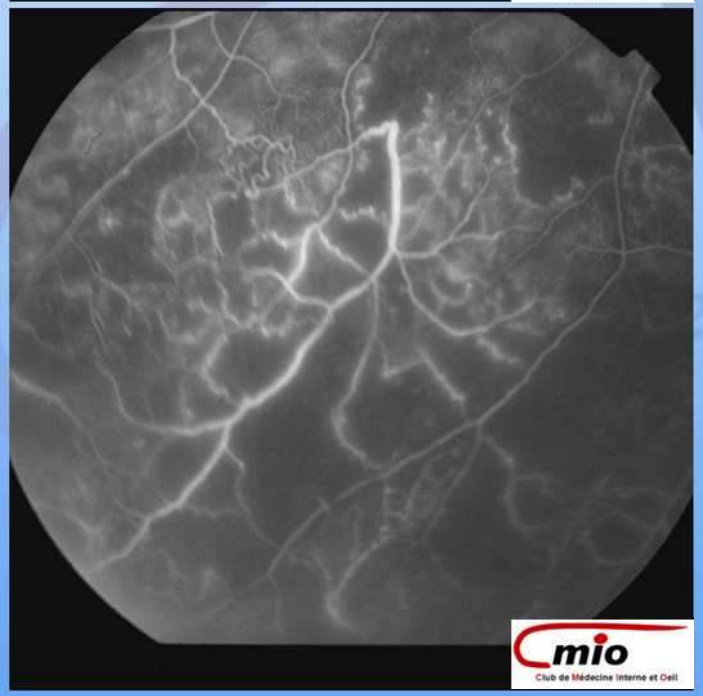
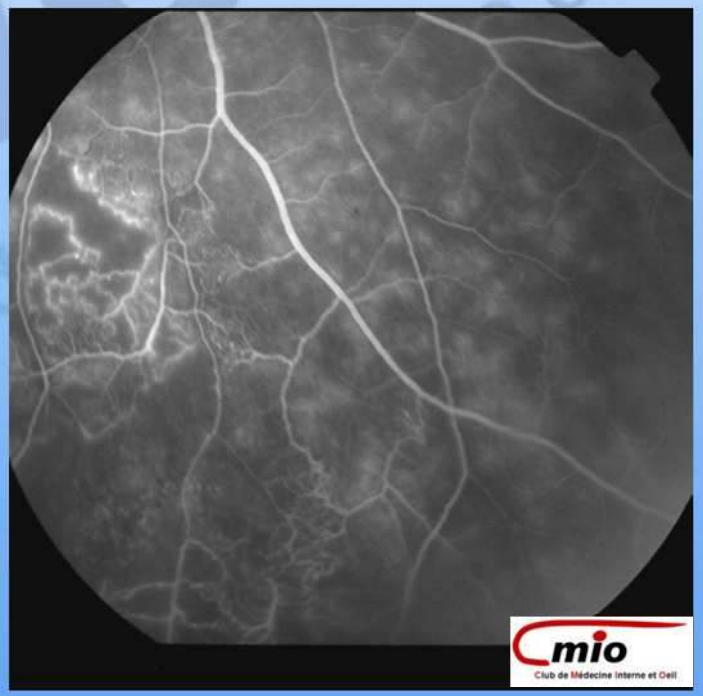
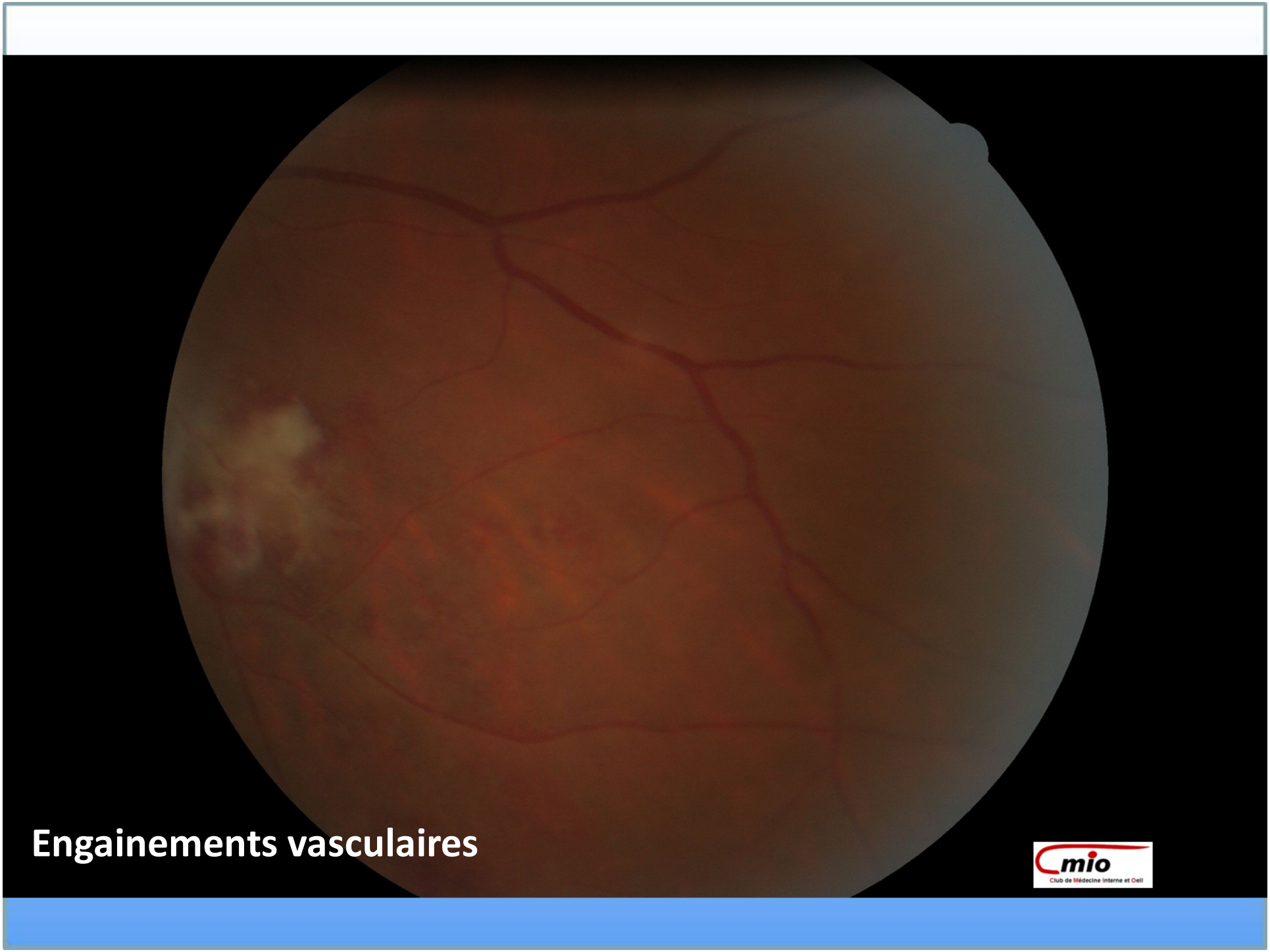






Vascularites occlusives
Touchant tous les calibres
Veines préférentiellement


Engainements vasculaires
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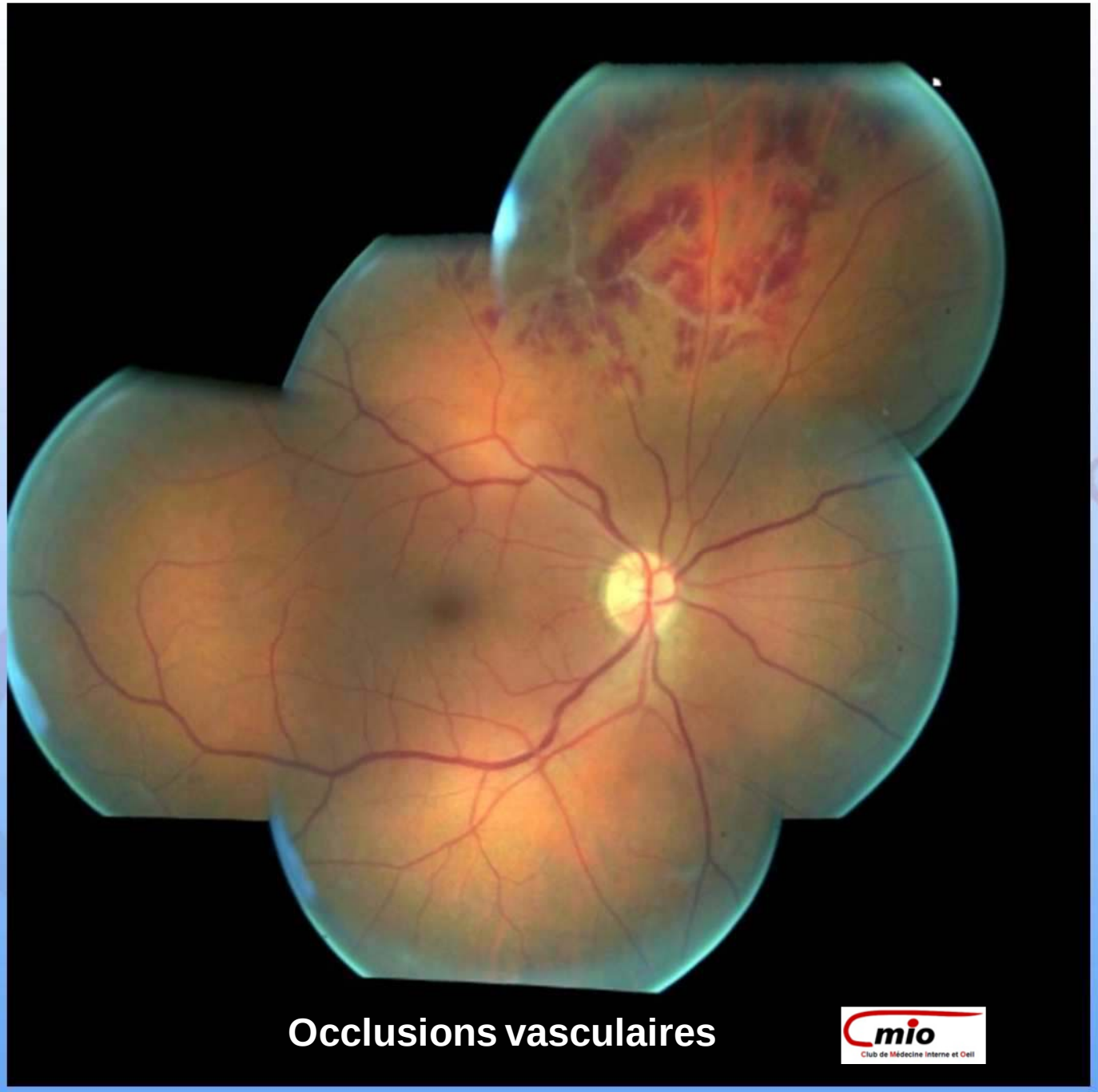
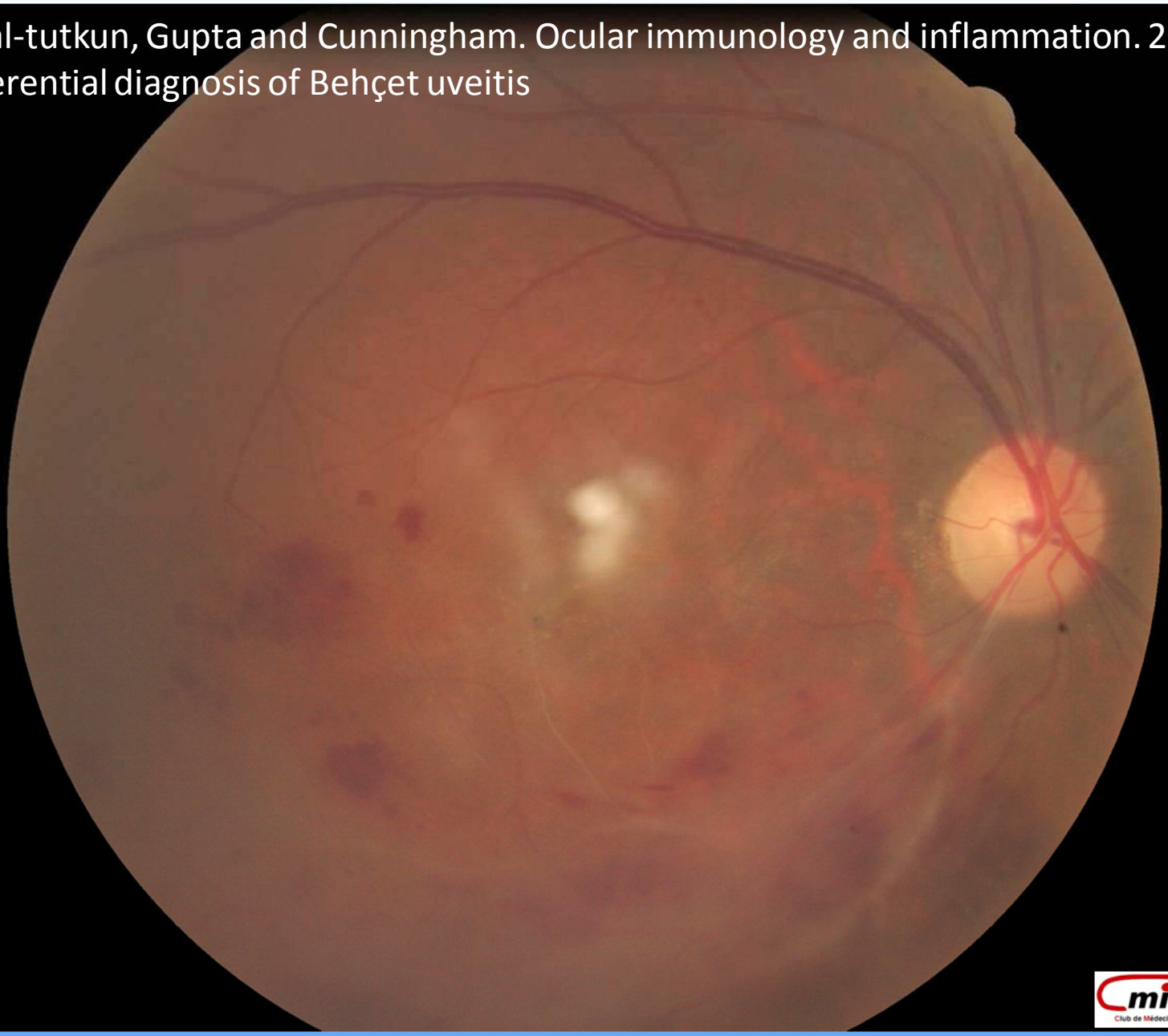
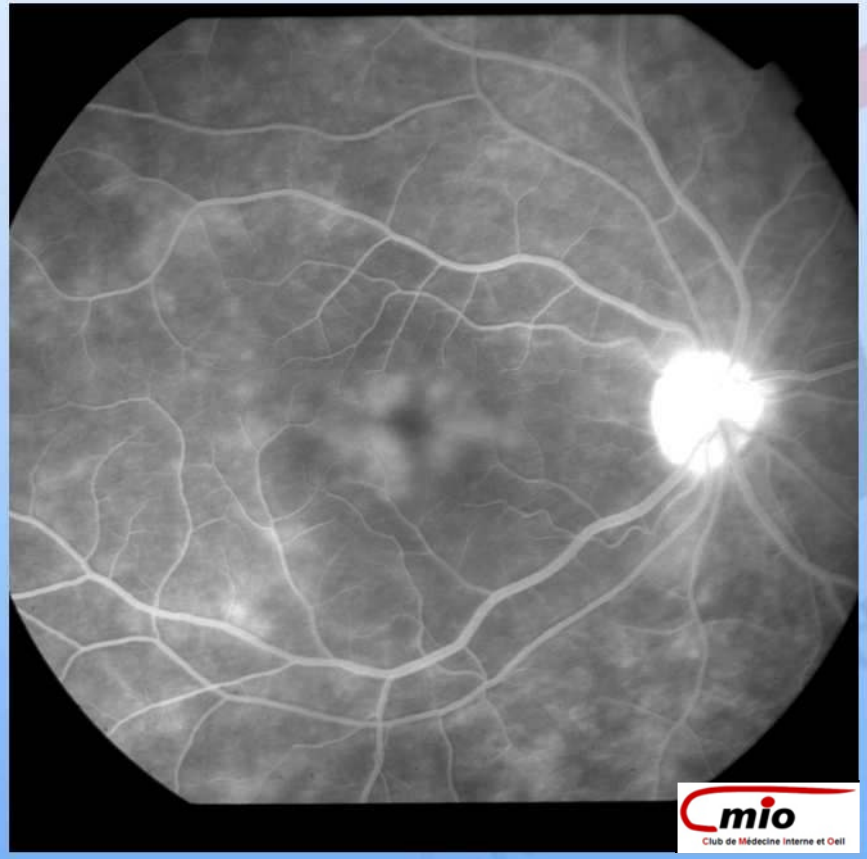


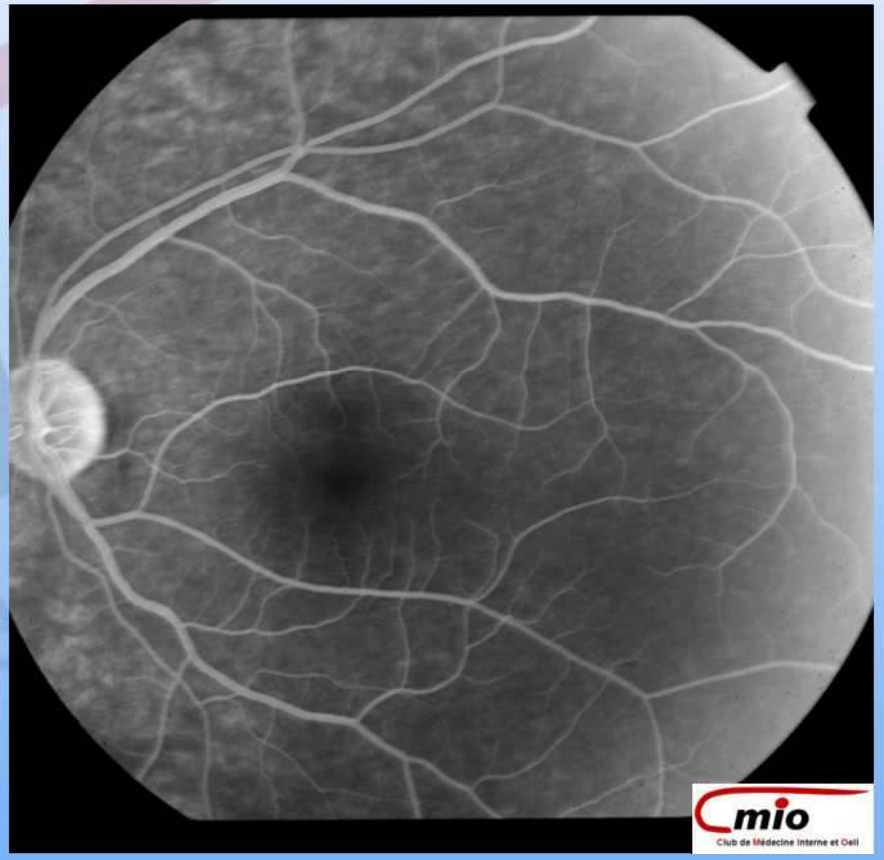
Occlusions vasculaires

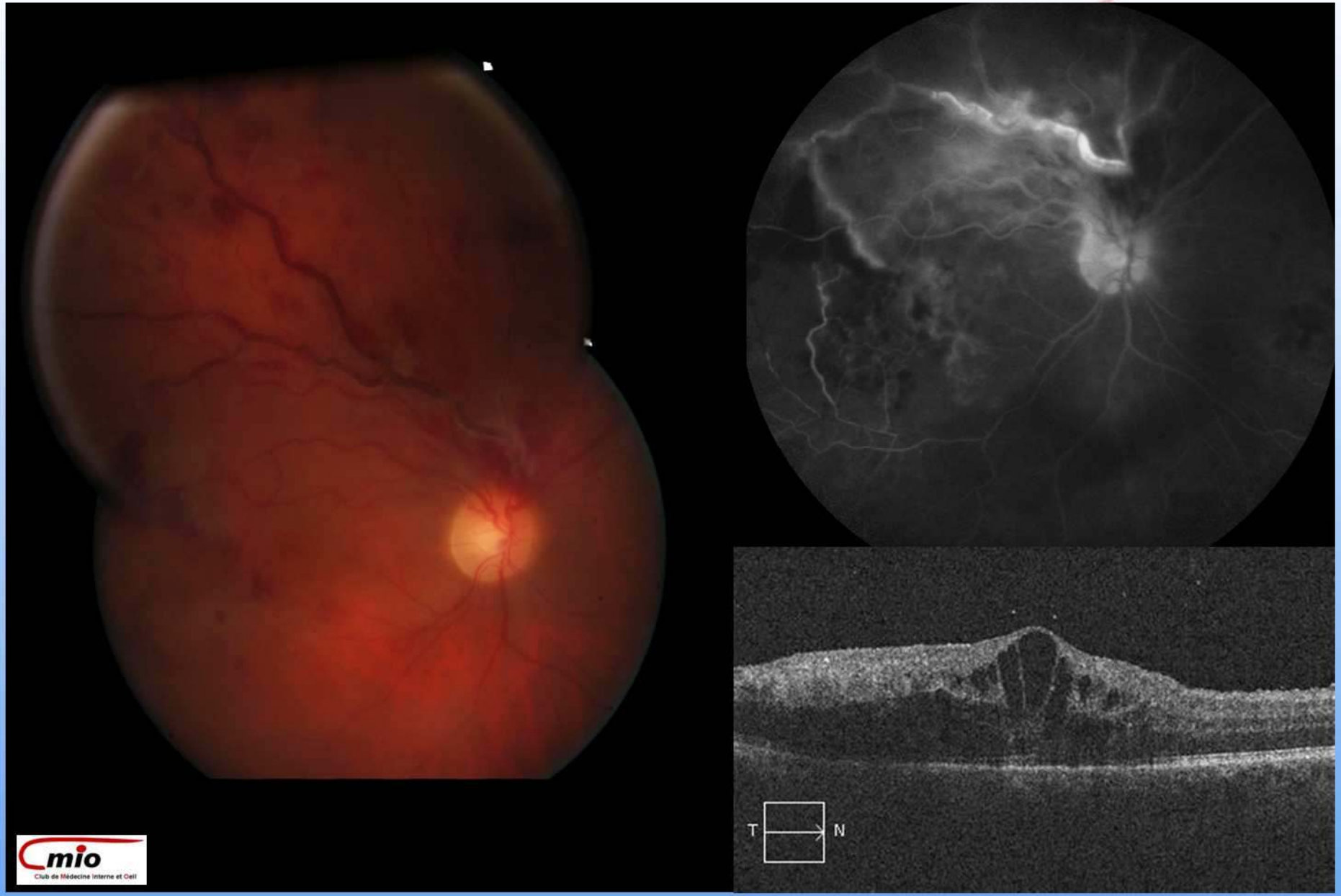
Tugal-tutkun, Gupta and Cunningham. Ocular immunology and inflammation. 2013
Differential diagnosis of Behçet uveitis



Œdème maculaire et papillite



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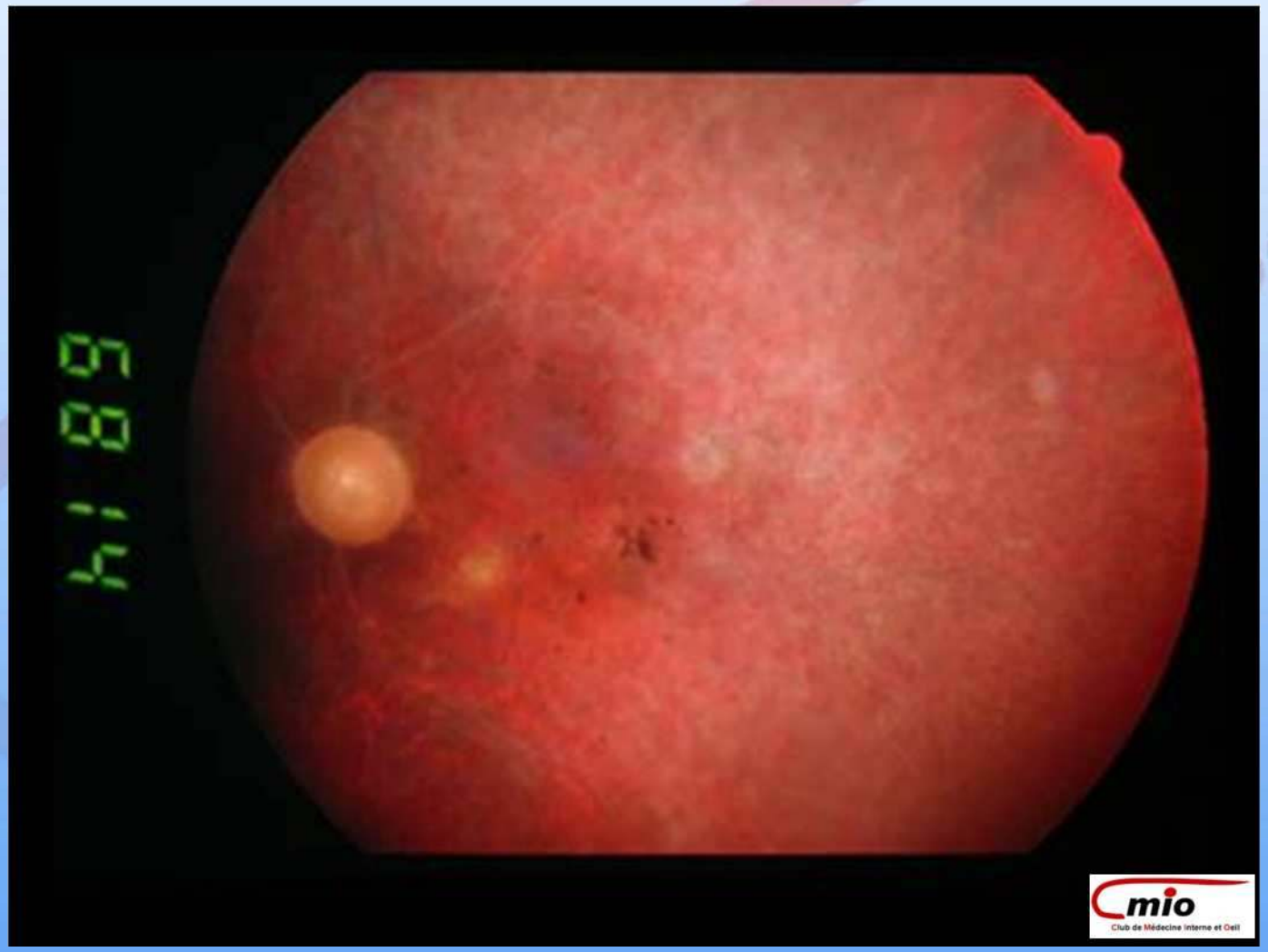
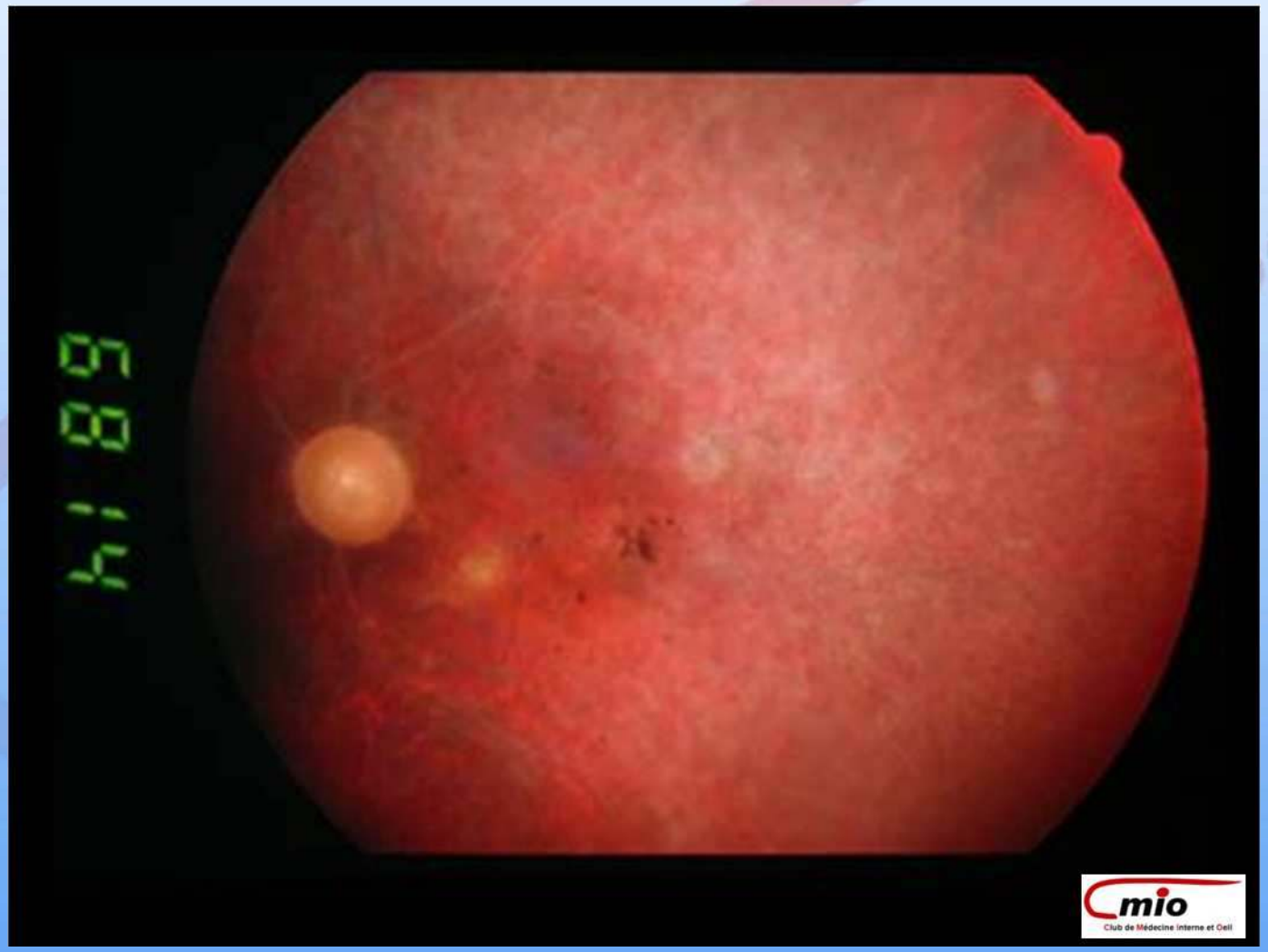
Maladie de Behçet et uvéite….



Traitement intraoculaire?

- Markomichelakis et al AJO 2012
  - Anti TNFα, 15 patients
  - Moins efficace qu'en IV (rapidité et Acuité visuelle à 1 mois, doute sur la tolérance)
- Markomichelakis et al Rheumatology 2011
  - Intravitréenne de kénacort, bolus de solumedrol et infliximab en IV
  - Supériorité de l'infliximab en IV
  - *Pour les patients intolérants aux autres traitements*

Maladie de Behçet et uvéite….



Maladie de Behçet et Œil/Traitement

David Saadoun MD PhD

Service de Médecine Interne

Centre de référence des Maladies Autoimmunes rares

Hôpital Pitié Salpétrière

Club Médecine Interne et Œil
FMC du 4 octobre 201

EULAR Recommendations for the Management of Behçet's Disease

Report of a Task Force of the European Standing Committee for International Clinical Studies Including Therapeutics (ESCISIT)

G. Hatemi, A. Silman, D. Bang, B. Bodaghi, A. M. Chamberlain, A. Gul, M. H. Houman, I. Kötter, I. Olivieri, C. Salvarani, P. P. Sfikakis, A. Siva, M. R. Stanford, N. Stübiger, S. Yurdakul and H. Yazici

Ann Rheum Dis 2008

Development of Recommendations

EULAR's standardised operating procedures for developing recommendations combining:

- **Best available evidence from the literature**
- **The opinion of experts**

Targeting:

- **All physicians and surgeons who are involved in the treatment of Behçet's Disease**

1

Any patient with BD and inflammatory eye disease affecting the posterior segment should be on a treatment regime, which includes azathioprine and systemic corticosteroids

- ***Category of evidence: Ib***
- ***Strength of Recommendation: A/D***
- ***Level of Agreement:***
  - ***among the whole group: 9.57 ± 0.51***
  - ***among "experts": 9.73 ± 0.47 (n=11)***

2

If the patient has severe eye disease defined as >2 lines of drop in visual acuity on a 10/10 scale and/or retinal disease, (retinal vasculitis or macular involvement), it is recommended that either cyclosporine A or infliximab be used in combination with azathioprine and corticosteroids; alternatively interferon-alpha with or without corticosteroids could be used

- ***Category of evidence: II***
- ***Strength of Recommendation: C/D***
- ***Level of Agreement:***
  - ***among the whole group: 8.71 ± 0.91***
  - ***among "experts": 8.9 ± 0.83 (n=11)***

Azathioprine in Severe Uveitis of Behçet's Disease

D. SAADOUN,[1] B. WECHSLER,[1] C. TERRADA,[1] D. HAJAGE,[2] D. LE THI HUONG,[1] M. RESCHE-RIGON,[2] N. CASSOUX,[1] P. LE HOANG,[1] Z. AMOURA,[1] B. BODAGHI,[1] AND P. CACOUB[1]

Table 1. Characteristics of the 157 patients with BD*

	Value
Age at diagnosis, mean ± SD years	29.9 ± 10.1
Male sex	112 (71.3)
Ethnic origin	
North Africa	70 (44.6)
Africa	5 (3.2)
Europe	77 (49.0)
Others	5 (3.2)
HLA–B5 (n = 120)	73 (60.8)
Characteristics of uveitis	
Unilateral	25 (15.9)
Bilateral	132 (84.1)
Panuveitis	66 (42.0)
Retinal vasculitis	54 (34.4)
Clinical features of BD	
Oral ulcerations	157 (100)
Genital ulcerations	83 (52.9)
Arthralgias	80 (51.3)
Skin lesions	97 (61.8)
Arterial involvement	13 (8.3)
Venous thrombosis	39 (24.8)
CNS involvement	52 (33.3)

* Values are the number (percentage) unless otherwise indicated. BD = Behçet's disease; CNS = central nervous system.

Arthritis 2010

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Table 4. Comparison of patients with Behçet's disease and severe uveitis who were complete responders versus partial/nonresponders*

	All (n = 157)	Complete responders (n = 81)	Partial/nonresponders (n = 76)	OR (95% CI)	*P*
Age, mean ± SD years	29.9 ± 10.1	29.3 ± 9.3	30.7 ± 10.9	0.98 (0.9–1.1)	0.37
Male sex	112 (71.3)	56 (69.1)	56 (73.7)	0.80 (0.4–1.7)	0.59
HLA–B5	72 (60.5)†	36 (60)	36 (61)	0.95 (0.4–2.1)	1
Previous immunosuppressant	31 (19.7)	14 (17.3)	17 (22.4)	0.71 (0.5–3.1)	0.55
Retinal vasculitis	54 (34.4)	21 (25.9)	33 (43.4)	0.45 (0.2–0.9)	0.02
Bilateral uveitis	132 (84.1)	66 (81.5)	66 (86.8)	0.66 (0.2–1.7)	0.39
Visual acuity, mean ± SD	4.3 ± 3.6	5.4 ± 3.2	3.1 ± 3.4	0.28 (0.2–0.7)	< 0.0001
Oral ulceration	157 (100)	81 (100)	76 (100)	–	–
Genital ulceration	83 (52.9)	40 (49.4)	43 (56.6)	0.75 (0.4–1.5)	0.42
Articular involvement	80 (51.3)	42 (51.9)	38 (50.7)	1.04 (0.5–2.1)	1
Venous involvement	39 (24.8)	23 (28.4)	16 (21.1)	1.48 (0.6–3.3)	0.35
Arterial involvement	13 (8.3)	10 (12.5)	3 (3.9)	1.47 (1.2–1.7)	0.08
CNS involvement	52 (33.3)	32 (39.5)	20 (26.7)	1.78 (0.8–3.7)	0.12

* Values are the number (percentage) unless otherwise indicated. OR = odds ratio; 95% CI = 95% confidence interval; CNS = central nervous system.
† N = 120.

Arthritis 2010

Tableau 50-V. L'interféron α2a en pratique.

MODALITÉS UTILISATION ET POSOLOGIE	– Voie sous-cutanée, 3 à 6 MU/jour ou × 3/semaine – Paracétamol juste avant ou au moment de l'injection
CONTRE-INDICATIONS	– Hypersensibilité au produit – Troubles psychiatriques graves – Infections en cours
EFFETS SECONDAIRES PRINCIPAUX	– Syndrome pseudo-grippal (100 %) – Manifestations psychiatriques : dépression, anxiété, psychose, risque suicidaire – Cytolyse hépatique – Troubles digestifs, alopécie, exacerbation d'un psoriasis, dysthyroïdie, etc. – Rétinopathie (rarement Harada et occlusions vasculaires)
SURVEILLANCE BIOLOGIQUE	Hémogramme, créatinine, bilan hépatique, TSHus/ mois pendant 3 mois, puis tous les 3 mois
INDICATIONS EN OPHTALMOLOGIE (NIVEAU DE PREUVE)	– Maladie de Behçet (études prospectives ouvertes) – Œdème maculaire cystoïde (étude prospective ouverte et étude rétrospective) – Sclérose en plaques (étude rétrospective) – Autres uvéites : idiopathique, Harada, Birdshot, serpigineuse (étude rétrospective)

TSHus : dosage de la Thyroid Stimulating Hormone par méthode ultrasensible.

Interferon-α

The only RCT with IFNα involves 9 patients with eye involvement (6 in IFNα, 3 in placebo arm)

- **Complete remission : 3/6 vs 0/3**
- **Partial remission : 2/6 vs 1/3**
- **Development of new eye disease: 0/23 vs 1/21**

Open studies with Interferon α

8 Open studies with IFN-α included patients with eye involvement:

- **Dose: 5 MU / week to 9 MU x 3 / week**
- **Total number of patients: 195**
- **Complete remission: 139/195**
  - **remission of macular edema**
  - **reperfusion of occluded retinal veins**
  - **complete remission of retinal neovascularisation**
  - **significant improvement in visual acuity**
  - **tapering the dose of steroids**
- **Time to remission: 2 weeks**

CLINICAL SCIENCE

Human recombinant interferon alfa-2a for the treatment of Behçet's disease with sight threatening posterior or panuveitis

I Kötter, M Zierhut, A K Eckstein, R Vonthein, T Ness, I Günaydin, B Grimbacher, S Blaschke, W Meyer-Riemann, H H Peter, N Stübiger

Br J Ophthalmol 2003;**87**:423–431

See end of article for authors' affiliations

Correspondence to: Ina Kötter, MD, Department of Internal Medicine II, (Hematology/Oncology/ Immunology/Rheumatology) University Hospital, Otfried-Müller Strasse 10, D-72076 Tübingen, Germany; ina.koetter@med.uni-tuebingen.de

Accepted for publication 14 October 2002

Background: Behçet's disease is a multisystem vasculitis of unknown origin. Standard treatment mainly comprises systemic immunosuppressive agents. Ocular involvement, mostly posterior uveitis with retinal vasculitis, leads to blindness in 20–50% of the involved eyes within 5 years. The efficacy of interferon alfa-2a was studied in patients with sight threatening posterior uveitis or retinal vasculitis.

Methods: 50 patients were included in this open, non-randomised, uncontrolled prospective study. Recombinant human interferon alfa-2a (rhIFNα-2a) was applied at a dose of 6 million units subcutaneously daily. Dose reduction was performed according to a decision tree until discontinuation. Disease activity was evaluated every 2 weeks by the Behçet's disease activity scoring system and the uveitis scoring system.

Results: Response rate of the ocular manifestations was 92% (three non-responder, one incomplete response). Mean visual acuity rose significantly from 0.56 to 0.84 at week 24 ($p<0.0001$). Posterior uveitis score of the affected eyes fell by 46% every week ($p<0.001$). Remission of retinal inflammation was achieved by week 24. Mean Behçet's disease activity score fell from 5.8 to 3.3 at week 24 and further to 2.8 at week 52. After a mean observation period of 36.4 months (range 12–72), 20 patients (40%) are off treatment and disease free for 7–58 months (mean 29.5). In the other patients maintenance IFN dosage is three million units three times weekly.

Conclusions: rhIFNα-2a is effective in ocular Behçet's disease, leading to significant improvement of vision and complete remission of ocular vasculitis in the majority of the patients.

Behçet's disease is a multisystem vasculitis of unknown origin, which is most prevalent in Mediterranean countries, Asia and the Middle East, which lie along the former "silk route."[1–3] Its main features[4–7] are oral and genital aphthous ulcers, skin manifestations such as erythema nodosum, papulopustules, or leucocytoclastic vasculitis, oligoarthritis, peripheral vascular manifestations such as thrombophlebitis, thrombosis, aneurysms, and neurological manifestations. The disease is associated with HLA B51. Ocular manifestations, mostly a bilateral panuveitis running a chronic relapsing course, are present in 60–80% of the patients. In most studies, blindness occurred in 20–50% of the patients within 5 years.[8–9] With the increasing use of immunosuppressive agents, ocular prognosis has improved.[10] Azathioprine has been shown to maintain visual acuity and prevent development of eye disease,[11 12] but in our experience, especially in severe panuveitis and retinal vasculitis, may not act rapidly enough. Cyclosporin A is an effective and rapidly acting drug for eye disease.[13–17] However, nephrotoxicity, particularly at doses higher than 5 mg/kg/day, and relapses after cessation of therapy often limit its use. Cytotoxic agents such as cyclophosphamide and chlorambucil are also used but have been less well studied. Colchicine is effective for mucocutaneous and articular manifestations, but only partially effective for posterior uveitis.[18] Brief courses of corticosteroids may shorten the duration of the attacks but they are not effective for long term treatment, probably because the dose necessary for maintenance of remission would be very high with unacceptable side effects.

Up to now, interferons have only been used in selected small cohorts with Behçet's disease. A few open studies with up to 20 patients without ocular disease, showed efficacy for interferon alfa (IFN) and in different doses.[19–25] Recently, there have been case reports on efficacy in four patients with severe refractory eye disease successfully treated with steroids, immunosuppressants, and IFN in various combinations[26–28] and four small open studies with a total of 86 patients, 21 of whom had ocular inflammation.[29–32] Eye disease was reported to respond to IFN treatment, but details were not described. A randomised controlled study recently published[33] with 135 patients (67 randomised to IFN plus colchicine plus penicillin, previous ocular disease was excluded) unfortunately had to be retracted owing to fabrications with respect to authorship and possibly also the reported data and ethical transgressions.[34–37] We treated a patient who had developed Kaposi's sarcoma under triple immunosuppressive therapy for his severe ocular Behçet's disease[38] with rhIFNα-2a and were able to induce remission of both diseases. This prompted us to initiate a pilot study on the efficacy of rhIFNα-2a in severe ocular Behçet's disease.[39 40] Because of the promising results, it was continued as a four centre, prospective, open, uncontrolled study.

METHODS

Study design

Fifty patients with highly resistant ocular Behçet's disease were included in four participating hospitals from March 1995 to March 2000, the last examination considered for evaluation was performed in March 2001. It was a prerequisite for entering the study for the patients to have active posterior uveitis or panuveitis which had been refractory to at least one conventional immunosuppressive drug (for example, azathioprine or cyclosporin A) or prednisolone in a dose of at least 1 mg/kg bodyweight and/or impossibility to taper the steroids to a maintenance dosage of less than 30 mg prednisolone equivalent per day. This drug had to be given for at least 2 weeks.

Interferon-α as an Effective Treatment for Noninfectious Posterior Uveitis and Panuveitis

JARKA PLSKOVA, KATHRIN GREINER, AND JOHN V. FORRESTER

• PURPOSE: Several studies have shown the capacity of interferon-α (IFN-α) to control ocular Behçet disease. The authors aimed to determine whether IFN-α was effective in treating patients with severe, refractory sight-threatening intraocular inflammation (uveitis) from a wider range of causes, including Behçet disease.
• DESIGN: Prospective, interventional case series.
• METHODS: Twelve patients with sight-threatening uveitis that failed to respond to one or more immunosuppressive regimens were enrolled to this study. Recombinant human IFN-α-2b was administered subcutaneously daily, and the dose was adjusted according to the clinical response. Main outcome measures were visual acuity, clinical activity of uveitis (including binocular indirect ophthalmoscopy [BIO] score and presence or absence of macular edema), and adverse effects of the treatment.
• RESULTS: The mean observation period was 11 months (range, one to 29 months). A positive clinical response was observed in 83% of patients. Median visual acuity improved from 0.54 to 0.2 (logarithm of the minimum angle of resolution units; $P < .001$) and median BIO score decreased from 1.0 to 0.5 ($P < .05$) within one month of treatment. Macular edema, if present, resolved in all patients within days of treatment. The main adverse events were tiredness, lymphopenia, flu-like symptoms, and transient increase of liver enzymes. Weight loss occurred in four patients. Four patients experienced depression, one of them attempting suicide. Three patients experienced typical features of IFN-α–associated retinopathy, which resolved on reducing the dose.
• CONCLUSIONS: IFN-α seems to have significant potential in treatment of severe, sight-threatening refractory uveitis from a variety of causes. A range of adverse events, including IFN-α–associated retinopathy, may occur and could limit the use of this immunomodulatory drug. (Am J Ophthalmol 2007;144:55–61. © 2007 by Elsevier Inc. All rights reserved.)

THE NEED FOR IMMUNOSUPPRESSION IN THE TREATment of posterior segment intraocular inflammation (uveitis) of a noninfectious cause has been well recognized for at least half a century.[1] However, even with regimens that include toxicity-minimizing, low-dose combinations of immunosuppressants and immunomodulants, there are patients whose ocular inflammation cannot be controlled and who therefore continue to lose vision.[2] The need for new therapeutic strategies that are more effective and have fewer side effects therefore is considerable. The range of available immunosuppressants becomes broader every year. Recently, it was reported that new biologic agents, such as anti–tumor necrosis factor-α[3–7] or the interferons (IFNs),[8–10] were effective even in patients resistant to conventional treatment. IFN-α-2a and infliximab have been shown to induce prompt remission in the vast majority of Adamantiades-Behçet patients with uveoretinitis (for review, see ref. [11]). It was also reported that treatment of multiple sclerosis-associated uveitis with IFN-β-1a seems to have beneficial effects on visual acuity (VA), intraocular inflammation activity, and the presence of cystoid macular edema (CME). However, according to our knowledge, there was only one study in which the effectiveness of IFN-α to treat uveitis was investigated in non-Behçet patients.[9]

IFN-α-2a (Roferon-A; Hoffmann-La Roche, Basel, Switzerland), IFN-α-2b (Intron-A; Schering-Plough, Kenilworth, New Jersey, USA), and IFN alfacon-1 (Infergen; Intermune, Brisbane, California, USA) are approved for the treatment of adults with chronic hepatitis B and C, various hematologic malignancies, and malignant melanoma as single agents.[12–15] Treatment with recombinant IFNs is associated with side effects including flu-like symptoms, depression, rashes, and abnormal blood counts. In this study, we determined whether IFN-α-2b was effective and well tolerated in the treatment of patients with severe, refractory sight-threatening intraocular inflammation resulting from a variety of causes, including Behçet disease.

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METHODS

• PATIENTS, ENTRY CRITERIA, AND STUDY DESIGN: A total of 12 patients with severe, refractory sight-threatening noninfectious posterior segment intraocular inflammation (uveitis) were recruited to this prospective study between April 2002 and May 2004. The clinical details are shown in Table 1. Refractory sight-threatening intraocular inflammation was defined for the purposes of the study as inflammation that failed to respond to one or more

Efficacy of interferon alpha in the treatment of refractory and sight threatening uveitis: a retrospective monocentric study of 45 patients

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Concise Report

Efficacy and safety of interferon-α in the treatment of corticodependent uveitis of paediatric Behçet's disease

S. Guillaume-Czitrom, C. Berger[1], C. Pajot[2], B. Bodaghi[3], B. Wechsler[4] and I. Kone-Paut

Objective. To report both the efficacy and safety of interferon-α-2a (IFN-α) therapy in corticodependent uveitis of paediatric Behçet's disease (BD).

Methods. Data from seven children affected with corticodependent uveitis of BD and treated with IFN-α were reviewed retrospectively. IFN-α was injected sub-cutaneously thrice a week at dosages of 1.5–3 M^{UI}/kg according to the children's weight. Efficacy was judged on the ability of IFN-α to induce a corticosteroid (CS)-sparing effect while maintaining remission. All adverse events (AE) were recorded.

Results. The children included four boys and three girls. Mean age at onset of uveitis was 8.6 yrs and mean follow-up duration was 7.14 yrs. All children had a high level of corticodependence and five of them received additional DMARDs. A remarkable CS-sparing effect with remission maintenance was achieved in 5 out of 7 patients after a mean period of 14.6 months of IFN-α administration. The remission was sustained in four of the five patients (mean = 4.8 yrs), even after IFN-α was discontinued in three of them. The other patient relapsed 1.5 yrs after IFN-α discontinuation. The last two patients faced early severe adverse events attributed to IFN-α: retinal venous thrombosis and major depression.

Conclusion. IFN-α has a potent CS-sparing effect in paediatric BD patients suffering from severe uveitis. However, the possibility of major side-effects with this treatment calls for careful monitoring.

Key words: Behçet's disease in children, Uveitis, Treatment, Interferon-α.

Introduction

Behçet's disease (BD) is a multisystemic inflammatory disorder that is classified among the vasculitic syndromes. BD is characterized by an association of bipolar aphthosis with uveitis as well as with skin, articular, neurological and potentially life-threatening vascular lesions [1]. Ocular manifestations represent a key feature of BD, ranging in frequency from 30% in children to 60–80% in adults [2–7]. The most typical lesions include posterior or total non-granulomatous uveitis affecting both eyes asymmetrically and retinal occlusive vasculitis [8]. The course of uveitis is more severe in children than in adults, being characterized by recurrent explosive attacks whose frequency and severity can result in permanent damage to visual structures, calling for fast-acting and efficient treatment [9].

Prompt remission of BD-uveitis can usually be obtained with high doses of corticosteroids (CSs); however, most children develop CS dependence together with their known side-effects. To spare CS and avoid recurrences, patients often require non-specific drugs like colchicine, azathioprine, cyclosporine, methotrexate or cyclophosphamide [1]. Despite these aggressive treatments, blindness occurs in 16–25% of the patients after 5 yrs [2–4]. More recently, adult patients suffering from sight-threatening BD-uveitis were successfully treated with anti-tumour necrosis factor (TNF)-α drugs, monoclonal antibodies giving seemingly better results than soluble TNF-R in this indication [10–12]; unfortunately, monoclonal anti-TNF-α antibodies are not currently allowed for use in children in France. Encouraging results have been published from case reports of adult BD patients treated with interferon-α-2a (IFN-α) for severe uveitis, as well as from a placebo-controlled study involving a whole population of BD patients, few of whom had uveitis [13–17]. Indeed, IFN-α was shown to be efficient not only on ocular manifestions of BD, but also on muco-cutaneous, neurological, articular symptoms and some vascular lesions [1]. While a recent publication showed the efficacy and safety of IFN-α in 19/23 adults with BD-uveitis (82.6%) [18], no specific paediatric series has been published. We report herein our experience with IFN-α treatment of seven paediatric BD patients affected with high-level corticodependent uveitis, who were followed for a mean period of 4.8 yrs starting with IFN-α introduction.

Patients and methods

Patient selection and study design

The charts of seven children with BD-uveitis occurring before the age of 16 yrs, and treated with IFN-α, were retrospectively studied. The parents' written consent was obtained according to the Declaration of Helsinki and the design of the work conformed to standards applied in France. Patients originated from three hospitals (St-Etienne, Toulouse and Pitié-Salpetrière-Paris) and were all referred to two BD experts (B.W. and I.K-P.) for therapeutic management. Extensive work-ups were performed in all cases to exclude other possible causes of uveitis. Microbial investigations included bacterial cultures and PCRs of Herpes viridae, Spirochetae cDNAs in the ocular fluid and serologies of Herpes viridae, HIV, Spirochetae, Leptospirae, Toxocara, Toxoplasma, Mycoplasma, Chlamydia and Gram-negative germs known to induce reactive arthritis; ANA, RF, ANCA and HLA B typing were performed. Since the ISG diagnostic criteria for BD [19] are not suitable for children, BD was diagnosed according to the combination of: (i) at least recurrent aphthous stomatitis and/or a familial history of BD since familial cases were shown to be more frequent when BD starts early in life [20, 21]; (ii) typical relapsing BD-uveitis and (iii) elimination of other causes of uveitis. All eyes were examined by an

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Discussion

	Kötter [2003]	Tugal-Tutkun [2006]	Gueudry AJO [2008]
Number of patients	50	44	33
Initial IFN dosage	6MIU/d	6MIU/d	3MIU 3x/ week
Efficacy	46 (92%)	40 (91%)	29 (88%)
Treatment duration	16.4 months (range 3-58)	22.2±13.4 months	32 months (range 16-50)
Discontinuation IFN assay	20 (40%)	9 (22.5%)	20 (60.6%)
Follow-up after discontinuation	29.5 months (range 7-58)	24 months at least	43 months (range 6-84)
IFN discontinuation without relapses	40%	18.1%	42.4%
Corticotherapy discontinuation	81%	Between 40 and 60 %	None
Side effects			
Flu-like syndrome	50 (100%)	44 (100%)	17 (51.5%)
Depression	4 (8%)	0	3 (9%)
Leucopenia	20 (40%)	6 (13.6%)	6 (18.2%)

Evaluation of safety from open studies with Interferon-α

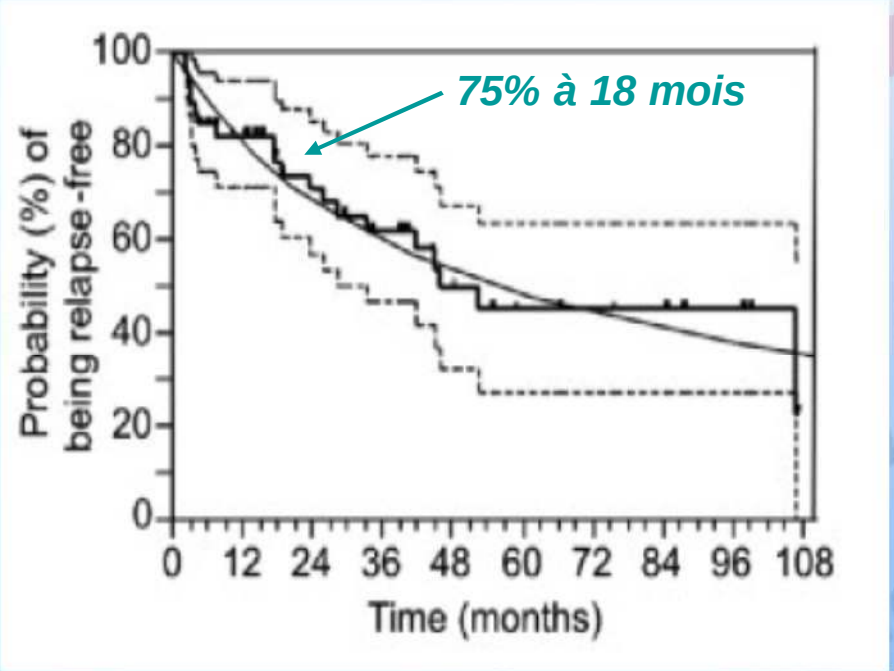
14 studies gave information about toxicity

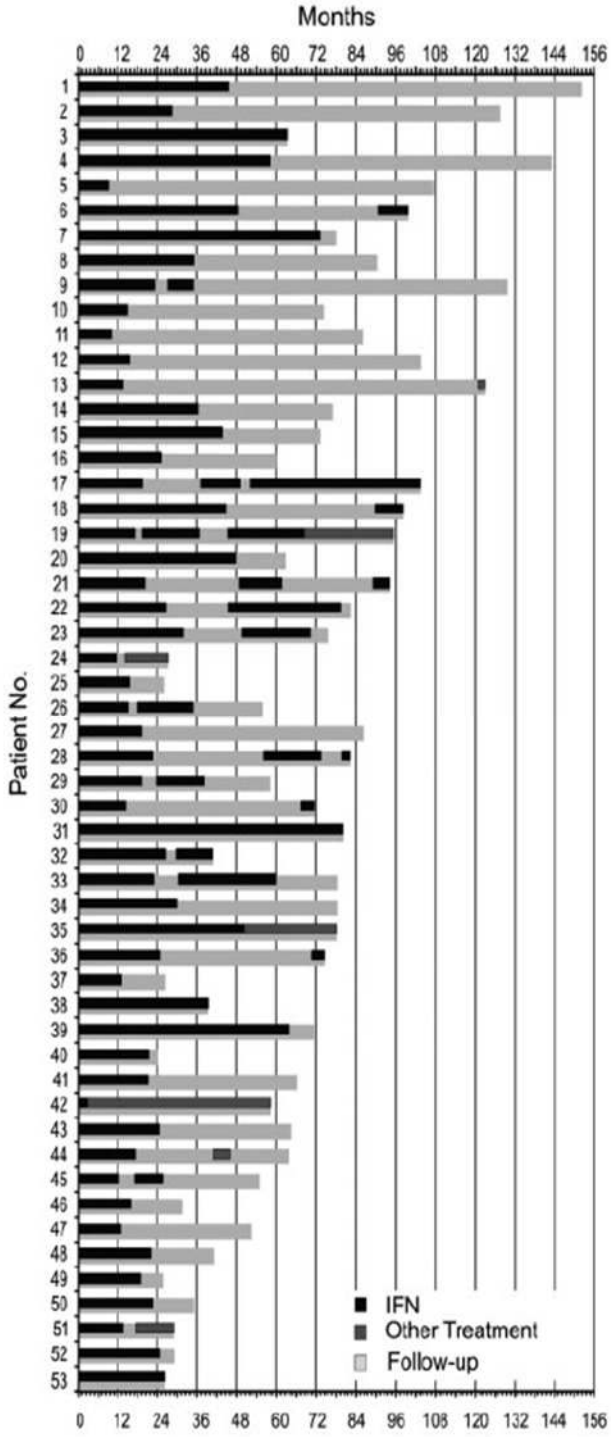
IFN-α should not be used in combination with azathioprine due to the risk of serious myelosuppression

Toxicity	Number of patients	Withdrawals due to toxicity
Flu-like symptoms	231/257 (90%)	-
Depression	7/ 257 (3%)	3/7
Alopecia	15/ 257 (6%)	2/14
Leukopenia	9/ 257 (4%)	-
Thrombopenia	1/ 257 (0.4%)	-
Injection site ulcers	1/ 257 (0.4%)	1/1
Epileptic seizures	1/ 257 (0.4%)	1/1
ALT/AST elevation	2/ 257 (0.8%)	1/1

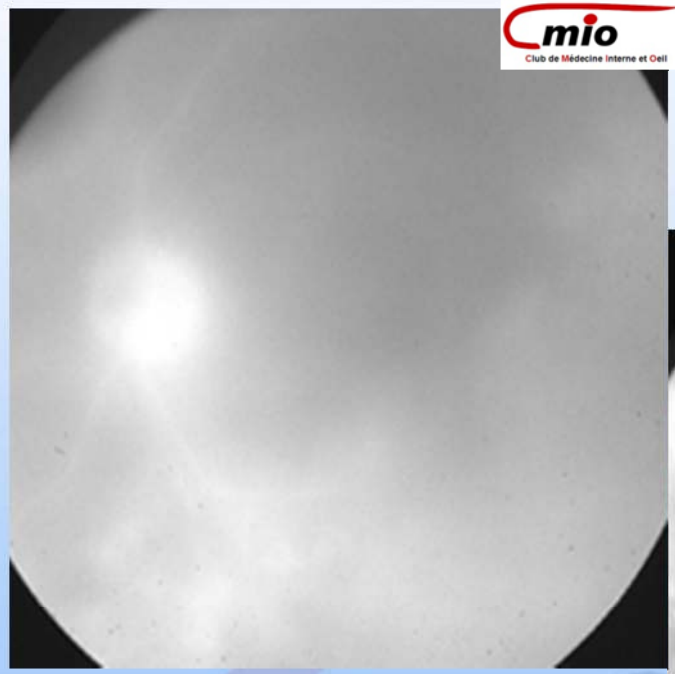
Long-Term Remission After Cessation of Interferon-α Treatment in Patients With Severe Uveitis Due to Behçet's Disease

Christoph M. E. Deuter,[1] Manfred Zierhut,[1] Antje Möhle,[1] Reinhard Vonthein,[2] Nicole Stübiger,[1] and Ina Kötter[1]



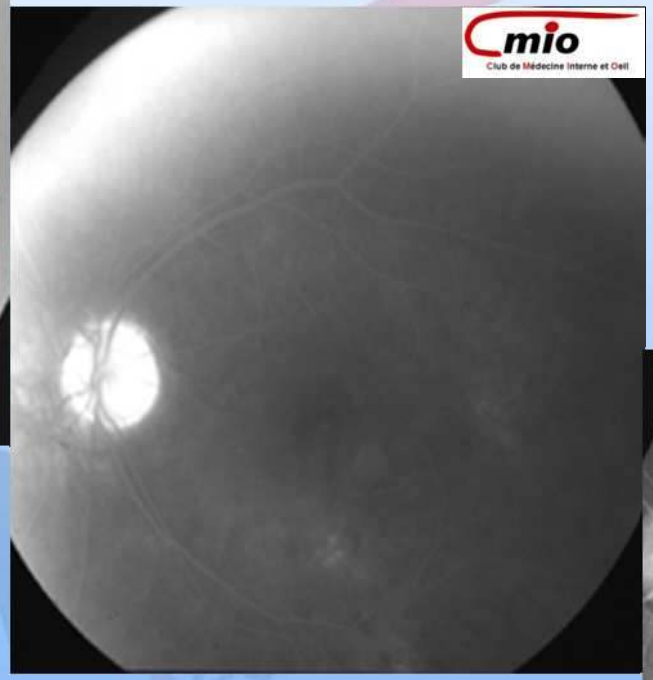


INFLIXIMAB



10/2

Rechute sous EDX
Hyalite++



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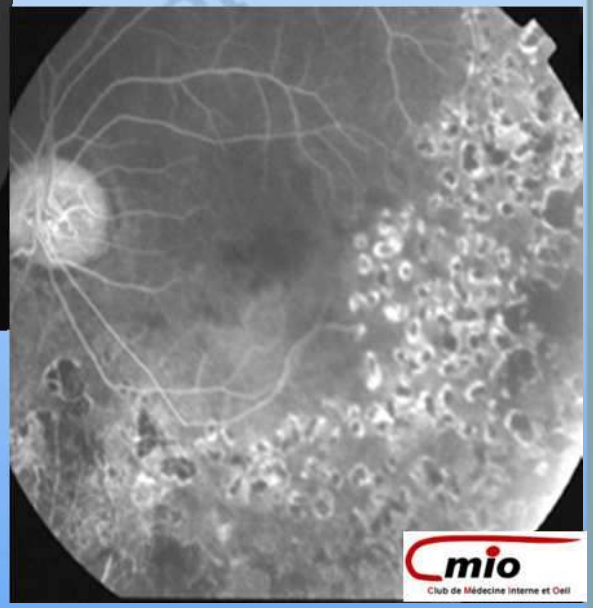
48h après aTNFa



10/25

S3 après aTNFa

Tableau 50-III. Les anti-TNF-α en pratique.

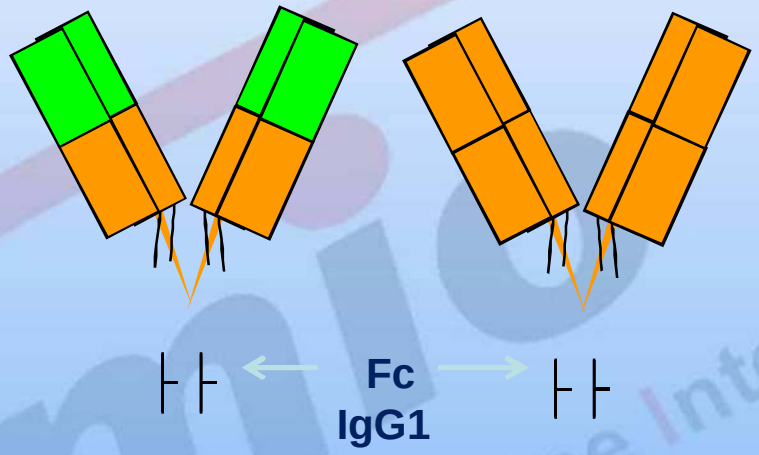
MODALITÉS UTILISATION ET POSOLOGIE	– Voie Intraveineuse : infliximab, 5 mg/kg S0, S2, S6 et toutes les 8 semaines. Prémédication par antihistaminique, antipyrétique et hydrocortisone. – Voie sous-cutanée : adalimumab, 40 mg/15 jours
CONTRE-INDICATIONS	– Hypersensibilité au produit – Insuffisance cardiaque modérée ou sévère (de classe III/IV dans la classification NYHA) – Infections sévères, évolutives
EFFETS SECONDAIRES PRINCIPAUX	– Réactions allergiques : rash, urticaire, prurit, irritation laryngée, fièvre, céphalée, hypotension – Infections +++ – Réactivation VHB – Lupus induit, maladies démyélinisantes – Lymphome
SURVEILLANCE BIOLOGIQUE	– Hémogramme tous les mois (risque de neutropénie tardive) – Bilan hépatique – Radiographie de thorax
INDICATIONS EN OPHTALMOLOGIE/ NIVEAU DE PREUVE	– Maladie de Behçet (études rétrospectives) – Uvéites (étude rétrospective) – Œdème maculaire cystoïde (étude rétrospective)

NYHA : New York Heart Association ; VHB : virus de l'hépatite B.

2 anti-TNF sont efficaces dans les Uvéites

Ac monoclonal chimérique

Ac monoclonal humain



Infliximab
mAb

Rémicade®
Isotype IgG_1
75% humain

Adalimumab
mAb

Humira®
Isotype IgG_1
100% humain

Anti-TNF Agents for Behçet's Disease: Analysis of Published Data on 369 Patients

Aikaterini Arida, MD, Kalliopi Fragiadaki, MD, Eirini Giavri, MD, and Petros P. Sfikakis, MD

Table 1 Disposition of Articles Appearing in Medline through March 2010 on the Use of Anti-TNF Agents in Patients[a] with Behçet's Disease

	Infliximab		Etanercept		Adalimumab	
	Studies	Patients	Studies	Patients	Studies	Patients
Case reports	53	59	9	11	8	8
Case series	11	30	2	6	3	9
Retrospective[b]	8	62	0	0	2	11
Prospective[b]	16	174	—	—	0	0
RCTs	—	—	1	20	—	—
Total articles	88	325	12	37	13	28

[a]Twenty patients received more than 1 anti-TNF agent.
[b]Studies describing 5 or more patients each.

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Table 2 Open-Label Studies Involving 10 Patients or More Treated with Infliximab for Refractory BD

Reference (no.)	Number of Patients	Major Organ Involvement
Sfikakis et al, 2004[a] (37)	25	Ocular
Ohno et al, 2004[a] (38)	13	Ocular
Tugal-Tutkun et al,[a] 2005 (42)	13	Ocular
Niccoli et al, 2007[a] (44)	12	Ocular
Accorinti et al, 2007[a] (45)	12	Ocular
Tabbara et al, 2008[b] (32)	10	Ocular
Yamada et al, 2009[b] (34)	17	Ocular
Al-Rayes et al, 2008[a] (47)	10	Ocular
Iwata et al, 2009[a] (49)	10	Gastrointestinal
Giardina et al, 2009[a] (50)	21	Ocular and CNS
Tanaka et al, 2010[a] (51)	19	Ocular

[a]Prospective study.
[b]Retrospective study.

Anti-TNF Agents for Behçet's Disease: Analysis of Published Data on 369 Patients

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Table 3 Anti-TNF Therapy-Induced Improvement of Various Clinical Manifestations in Patients with Behçet's Disease, Published through March 2010

	Improving Patients/Treated Patients[a]		
	Infliximab	Etanercept[b]	Adalimumab
Oral ulcers	110/122 (91%)	8/10 (82%)	8/11 (73%)
Genital ulcers	76/80 (96%)	5/7 (71%)	6/7 (86%)
Skin involvement	51/67 (77%)	2/3 (67%)	4/5 (80%)
Erythema nodosum	13/16 (81%)	1/1 (100%)	1/1 (100%)
Ocular involvement	233/262 (89%)	6/10 (60%)	16/16 (100%)
Gastrointestinal involvement	29/32 (91%)	—	3/3 (100%)
Central nervous system involvement	27/30 (90%)	2/2 (100%)	3/3 (100%)
Joint involvement	50/53 (94%)	6/6 (100%)	3/5 (60%)
Thrombophlevitis	7/10 (70%)	—	1/1 (100%)

[a]Patients with variable degree of improvement according to treating physicians are shown.
[b]Patients treated in the course of the RCT were excluded since they were not refractory to conventional immunosuppressants.

Anti-TNF Agents for Behçet's Disease: Analysis of Published Data on 369 Patients

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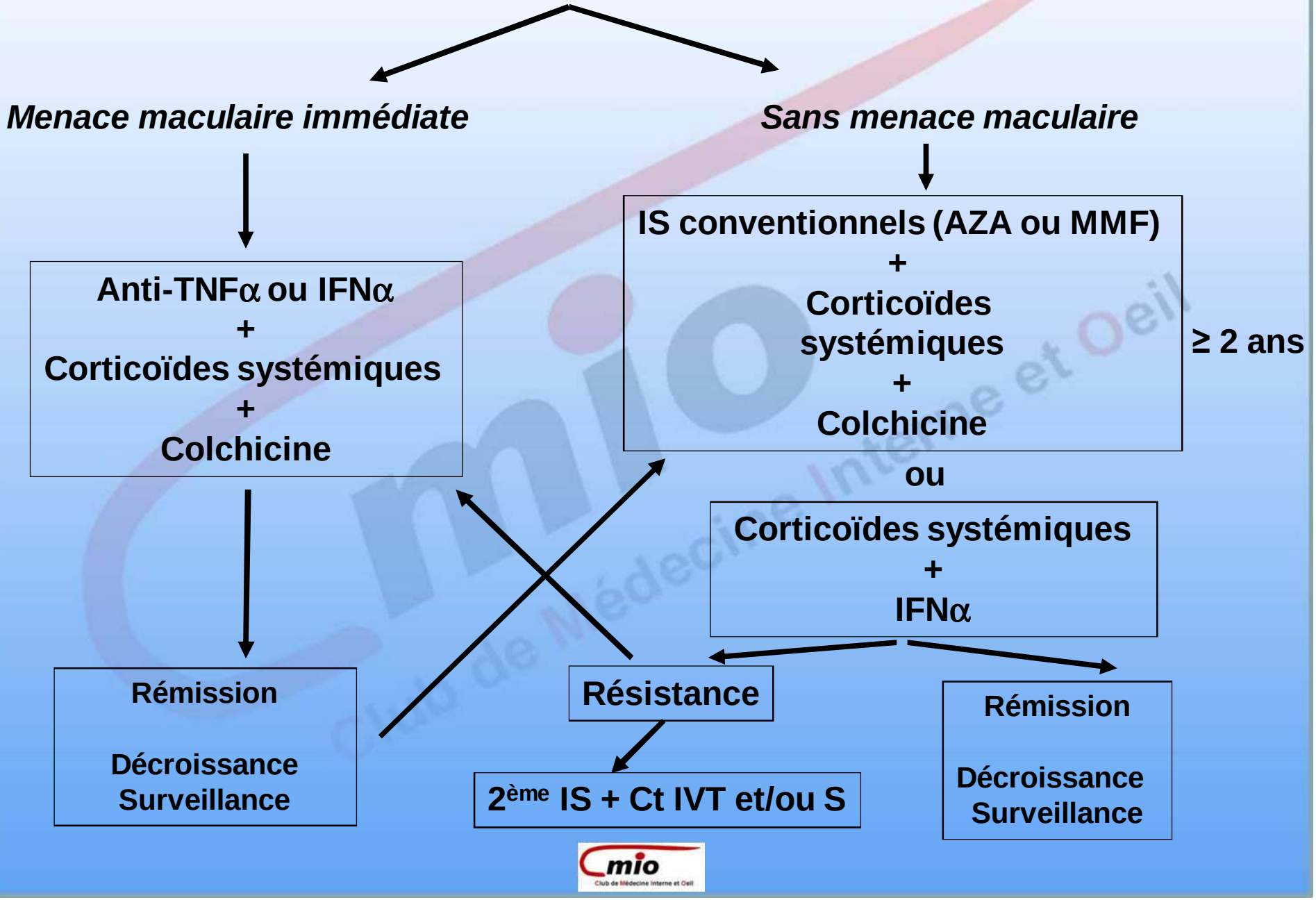
Table 5 Reported Adverse Events in 369 Patients with BD Treated with Anti-TNF Agents (approximately 300 patient/yr)

Reported Adverse Reaction	Number of Patients (Ref. no.)
Respiratory track infection	14 (19,42,44,47)
Pneumonocystis carinii pneumonia	2 (13,48)
Legionella pneumophila pneumonia	1 (58)
Reactivation of TB	4 (14,38,45,58)
De novo TB	1 (90)
Non-Hodgkin lymphoma	1 (50)
Cryptococcal meningitis	1 (89)
Perianal abscess	1 (32)
Varicella zoster infection.	2 (18,88)
Upper arm pyomyostitis	1 (96)
Worsening of osteomalacia	1 (86)
CMV colitis	1 (57)
Psoriasis	2 (91)
Erythema nodosum (de novo)	2 (97)
Cellulitis of forearm (ETN)	1 (20)
Bacterial endocarditis by Staphylococcus warneri (ETN)	1 (24)
Urticaria and Angioedema (ADL)	1 (98)

Maladie de Behçet avec uvéite postérieure



Conclusions

- 2 options thérapeutiques majeures (aTNFa,IFNa)
- Risque cécité ++
- Bilatéralisation ++
- Corticoïdes et IS d'emblée si uvéite postérieure
- Nécéssité études randomisées
- Anti IL1, anti IL6?